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Review article

The role of nanotechnology in skin cancer therapy

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ABSTRACT

The escalating global burden of melanoma and non-melanoma skin malignancies necessitates advanced treatment strategies beyond conventional modalities. Current interventions, including wide local excision and systemic chemotherapy, frequently demonstrate suboptimal therapeutic indices characterized by non-specific cytotoxicity and frequent disease recurrence. Recent advances in nanoscale engineering have yielded multifunctional platforms employing metallic (Au, Ag) and ceramic (ZnO, SiO_2) nanoparticles that address these limitations through: (i) enhanced epidermal permeability and retention, (ii) spatiotemporal control of drug release.

Particularly noteworthy are tumor-targeted formulations such as RGD-conjugated TiO_2 nanoparticles and cetuximab-functionalized liposomes, which demonstrate >50% improvement in tumor regression compared to conventional therapies in preclinical models. However, translational implementation confronts substantial barriers, including batch-to-batch variability in nanomanufacturing and undefined long-term biodistribution profiles. Emerging paradigms integrating CRISPR-based gene editing with stimuli-responsive nanocarriers present novel opportunities for personalized oncodermatology. This comprehensive analysis aims to delineate critical pathways for clinical adoption of nanotherapeutic interventions in cutaneous oncology.

KEYWORDS: Skin cancer, nanotechnology, TiO_2, Nanoparticles.

INTRODUCTION

Skin cancer, a leading global malignancy, originates from uncontrolled cell division due to disrupted regulatory mechanisms. It is classified into melanoma (from melanocytes) and non-melanoma types (basal and squamous cell carcinomas). According to WHO (2020), it ranks as the fifth most common cancer worldwide, with ~9,500 daily diagnoses in the U.S. (AAD, 2022). Risk factors include UV exposure, chemical carcinogens, genetic predisposition, and immunosuppression (1-3).

The skin's epidermis and dermis layers house different cancer origins: Melanomas arise from mutated melanocytes, while non-melanoma cancers (NMSC) develop in epithelial cells. Although NMSC is typically treatable when detected early, advanced cases can metastasize, causing severe physical and psychological impacts. Traditional treatments (surgery, chemotherapy, radiation) often harm healthy tissues and lack precision. In contrast, photodynamic (PDT) and photothermal (PTT) therapies use light-activated agents for targeted destruction of cancer cells with fewer side effects (4-5).

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Nanotechnology has revolutionized oncology by enabling precise, nanoscale (1-100 nm) drug delivery systems. Nanoparticles enhance tumor targeting, controlled drug release, and biological barrier penetration, offering promising solutions for both melanoma and NMSC with minimal off-target effects (6).

The Physiology of the Skin

The skin, the body's largest organ, serves critical protective and regulatory functions. It forms a physical barrier against pathogens, UV radiation, and environmental damage while maintaining thermoregulation and waste excretion through sweat production [7]

Layers of the Skin

The skin has three main layers:

- **Epidermis** – Outer protective layer.
- **Dermis** – Middle layer supporting structure and function.
- **Hypodermis** – Deepest fat and connective tissue layer.

Each has unique features [8].

Each layer has distinct structural and physiological features (Figure 1) [8].

