RESEARCH PAPER

ELECTROSPUN NANOFIBER-BASED THERAPEUTIC SYSTEMS FOR SKIN CANCER MANAGEMENT

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ABSTRACT

Skin cancer represents a growing global health burden with limited efficacy from conventional treatment approaches. Electrospun nanofibers have emerged as promising drug delivery platforms for localized skin cancer therapy, offering advantages including large surface area, tunable porosity, and capacity to maintain drug levels at the tumor site while minimizing systemic exposure. This review consolidates recent advances in electrospinning-based systems for dermatological malignancies, emphasizing material selection, therapeutic incorporation strategies, and functional modifications that enhance treatment effectiveness and skin penetration. Clinical translation challenges and regulatory considerations are addressed to provide a comprehensive overview of electrospun nanofiber technology for future clinical applications in skin cancer management. Additionally, clinical translation challenges, regulatory considerations, and future perspectives encompassing stimuli-responsive systems, targeted delivery, and scalable manufacturing are addressed. Overall, electrospun nanofibers hold significant potential as next-generation, patient-friendly platforms for effective and safe localized skin cancer therapy.

Keywords: Nanofibers, Electrospinning, skin cancer, Melanoma, drug delivery, controlled release, topical therapy, polycaprolactone, PLGA, nanotechnology.

How to cite this article: Priya.P*1 Allimalarkodi. S*1 Manimegalai Karnan2 Venkatesh A.N1 Sambathkumar. R1 Surenthiran M1 Vanitha. S1 Revathi S1.. ELECTROSPUN NANOFIBER-BASED THERAPEUTIC SYSTEMS FOR SKIN CANCER MANAGEMENT. Int J Drug Deliv Technol. 2026;16(80s):356-367. DOI: 10.25258/ijddt.16.80s.43.

1. INTRODUCTION

The global incidence of skin cancer has risen dramatically over the past several decades, posing a significant and escalating public health challenge worldwide [1]. Skin cancer is broadly categorized into two main groups: melanoma and non-melanoma skin cancers (NMSC), the latter including basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) [2]. Available epidemiological data consistently demonstrate a progressive increase in the incidence of both melanoma and non-melanoma subtypes across multiple geographic regions and demographic groups [3]. Despite having a considerably lower incidence rate compared to NMSC, melanoma accounts for the majority of skin cancer-related deaths owing to its highly aggressive nature and substantial metastatic potential [4]. The pathogenesis of skin cancer is fundamentally linked to ultraviolet (UV) radiation-induced DNA damage, which triggers mutations in critical oncogenes and tumor suppressor genes, thereby disrupting normal cellular regulatory mechanisms and promoting uncontrolled proliferation [5,6].

Currently available therapeutic approaches for skin cancer include surgical excision, systemic chemotherapy, radiation therapy, immunotherapy, and molecularly targeted therapies, each selected according to tumor histology, stage, and anatomical location [7,8]. Surgery remains the definitive first-line treatment for early localized disease; however, it carries risks of scarring, functional impairment, and cosmetic complications, particularly in anatomically sensitive regions [8]. For elderly patients, immunocompromised individuals, or those presenting with multiple or recurrent lesions, surgery may not represent the most appropriate therapeutic option [9]. Systemic chemotherapy and targeted biological agents for advanced disease are limited by poor tumor selectivity, systemic adverse effects, and the emergence of acquired drug resistance [10]. Topical and localized delivery approaches have therefore been increasingly explored as viable alternatives, offering direct administration to the tumor site with reduced systemic exposure [11]. Nevertheless, conventional topical vehicles such as creams, gels, and ointments are hindered by inadequate penetration through the stratum corneum barrier, inconsistent drug release profiles, and poor retention at the site of application [12].

