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Nanoparticles for Skin Cancer Therapy: Current Progress and Challenges

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Abstract: With increasing incidence of both nonmelanoma skin cancer (NMSC) and melanoma, skin cancer is the most often diagnosed malignancy worldwide. Particularly in situations of aggressive or recurrent disease, traditional treatment modalities like surgery, chemotherapy, and radiotherapy are sometimes limited by systemic side effects and low efficacy. Among the practical choices now available are tailored administration, improved drug absorption, and reduced toxicity based on nanoparticles. Focussing on types of nanoparticles, approaches to action, new developments, and possible negative consequences, this review deals with the present achievements in nanoparticle development for skin cancer treatment. Clinical translation presents challenges including nanoparticle stability, long-term toxicity, and regulatory issues, even with the several benefits. With ongoing research targeted at improving formulations and avoiding negative effects, the future of nanoparticle-based therapy seems bright.

Keywords: Skin cancer, Nanoparticle, Melanoma, Dendrimers

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Introduction

Cancer is one of the most frightening diseases still afflicting mankind, and its increasing frequency in the twenty-first century shows no sign of slowing down. Skin cancer, in particular, is the most common cancer diagnosed worldwide and presents major health issues. Notwithstanding public awareness programs on early detection and sun protection as part of attempts to fight this disease, skin cancer incidence keeps increasing. This emphasises the need for cutting-edge and improved treatments, where nanotechnology shows enormous potential.

Melanoma and non-melanoma skin cancer (NMSC), the latter of which consists of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), can be two main forms of skin cancer. NMSC accounts for the majority of skin cancer cases. This review focuses on current developments in nanoparticle-based treatments for skin cancer, their modes of action, and

address issues in creating sensible treatments.

Cancer is one of the most important health risks of the twenty-first century; skin cancer is the most frequently diagnosed type globally. The urgent need for creative treatments is highlighted by the rising incidence of skin cancer, especially nonmelanoma skin cancers (NMSC), such as basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), together with the more hazardous melanoma (Sangeetha *et al.*, 2021). More than 1.5 million skin cancer cases were reported worldwide in 2020 alone (WHO, 2020). Skin cancer is also quite common in countries like the United States, Australia, and New Zealand (Baba *et al.*, 2024). This rise in incidence calls for the development of new, more efficient therapeutic strategies, including the use of nanoparticles in skin cancer treatment.

Overview of Skin Cancer

Although environmental pollutants like chemicals aid to induce skin cancer, its primary cause is prolonged UV radiation; hereditary elements also play a part. The skin is the largest organ in the body, with three main layers—the epidermis, dermis, and hypodermis—each with a special purpose in protecting the body.

Epidermis

The layer furthest from which Langerhans cells, melanocytes, and keratinocytes find home. Melanin, produced by melanocytes, protects the skin from UV damage.

Dermis

In this layer, blood veins, nerves, and connective tissue feed and oxygenate the epidermis.

Hypodermis

Made mostly of fat, the thickest layer acts as a shock absorber and insulator.

Skin structure and cancer development

One of the main causes of skin cancer (Woo *et al.*, 2019), the epidermis acts as a barrier to guard against environmental assaults like UV radiation. UV radiation-induced DNA damage in skin cells results in mutations in oncogenes such as PTCH1, BRAF, and p53, as well as tumour suppressor genes (Becker *et al.*, 2017). Long-term UV exposure also causes immunosuppression by compromising the activity of skin-resident immune cells, such as Langerhans cells (D'Orazio *et al.*, 2013). Furthermore, greatly influencing the development of skin cancer are chemical carcinogens, including arsenic, polycyclic aromatic hydrocarbons (PAHs), and genetic alterations; viral infections also play a role.

Types of skin cancer

Basal cell carcinoma (BCC), squamous cell carcinoma (SCC), melanoma, and merkel cell carcinoma (MCC) are four primary forms and are displayed in Fig. 1.

(a) *Basal cell carcinoma* (*BCC*): Mostly resulting from extended UV exposure, BCC is the most often occurring type of skin cancer (Dika *et al.*, 2020). Untreated instances, which typically appear as a reddish patch of skin or a pearl-like bump, can become life-threatening even if they do not spread (Baba *et al.*, 2024).

(b) *Squamous cell carcinoma* (*SCC*): The second most often occurring kind of skin cancer, squamous cell carcinoma (SCC), develops from keratinocytes in the outer layer of the epidermis (Hennessy *et al.*, 2005). Usually showing up as a hard, red nodule or a crusted lesion, it can spread without treatment at initial stage (Stanganelli *et al.*, 2020).