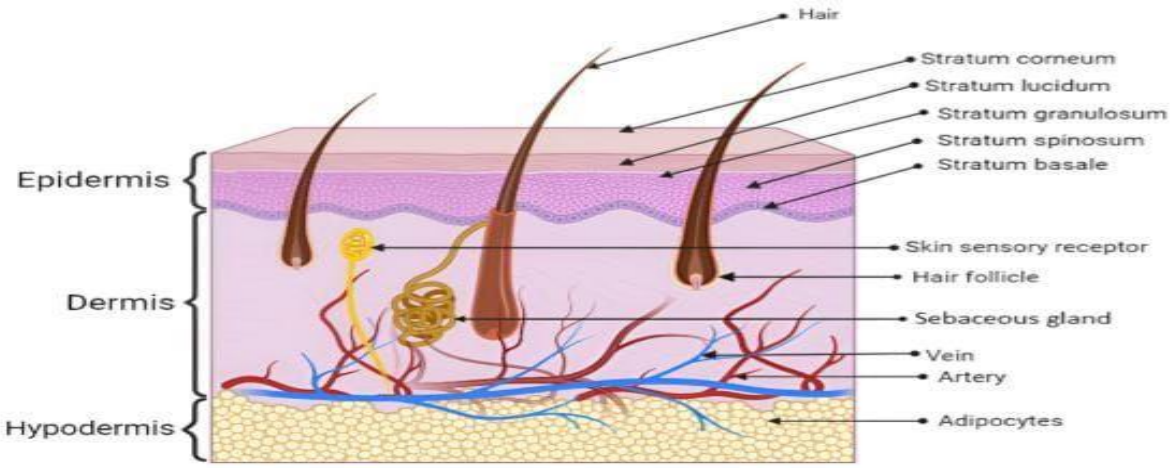

Fig. 1. The skin's three-layer organization includes the multi-layered epidermis (with five sub-layers), the vascularized dermis, and the equally vascularized hypodermis [9].

Skin Cancer and Its Classification

Skin cancer encompasses a wide range of malignant conditions that have become a significant global health concern. Medically, it is categorized into two main types: Melanoma Skin Cancer (MSC)– A less common but more aggressive form. Non-Melanoma Skin Cancers (NMSCs) – Including basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), which are far more prevalent. As shown in Figure 2, these two subtypes collectively make up more than 90% of all skin cancer cases. Epidemiological studies indicate that cutaneous malignancies represent nearly one-third of all cancer diagnoses globally, with NMSCs being the most frequently diagnosed form [10].

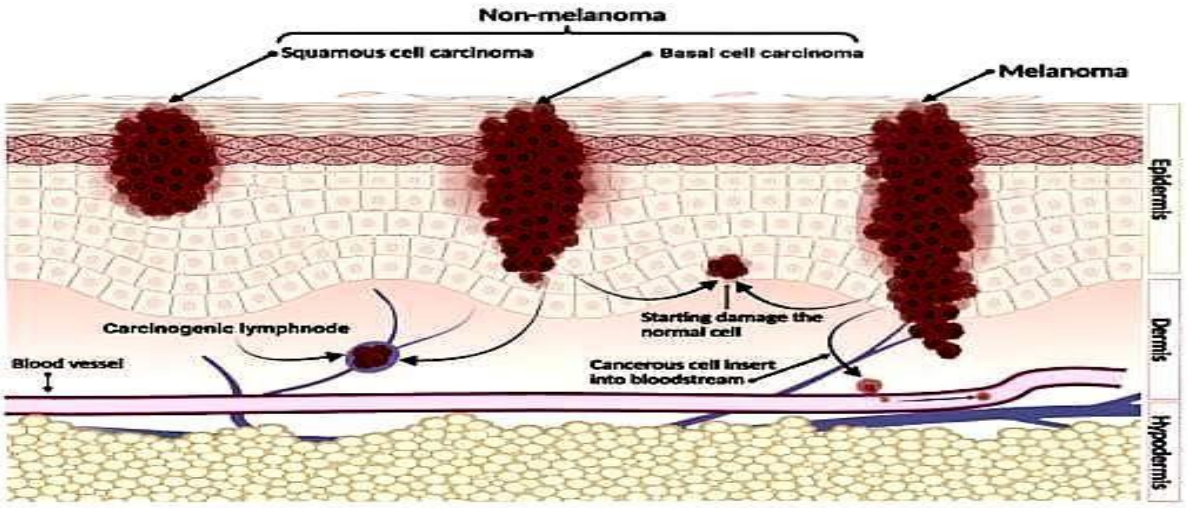

Figure 2. Classification of primary skin cancer types, comprising melanoma and non-melanoma variants (basal cell carcinoma and squamous cell carcinoma). The illustration demonstrates their distinct cellular origins within various epidermal layers and depicts the characteristic vascular invasion process that contributes to disease progression and metastatic potential [9].