In this context, electrospun nanofibers have attracted considerable scientific interest as advanced platforms for topical and localized skin cancer therapy [13]. Their distinctive physicochemical characteristics, including high surface-to-volume ratio, adjustable porosity, nanoscale fiber architecture, and capacity to closely mimic the extracellular matrix, render them uniquely suited for efficient drug incorporation and sustained local release [14,15]. The solid fibrous matrix of electrospun nanofibers physically retains incorporated drugs and releases them in a controlled manner through diffusion, polymer degradation, and swelling mechanisms, resulting in sustained therapeutic drug levels at the tumor site [16]. Electrospinning further facilitates the engineering of multifunctional constructs by permitting the precise control of fiber composition, morphology, and surface functionalization, enabling the simultaneous incorporation of chemotherapeutic agents, photosensitizers, phytochemicals, and targeting ligands [17,18]. The present review provides a comprehensive overview of nanofiber-based systems for skin cancer therapy, encompassing polymer selection, electrospinning techniques, drug-loading strategies, mechanisms of anticancer action, recent preclinical evidence, and challenges pertaining to clinical translation and regulatory compliance.

2. SKIN CANCER

2.1 Epidemiology and Classification

Skin cancer represents one of the most prevalent malignancies globally, with over 1.5 million new cases reported in 2022 [19]. Melanoma accounted for approximately 331,722 new cases and 58,667 deaths, while non-melanoma skin cancers contributed to 1,234,533 diagnoses and 69,416 fatalities in the same period [19,20]. Epidemiological data indicate a sustained upward trajectory in the incidence of both melanoma and NMSC across most regions over the past three to four decades, with fair-skinned populations bearing the greatest burden of disease [20,21]. Although the overall mortality rate from NMSC remains comparatively low, melanoma carries a disproportionately high lethality rate relative to its incidence, primarily due to its aggressive biological behavior and capacity for early regional and distant metastasis [4].

Skin cancers are broadly divided into melanoma and non-melanoma categories, collectively accounting for approximately 95% of all cutaneous malignancies [22]. Melanoma originates from melanocytes located in the basal layer of the epidermis and is recognized as the most lethal form of skin cancer despite constituting only a small proportion of total cases [4]. Histologically distinct subtypes include superficial spreading melanoma, nodular melanoma, lentigo maligna melanoma, and acral lentiginous melanoma, each demonstrating unique clinical presentations, growth patterns, and prognostic characteristics [4]. The prognosis of melanoma is strongly influenced by tumor thickness (Breslow depth), ulceration status, anatomical location, and the presence of lymph node or distant organ involvement [4].

Non-melanoma skin cancers encompass a wide spectrum of malignancies derived from epidermal keratinocytes and other non-melanocyte cell populations [22]. BCC is the most common cutaneous malignancy worldwide, predominantly arising in sun-exposed areas and displaying locally invasive growth with a very low propensity for metastasis [23]. Its molecular pathogenesis is primarily driven by aberrant activation of the Hedgehog signaling pathway, most frequently resulting from loss-of-function mutations in the PTCH1 gene [23,24]. SCC arises from keratinocytes of the epidermis and is the second most common form of skin cancer, with a significantly higher risk of regional and distant metastasis compared to BCC [25]. Chronic ultraviolet radiation exposure, immunosuppression, and infection with oncogenic human papillomaviruses are recognized as the major etiological risk factors for SCC development [22,25].

2.2 Molecular Mechanisms of Skin Cancer Progression

UV radiation, particularly UVA (315–400 nm) and UVB (280–315 nm), plays a pivotal role in skin cancer initiation and progression by inducing direct DNA damage in the form of cyclobutane pyrimidine dimers and (6-4) photoproducts, generating oxidative stress, suppressing cutaneous immune surveillance, and triggering downstream oncogenic signaling cascades [26]. At the molecular level, skin cancer progression is governed by dysregulation of key cell signaling pathways controlling proliferation, differentiation, and survival. The MAPK (RAF–MEK–ERK) pathway is critically implicated in melanoma pathogenesis, most commonly activated by point mutations in the BRAF proto-oncogene (predominantly BRAF V600E), which drive constitutive cell proliferation and metastatic dissemination [26]. Concurrent hyperactivation of the PI3K/AKT/mTOR pathway further augments tumor cell survival and resistance to apoptosis, while loss of key tumor suppressor genes such as TP53 and PTEN removes critical anti-proliferative checkpoints and potentiates oncogenic signaling [26].