(c) *Melanoma*: The most lethal kind of skin cancer is melanoma. Originating in melanocytes, the pigment-producing cells, it is distinguished by fast metastases (Domingues *et al.*, 2018). Melanoma risk factors include fair skin, excessive sun exposure, and a family history of the illness (Houghton *et al.*, 2002).

(d) *Merkel cell carcinoma* (*MCC*): MCC, or Merkel cell carcinoma, is an uncommon but aggressive skin cancer. Commonly on sun-exposed areas such as the face, neck, or arms, it often shows as firm, red or purple nodules (Becker *et al.*, 2017).

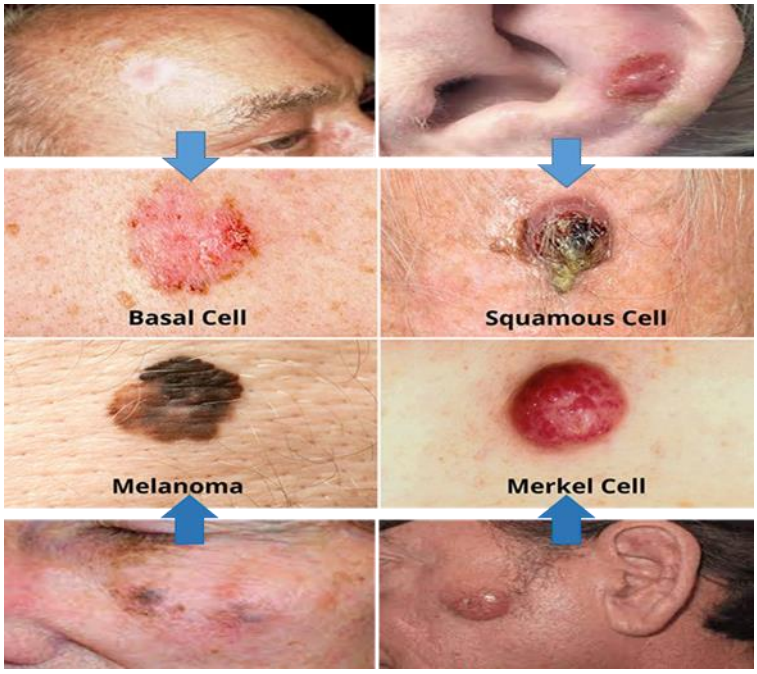

Fig. 1: Four main types of skin cancer.

Its quick spread makes it linked with a poor prognosis (Goessling *et al.*, 2002).

Challenges in Treating Skin Cancer

Skin cancer, especially advanced melanoma, remains challenging to treat. Although early stages of standard treatments such as surgery, radiation, and chemotherapy are successful, often they fall short in advanced or metastatic cases. Immunotherapy and targeted therapy have shown promise, even if drug resistance and toxicity limit their efficacy. This is where nanotechnology is having a transformative effect. Their distinctive size and surface properties allow nanoparticles (NPs) to be tailored to lower undesirable effects, pass through tumours more quickly, and deliver drugs more precisely.

Nanoparticles used in skin cancer therapy

Nanotechnology shows great promise in treating skin cancer by using improved drug delivery methods like nanoparticles, nanogels, and liposomes (Fig. 2) (Nasim *et al.*, 2024). Nanoparticles can incorporate chemotherapeutic drugs to target cancer cells while conserving healthy tissue, thereby reducing adverse effects. Recent studies of many nanoparticle-based delivery approaches, including those for paclitaxel, doxorubicin, and siRNA therapies, have shown notable effectiveness in preclinical animals (Cheng *et al.*, 2020). For example, paclitaxel-loaded nanoparticles have shown more efficacy in treating melanoma by enhancing drug retention and cellular absorption (Ramirez *et al.*, 2023). Similarly, gene treatment using siRNA and mRNA-loaded nanoparticles shows amazing ability to stop melanoma development and spread (Sasaki *et al.*, 2022). Recent developments in nanoparticle formulations, including silver-infused nanoparticles, have also shown efficacy in clinical studies, therefore underscoring their likely potential in treating cutaneous malignancies like BCC and SCC (Ramirez *et al.*, 2023).

Types of nanoparticles used in skin cancer therapy:

The numerous types of nanoparticles used in the therapy of skin cancer are solid lipid nanoparticles, dendrimers, and liposomes. Liposomes directly carry chemotherapy drugs to cancer cells, therefore reducing side effects. Dendrimers, which are highly branched spherical nanoparticles designed for customized medication