Melanoma Skin Cancer (MSC)

Despite accounting for only about 5% of skin cancer cases, melanoma is the most aggressive form, responsible for nearly 80% of skin cancer-related deaths. This highly malignant tumor develops from melanocytes—the pigment-producing cells that synthesize melanin. When these cells undergo uncontrolled growth, they can rapidly metastasize (Figure 2) [11].

Staging Classification of Melanoma Skin Cancer:

Melanoma progresses through five stages (Fig. 3) [12]: Stage 0 (in situ) is confined to the epidermis. Stages I-II show localized vertical growth (classified by Breslow thickness/ulceration). Stage III involves lymph nodes, while Stage IV indicates distant organ metastasis

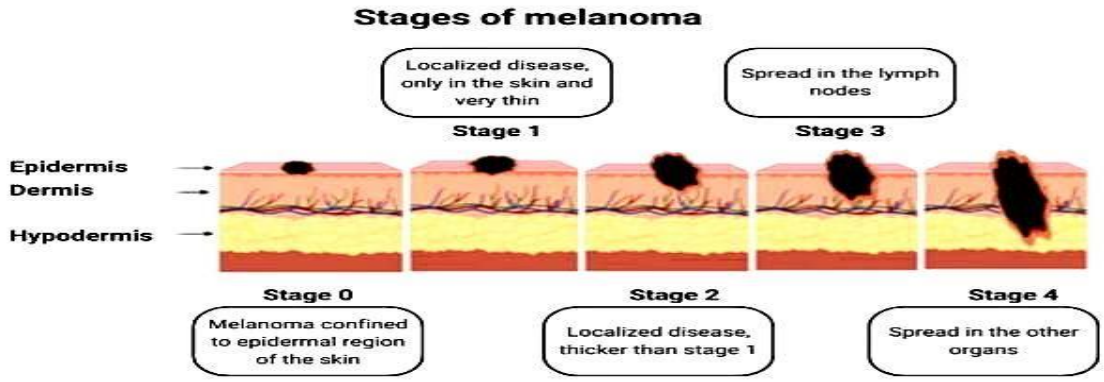

Fig. 3. Melanoma has five stages. These are stage 0, stage 1, stage 2, stage 3, and stage 4 [9].

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Non-Melanoma Skin Cancers

NMSCs arise from non-melanocyte skin cells, mainly basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). These cancers form in epidermal keratinocytes and are the most common human cancers, with increasing rates globally. Studies show BCC makes up about 70% of NMSC cases, while SCC represents nearly 25% [13].

Basal cell carcinoma

Basal cell carcinoma (BCC), a less aggressive non-melanoma skin cancer, arises from the basal layer's non-keratinizing cells. It typically appears as small, pale/pink lesions and is driven by patched/hedgehog pathway activation. Fair-skinned individuals (Fitzpatrick types I-II) have a 30% lifetime risk, while immunocompromised patients face 5–10× higher odds. Multiple lesions may signal basal cell nevus syndrome (Fig. 4) [14].

Squamous cell carcinoma

Squamous cell carcinoma (SCC), the second most common NMSC, originates from epidermal keratinocytes or skin appendages [Fig. 5]. While predominant in fair-skinned individuals, it shows lower UV-associated incidence in darker skin. Unlike BCC's link to intermittent sun exposure, SCC relates to chronic UV damage, accounting for ~16% of skin cancers. Patients often develop subsequent SCCs post-initial diagnosis [15].

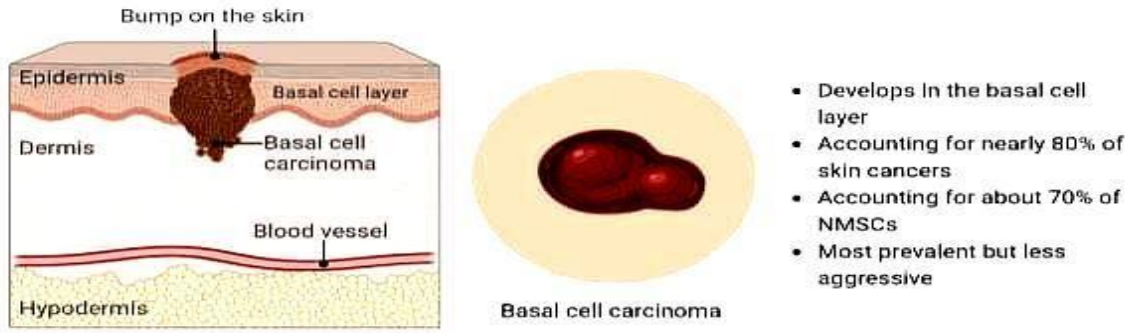

Figure 4. Basal cell carcinoma (BCC) originates in the epidermis' basal layer, typically presenting as a small, raised skin lesion. (NMSCs: Non-melanoma skin cancers) [9].