In the context of BCC, constitutive activation of Hedgehog-GLI signaling following inactivation of PTCH1 or activating mutations in Smoothened (SMO) are the hallmark molecular events driving carcinogenesis [23,24]. For SCC, loss-of-function

mutations in TP53, CDKN2A, and NOTCH1, combined with upregulation of epidermal growth factor receptor (EGFR) signaling, collectively promote a keratinocyte phenotype characterized by uncontrolled proliferation, resistance to differentiation, and invasive growth [25]. These molecular alterations provide the mechanistic rationale for the development of nanofiber-based drug delivery systems that target specific oncogenic vulnerabilities in the tumor microenvironment, offering superior therapeutic selectivity compared to conventional cytotoxic agents [13,14].

Fig. 1. Molecular Mechanisms of Skin Cancer Progression

3. CONVENTIONAL AND EMERGING TREATMENTS FOR SKIN CANCER

Treatment selection for skin cancer is determined by the tumor subtype, clinical stage, anatomical location, and patient comorbidities, with the armamentarium of available options ranging from surgical interventions to targeted molecular therapies [7,27]. Surgery remains the cornerstone of management for early-stage localized NMSC, with Mohs micrographic surgery offering the highest cure rates and maximal tissue conservation for high-risk BCC and SCC lesions [8]. Radiation therapy serves as a useful adjunct or alternative for patients unsuitable for surgery, locally advanced disease, or cases with perineural invasion [27]. Topical chemotherapy with 5-fluorouracil (5-FU) or imiquimod is employed for superficial BCC and actinic keratoses, though its penetration and efficacy are limited by the stratum corneum barrier [27].

Immunotherapy, particularly with PD-1 checkpoint inhibitors such as cemiplimab and pembrolizumab, has transformed the management of advanced and metastatic cutaneous SCC and melanoma, achieving durable responses in a substantial proportion of patients [28]. Similarly, BRAF-targeted agents (vemurafenib, dabrafenib) and MEK inhibitors (trametinib, cobimetinib) have demonstrated significant clinical benefit in BRAF-mutant melanoma, although acquired resistance invariably limits long-term efficacy [26,27]. Nanomedicine-based drug delivery platforms, including polymeric nanoparticles, liposomes, and, more recently, electrospun nanofibers, are increasingly investigated as strategies to overcome the intrinsic limitations of conventional topical and systemic therapies by enabling localized, controlled drug release directly at the tumor site [29,30].

4. NANOFIBERS

4.1 Definition, Classification, and Historical Development

Nanofibers are defined as one-dimensional materials with at least two dimensions in the nanometric range (typically diameters of 50–1000 nm) and axial lengths vastly exceeding their lateral dimensions [13,14]. Depending on composition, morphology, and degree of structural rigidity, nanofibers may be further categorized as solid fibers, hollow fibers, core–shell fibers, or composite structures, each imparting distinct physicochemical properties suited to specific biomedical applications [13,15]. Based on material composition, nanofibers are classified into organic (polymer-based), inorganic (metal oxides, carbon-based), and composite types, with polymer-based nanofibers predominating in pharmaceutical and biomedical applications owing to their ease of fabrication, compositional versatility, biocompatibility, and biodegradability [15,16].

The historical development of nanofiber technology spans several centuries, originating with William Gilbert's observation of electrostatic liquid attraction in 1600, progressing through key milestones including Cooley's electrospinning device patent in 1900, Anton Formhals' foundational electrospinning patents filed between 1931 and 1944, and Geoffrey Taylor's establishment of the theoretical framework for Taylor cone formation in the 1960s [16,17]. The modern era of nanofiber research was catalyzed by Doshi and Reneker's seminal 1995 publication introducing the term "electrospinning" and demonstrating the production of continuous polymer nanofibers from over 20 different polymer solutions [18]. Since then, the field has expanded exponentially, with current research encompassing a diverse range of applications in drug delivery, tissue engineering, wound healing, cancer therapy, filtration, and environmental remediation [9,13,18].