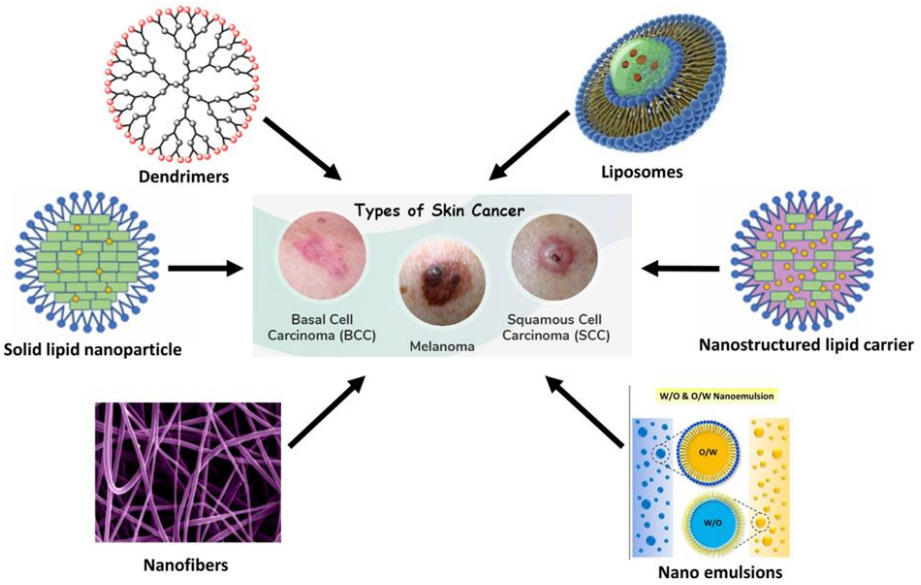

Fig. 2: Nanoparticles used in skin cancer treatment (Lalan *et al.*, 2021).

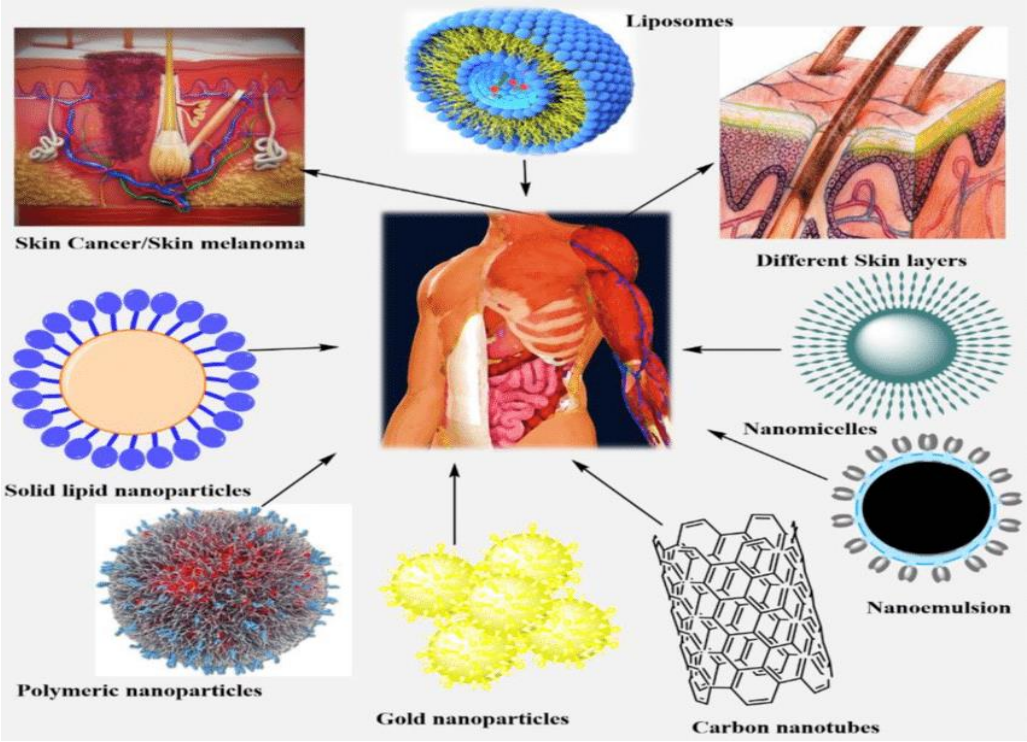

Fig. 3: Different treatment procedures for skin cancer (Sabir *et al.*, 2021).

delivery, improve therapeutic efficacy. Solid lipid nanoparticles increase drug stability and provide controlled release of anticancer agents. Moreover, highly used to improve the bioavailability of hydrophobic treatments and target cancer areas more specifically depicted in Figure 3 are nanostructured lipid carriers and nanoemulsions.

Lipid-based nanoparticles

These can encapsulate hydrophilic and hydrophobic drugs, and they are quite biocompatible. For lesser systemic toxicity, chemotherapy medicines like paclitaxel have been delivered straight to skin tumours using liposomal nanoparticles.