Figure 5. Squamous cell carcinoma (SCC) develops from keratinocytes or squamous cells in the skin's outermost layer, typically presenting as a firm, hyperkeratotic plaque or nodule, often with ulceration. (NMSCs: Non-melanoma skin cancers; UV: Ultraviolet) [9].

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Mechanism of Skin Cancer Development

Skin cancer develops through complex genetic, molecular, and environmental interactions that drive malignant transformation [Fig. 6]. Primary risk factors include: chronic UV exposure (particularly in sun-exposed areas), immunosuppression, cumulative DNA damage, reduced skin pigmentation (higher risk in lighter skin), and artificial tanning device use. The pathogenesis involves multiple synergistic factors, as detailed below.

UV rays

Ultraviolet (UV) radiation represents the primary environmental carcinogen in skin cancer development, responsible for >80% of cases [17]. Solar UV comprises predominantly UV-A (90%) and UV-B (10%), both capable of inducing DNA damage through mutagenesis, impaired repair mechanisms, and apoptotic pathways [18]. These cumulative genomic alterations significantly elevate malignant transformation risk, particularly for basal cell carcinoma [19-21].

Skin color

Skin cancer demonstrates significant ethnic disparities in incidence and outcomes. In the U.S., Caucasians experience 35-45% of cases, compared to 4-5% in Hispanics and 1-4% in Asian/Black populations [22]. Reduced melanin in fair skin increases UV susceptibility and doubles melanoma/NMSC risk [20]. While less frequent in darker-skinned groups, diagnoses often occur at advanced stages with worse outcomes, despite standardized treatment approaches [22].

Indoor tanning

Artificial tanning devices elevate melanoma and NMSC risk through the emission of carcinogenic UV radiation [23]. Recognized as a definitive carcinogen by the IARC, this association prompted Australia's commercial tanning bed ban [24]. Epidemiologic models estimate that such bans may prevent 17% of melanoma cases in young adults (18-29 years) [25]

Age

Age significantly elevates skin cancer risk due to accumulated DNA damage over time. Studies confirm this risk becomes particularly pronounced after age 40, with women showing higher susceptibility to basal cell carcinoma [26]

Viral agent

Research confirms that certain viruses contribute to skin cancer development. B-Human papillomaviruses (β-HPVs) are particularly associated with squamous cell carcinoma, especially in immunocompromised patients [27]. Animal studies demonstrate these viruses can directly cause skin tumors [17], though their role in healthy individuals remains uncertain [28]

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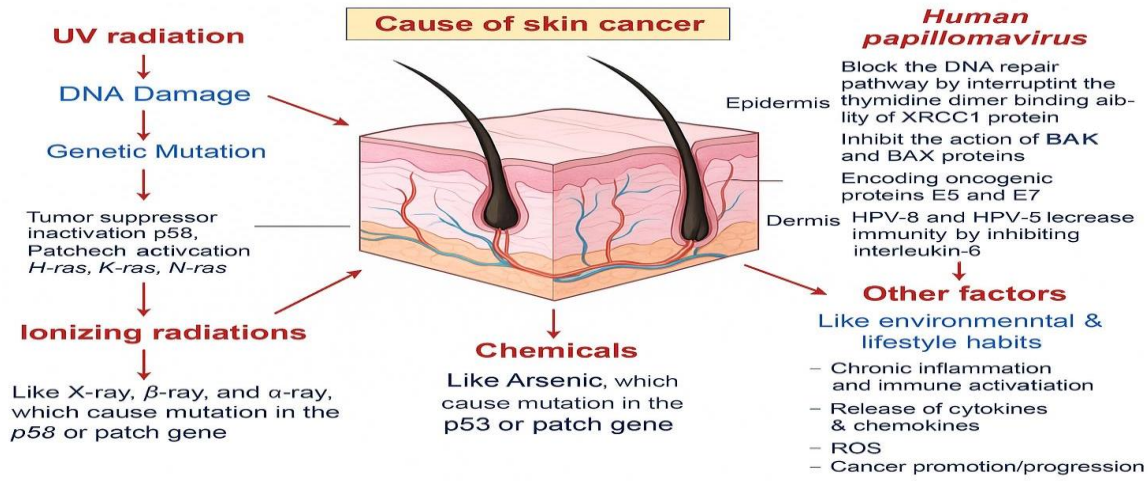

Fig. 6. Different factors are involved in the progression of skin cancer [16].

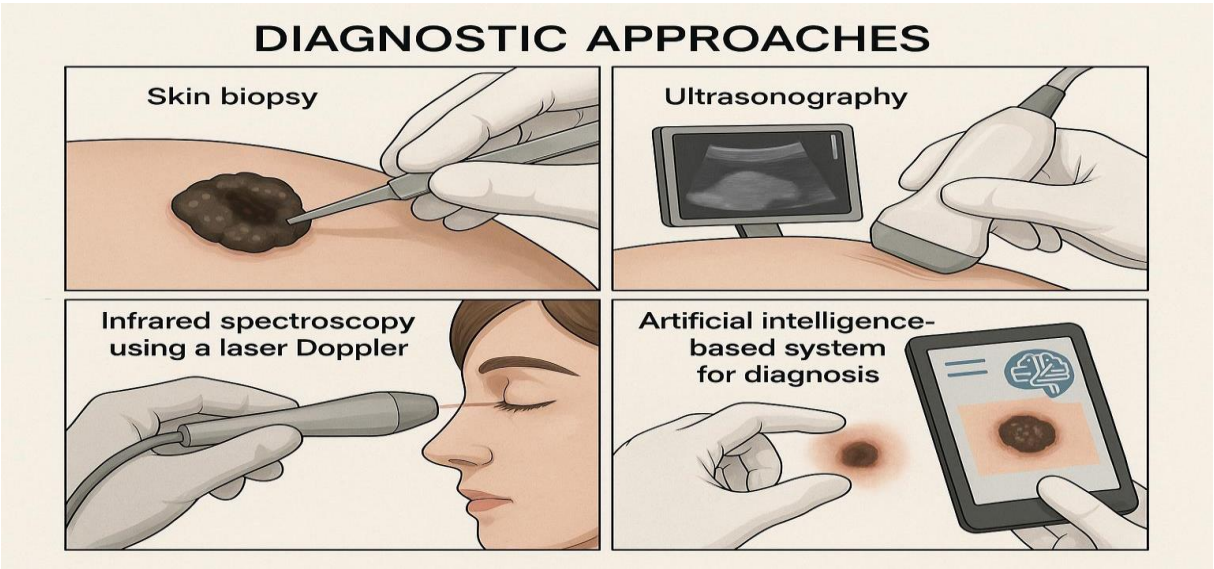

Fig. 7: Diagnostic approaches of skin cancer [29].

Diagnostic approaches:

Skin Biopsy for Melanoma Detection

Diagnosing basal cell carcinoma (BCC) requires a skin biopsy to confirm the histological subtype. For suspicious pigmented lesions, excisional or punch biopsies are preferred as they enable evaluation of lesion depth, crucial for differentiating melanoma from pigmented BCC [30]. Notably, ulcerated BCC may show surface healing while tumor progression continues underneath. Large or heterogeneous tumors often need multiple biopsies for accurate diagnosis [31]

Cytology

Although histopathology of excisional biopsies (punch/shave) remains the diagnostic gold standard for BCC, cytology serves as a rapid preliminary assessment tool [32]. Barton et al. reported 92% sensitivity and 75% predictive accuracy in cytological analysis, with improved performance in validation cohorts (100% detection rate, 96% accuracy) for BCC identification.