Polymeric nanoparticles

Designed from biodegradable polymers such as polylactic-co-glycollic acid (PLGA), these nanoparticles provide regulated medication release over time. Targeting particular receptors on cancer cells helps polymeric nanoparticles to be adjusted to improve medication delivery to melanomas.

Metal-based nanoparticles

The photothermal characteristics of gold and silver nanoparticles enable them to transform light into heat, therefore destroying cancer cells. Particularly promising in combination with laser treatments, gold nanoparticles present a minimally invasive solution for skin cancer.

Silica nanoparticles

Because of their porous nature and enormous surface area, they are outstanding transporters of medications. Effective for combination therapies, silica nanoparticles can be loaded with several therapeutic substances, therefore improving the general efficacy of the treatment.

Mechanisms of Action

Targeted drug delivery

The ability of nanoparticles to be functionalised with ligands aiming at cancer-specific receptors is among their most important benefits. Hyaluronic acid-coated nanoparticles, for example, target CD44 receptors, which are overexpressed in melanoma cells, therefore delivering the medicine straight to the tumour site.

Photothermal therapy (PTT)

In photothermal treatment, PTT uses metal-based nanoparticles, such as gold and iron oxide. These nanoparticles absorb light and translate it into heat, therefore destroying cancer cells without harming the surrounding healthy tissue.

Gene therapy

Delivering gene-editing technologies like CRISpen/Cas9 to fix genetic abnormalities causing skin cancer has been achieved with nanoparticles. Another exciting approach is RNA interference (RNAi), where nanoparticles provide short interfering RNA (siRNA) to quiet oncogenes in skin cancer cells.

Clinical progression and results

With nanoparticle-based treatments for skin cancer, preclinical and early clinical studies have shown encouraging outcomes.

- *Paclitaxel-loaded nanoparticles*: Research employing liposomal paclitaxel-loaded nanoparticles has shown that, in mouse models of melanoma with less systemic damage, liposomal paclitaxel dramatically reduces tumour size when compared to free paclitaxel. This suggests that nanoparticles could help to make present chemotherapy treatments more successful.
- *Gold nanoparticles in PTT*: A phase I clinical research combining gold nanoparticles with laser treatment generated a complete response in certain BCC patients. This non-invasive approach offers an intriguing alternative to surgery for early-stage skin cancers.
- *Gene therapy using nanoparticles*: Usually found in melanoma, preclinical models of gene treatments aimed at the BRAF mutation have shown promise. In mice, siRNA-carrying nanoparticles to block BRAF have slowed down tumour growth and raised survival.

Nanoparticle-Based Therapies: Challenges

Even though nanoparticles have immense promise, some challenges still exist:

(i) *Toxicity and biocompatibility*: Particularly metal-based nanoparticles may accumulate in the body and cause long-term damage based on their toxicity and biocompatibility. Human-safe use of nanoparticles depends on their non-toxic and biodegradable character.

(ii) *Drug resistance*: Cancer cells can develop against treatments supplied by nanoparticles, same as with traditional chemotherapy. The

development of nanoparticles capable of either overcoming or bypassing resistance mechanisms is currently being studied.

(iii) *Regulatory approval*: Although preclinical research shows promising results, few medicines based on nanoparticles have been licensed for clinical use. Given the complexity of nanoparticle compositions, meeting the rigorous safety and efficacy standards necessary for novel cancer treatments is challenging.

Side Effects of Nanoparticle-Based Therapies

Some studies have identified adverse effects including systemic toxicity, immunological responses, and possible bioaccumulation in non-target organs (Wang *et al.*, 2010), notwithstanding the promise of nanoparticle-based therapy. For larger doses, for instance, silver nanoparticles have exhibited cytotoxicity in keratinocytes (Ramirez *et al.*, 2023). Long-term exposure to nanoparticle-based treatments also may cause unexpected inflammatory reactions, which calls for more research (Mohammadpour *et al.*, 2019; Tirumala *et al.*, 2021).

Conclusion

With the possibility to transform treatment by improving drug distribution, lowering toxicity, and overcoming resistance, nanoparticles present a fresh and very promising method to treat skin cancer. Although obstacles still exist, continuous research and clinical trials give hope that soon nanoparticle-based treatments for skin cancer will be the accepted therapy of choice. Personalised, tailored cancer treatments, providing better outcomes for people with skin cancer, are predicted to dawn as our knowledge of nanotechnology develops. In clinical uses, especially for nonmelanoma skin tumours and melanoma, the usage of nanoparticles is predicted to rise dramatically in the next few years. With the possibility to not only raise survival rates but also improve patients' quality of life, nanoparticle-based skin cancer treatment has great future prospects. Still, the possible adverse effects, long-term toxicity, and regulatory difficulties have to be carefully addressed by continuous research and clinical studies.

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Conflict of Interest

The authors declare no conflicts of interest.

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