Ultrasonography

Despite its common application, there is considerable doubt regarding the effectiveness of high-frequency (20 MHz) and ultra-high-frequency (40–100 MHz) ultrasound devices. Studies indicate that these tools accurately distinguish malignant tumors from benign ones in only 20% of cases. Additionally, claims about precise tumor measurements and invasion depth remain controversial among researchers [33].

Infrared spectroscopy using a laser Doppler

Laser Doppler technology could serve as a useful supplementary tool for ophthalmologists in differentiating benign and malignant adnexal skin lesions, as well as defining tumor margins. Research has shown that patients with eyelid basal cell carcinoma (BCC) exhibit significantly higher cutaneous perfusion compared to healthy individuals [34].

Artificial intelligence-based system for diagnosis

Emerging evidence supports AI's role in early skin cancer detection, with convolutional neural networks (CNNs) demonstrating effective lesion classification [35,36]. While mobile health applications have increased public access to these tools, optimal clinical implementation—including patient selection criteria—requires further investigation [37]. Current guidelines recommend AI as an adjunct to, rather than a replacement for, clinical judgment in skin cancer screening.

Current treatment approaches and their limitations

Treatment selection is guided by tumor characteristics (type, size, location, stage). Early-stage lesions typically undergo surgical excision, Mohs surgery, or radiotherapy, often combined with immunotherapy/targeted agents. Smaller tumors may be treated with minimally invasive options (curettage, cryoablation, PDT) plus adjuvant therapy. For metastatic disease (e.g., lung, liver, bone), systemic chemotherapy (oral/parenteral/topical) is primary [38]. (See Fig. 8 for therapeutic overview).

Fig. 8 | Schematic overview of contemporary skin cancer treatment modalities and their respective clinical limitations [39].

Excisional surgery:

Excisional surgery is a fundamental cutaneous oncology procedure, providing three key benefits: (1) favorable cosmetic outcomes, (2) histopathologic margin verification, and (3) swift recovery. However, risks include wound infections, fluid collections (seroma/hematoma), and complex defects requiring reconstruction [40].

Mohs micrographic surgery

Mohs micrographic surgery enables precise tumor excision with optimal tissue sparing, demonstrating greater cost-effectiveness and significantly reduced recurrence rates for both BCC and SCC compared to standard excision [41]

Curettage and electrodessication

Curettage and electrodesiccation combine mechanical tumor removal with thermal ablation, suitable only for small, low-risk lesions due to limited margin assessment. Its restricted applicability for larger or high-risk tumors relegates it to a secondary treatment option [42].

Cryotherapy

Cryotherapy uses liquid nitrogen to destroy small BCCs and SCCs through freezing. While offering benefits like minimal scarring and hemorrhage-free treatment, its use is restricted by a lack of margin evaluation and operator variability, making it a specialized rather than primary option [43].

Radiation therapy/radiotherapy

Radiotherapy serves as a viable alternative for elderly patients with extensive or recurrent cutaneous malignancies who are poor surgical candidates or present with inoperable lesions. While offering non-invasive tumor control, this modality presents significant drawbacks, including substantial treatment costs, requirement for multiple treatment sessions, and potential development of aggressive tumor phenotypes in recurrent cases [44].

Photodynamic therapy (PDT)

Photodynamic therapy (PDT) combines photosensitizers with targeted light exposure to selectively eradicate cancer cells [45]. While synergistic effects occur with topical chemotherapy, PDT shows limited efficacy for deep or nodular tumors and carries high treatment costs [46].

Immunotherapy, targeted therapy, and chemotherapy

Immunotherapy, targeted therapy, and chemotherapy are vital adjuvant treatments for advanced skin cancers (BCC, SCC, melanoma), showing improved survival outcomes. However, challenges like high costs, patient adherence issues [47], chemotherapy toxicity, and drug resistance in aggressive cases limit their effectiveness [48].

Nanotechnology in skin cancer therapy

Recent advances in nanoscale material engineering are transforming skin cancer therapy. These innovative approaches utilize particles at the molecular scale to simultaneously transport medications and exert direct anticancer effects [49]. Unlike conventional chemotherapy that often affects healthy tissues, nanoparticle systems demonstrate enhanced precision in reaching malignant cells while minimizing damage to normal tissues [50,51] [Fig. 9]. Current nanoparticle platforms fall into three categories: metallic particles with inherent therapeutic properties, biodegradable polymer carriers, and lipid-based delivery vehicles – each offering distinct advantages for tumor targeting and drug release control [53]. These technological developments represent a significant improvement over traditional treatment modalities by potentially increasing effectiveness while reducing undesirable complications.

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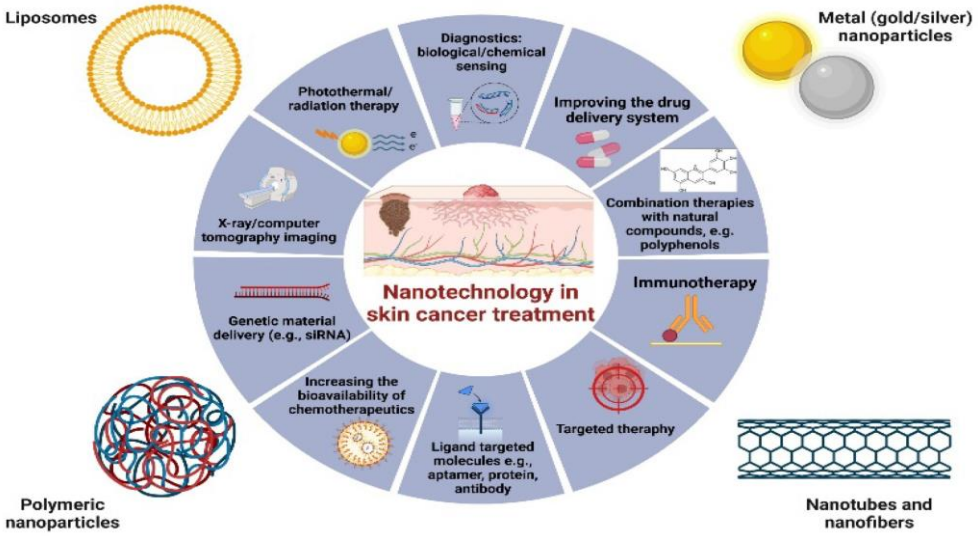

Fig. 9. Schematic diagram showing nanoparticle applications for skin cancer treatment [52].

Inorganic nanoparticles

1. **Mesoporous Silica Nanoparticles (MSNs)**

MSNs are nanoparticles with uniform mesopores (2–7 nm) and a particle diameter of 50–300 nm. They possess a large surface area, tunable size, and high biocompatibility, making them ideal for drug delivery [54]. **Cisplatin-loaded MSNs** showed enhanced anticancer effects and reduced toxicity [54]. **Dacarbazine-loaded MSNs** improved uptake when coated with cancer cell membranes [55]. Resveratrol-loaded MSNs improved solubility and cytotoxicity in melanoma cells [55]. MSNs have also been used for **siRNA delivery**, **chemo-photothermal therapy**, and with agents like curcumin, indomethacin, and ruthenium [56].

2. **Carbon Nanotubes (CNTs)**: CNTs are cylindrical nanostructures with high surface area and photothermal efficiency. They can induce intrinsic anticancer effects through mitochondrial disruption and ROS generation [57]. **SWCNTs** showed more cytotoxicity than **MWCNTs**. CNTs loaded with **paclitaxel**, **curcumin**, or **doxorubicin** have been used for melanoma therapy [58]. CNTs also act **as agents for combinatorial chemo-photothermal-immunotherapy** [59-64].

3. **Titanium Dioxide Nanoparticles (TiO_2 NPs)**: TiO_2 nanoparticles are widely used in sunscreens for their ability to block UVB radiation, complementing ZnO's UVA protection, thereby reducing skin cancer risk. Beyond UV shielding, TiO_2 can generate reactive oxygen species (ROS) through photocatalytic reactions under light exposure, offering potential anticancer effects. However, their nonspecific action may damage healthy cells. To enhance precision, researchers developed TiO_2 nanoparticles conjugated with RGD peptides, which selectively target melanoma cells expressing αvβ3 integrin. When activated by UVA light, this targeted system produces ROS locally, effectively killing cancer cells while minimizing harm to normal tissue [65 -68].

Polymeric Nano-micelles

Polymeric nano-micelles are promising drug carriers for skin applications due to their ability to accumulate in hair follicles, reducing some delivery limitations. However, their penetration into deeper skin layers remains restricted [69]. **Kahraman et al.** investigated terpene-loaded nano-micelles for skin delivery and observed that terpinolene-based formulations enhanced drug retention in stripped

skin compared to both commercial products and terpene-free micelles [70]. **Wang et al.** engineered cationic polymeric nano-carriers for transdermal siRNA delivery to treat melanoma, demonstrating their potential as effective gene therapy vehicles [71]. **Xu et al.** developed paclitaxel-loaded micelles embedded in a hydrogel system, which exhibited superior cellular uptake and anticancer effects against B16 melanoma cells compared to conventional Taxol [72]. **Lamch et al.** designed folate-targeted micelles loaded with zinc (II) phthalocyanine (ZnPc) for photodynamic therapy (PDT). These micelles showed enhanced uptake in cancer cells overexpressing folate receptors, improving ZnPc delivery and making them a viable PDT strategy for skin cancer [73].

Lipid Nanoparticles

Lipid-based nanocarriers, particularly liposomes, SLNs, NLCs, and nanoemulsions, have emerged as superior delivery systems for topical applications due to their biocompatibility and enhanced skin penetration capabilities. These platforms enable controlled drug release while minimizing adverse effects through targeted delivery [74-76].

Nanoemulsions:

Nanoemulsions are optically transparent, thermodynamically stable colloidal systems with unique rheological properties. They are widely utilized as carriers for sustained drug delivery into deeper skin layers. A key advantage of nanoemulsions is their ability to enhance skin hydration by minimizing transepidermal water loss (TEWL), while also improving the permeation of active pharmaceutical ingredients (APIs) [77].

These nanocarriers provide enhanced chemical stability and enable controlled drug release, leading to higher intracellular drug accumulation with minimal cytotoxic effects. For example, a chitosan-coated nanoemulsion designed for melanoma treatment demonstrated approximately 2.8 times greater cytotoxicity compared to standard drug formulations, highlighting its potential for targeted therapy [78].

Liposomes

Liposomes are nanoscale vesicles (50–100 nm) composed of phospholipids and cholesterol, widely used as drug carriers to enhance therapeutic efficacy while reducing systemic side effects, particularly in anticancer treatments. Their ability to selectively deliver drugs to target sites makes them a promising alternative to conventional drug delivery systems. **Jose et al.** developed cationic liposomes co-encapsulating curcumin and anti-STAT3 siRNA for treating cutaneous melanoma. **In vitro** studies on B16F10 mouse melanoma cells revealed that this dual-loaded formulation significantly inhibited cancer cell proliferation compared to single-drug formulations. **Raquel et al.** formulated 5-fluorouracil (5-FU)-loaded immunoliposomes using iontophoresis. Their findings demonstrated that cetuximab-conjugated liposomes improved cellular uptake in EGFR-positive squamous cell carcinoma (SCC) cells by **3.5-fold** compared to non-targeted liposomes. Furthermore, iontophoresis enhanced 5-FU penetration into the viable epidermis, suggesting a more effective delivery approach than passive diffusion [79,80].

Conclusion

Skin cancer, including melanoma and non-melanoma types, presents significant treatment challenges, with conventional therapies often limited by recurrence, toxicity, and lack of specificity. Nanotechnology has emerged as a promising approach, offering targeted drug delivery and improved therapeutic outcomes.

To overcome these challenges, future research should focus on optimizing nanoparticle formulations for better tumor specificity, developing biodegradable and biocompatible carriers, integrating nanotechnology with immunotherapy and gene therapy, improving regulatory processes, and leveraging AI for personalized treatment development. Nanotechnology holds great promise for revolutionizing skin cancer treatment, and with

continued advancements, it could play a key role in precision oncology, providing more effective and targeted therapies.

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