4.2 Advantages and Limitations of Nanofibers in Drug Delivery

The principal advantages of nanofiber-based drug delivery systems arise from their distinctive structural and physicochemical properties [13,14,15]. The exceptionally high surface-to-volume ratio of electrospun nanofibers, several orders of magnitude greater than conventional semisolid topical dosage forms, maximizes drug–skin contact area and enhances drug diffusion gradients across the epidermal barrier [14]. High porosity and interconnected pore architecture facilitate fluid transport and molecular diffusion, while simultaneously permitting adequate oxygen and nutrient exchange essential for tissue compatibility [13]. The nanoscale fiber dimensions allow close approximation with skin surface microstructures, promoting firm adhesion and minimizing drug loss due to physical removal [14,15]. Furthermore, electrospinning enables the efficient encapsulation of both hydrophilic and hydrophobic drugs in amorphous dispersion within the polymer matrix, enhancing apparent drug solubility and

thermodynamic activity compared to crystalline drug forms, thereby improving the driving force for transdermal permeation [15,16]. Controlled and sustained drug release over days to weeks, achievable through appropriate polymer selection and fiber architecture, maintains therapeutic drug concentrations at the tumor site while avoiding systemic toxicity [16,17].

Despite these compelling advantages, nanofiber-based systems face several significant challenges that currently limit their clinical translation [31,32]. Scale-up of electrospinning from laboratory to industrial manufacturing remains technically challenging due to low production rates, batch-to-batch variability, and difficulties in maintaining process reproducibility under good manufacturing practice (GMP) conditions [31]. The delicate porous structure of nanofiber mats requires specialized handling, sterilization, and packaging procedures [32]. Burst release of surface-associated drugs during initial contact with physiological fluids remains a persistent challenge, particularly for blend electrospun systems [30]. Furthermore, comprehensive in vivo toxicology, biodistribution, and long-term safety data for many polymer–drug nanofiber combinations are lacking, and regulatory classification of nanofiber-based products as drug–device combination systems introduce additional complexity into the approval pathway [31,32].

5. FABRICATION OF NANOFIBERS: ELECTROSPINNING AND ALTERNATIVE METHODS

5.1 Electrospinning: Principles and Setup

Electrospinning is the most widely adopted technique for the production of polymer nanofibers for biomedical applications, owing to its simplicity, versatility, scalability, and capacity for producing fibers across a broad diameter range from tens of nanometers to several micrometers [9,16,17]. The electrospinning process is governed by electrohydrodynamic principles: a high-voltage electrostatic field (typically 5–30 kV) is applied to a droplet of polymer solution extruded through a spinneret needle, generating electrostatic repulsion within the charged solution that overcomes surface tension to form the characteristic Taylor cone [16,17]. A fine, highly charged polymer jet is subsequently ejected from the apex of the Taylor cone and undergoes rapid elongation, bending instabilities (whipping), and solvent evaporation during its trajectory toward the grounded collector, resulting in the deposition of solid polymer nanofibers [17,18]. The standard electrospinning setup consists of a syringe pump for precise solution delivery, a high-voltage power supply, a metallic needle or spinneret, and a flat or rotating collector plate maintained at an appropriate working distance from the spinneret [16,17,18].

5.2 Advanced Electrospinning Configurations

Single-nozzle electrospinning represents the simplest and most commonly employed configuration, in which a single polymer solution is electrospun to produce a nonwoven mat of randomly oriented solid fibers [30]. While this approach offers simplicity and ease of operation, its principal limitation lies in the risk of drug degradation during solvent evaporation and in the difficulty of independently controlling the release rates of multiple therapeutic agents [30].

Coaxial electrospinning employs a specialized concentric spinneret assembly through which two distinct polymer solutions—a core fluid and a shell fluid—are simultaneously co-extruded, producing core–shell nanofibers in which the active pharmaceutical ingredient is encapsulated within the inner core reservoir [30,33]. This architecture effectively protects thermolabile or chemically sensitive drugs from degradation, substantially reduces burst release by providing a rate-controlling polymer shell, and enables the independent tuning of core and shell release kinetics [33,34]. The outer shell polymer flow rate is typically maintained at twice the inner core flow rate to ensure adequate encapsulation and formation of a coherent Taylor cone [34].

Triaxial electrospinning extends the coaxial concept by employing three concentric needles to simultaneously spin three distinct polymer solutions, yielding complex three-layer nanofiber architectures capable of sequential or multiphasic drug release [34]. This configuration is particularly advantageous for combination drug delivery systems where precise sequential release of different therapeutic agents is desired, such as initial rapid cytotoxic drug release followed by sustained anti-inflammatory phytochemical delivery [34,35]. Emulsion electrospinning achieves core–shell fiber formation using a single conventional spinneret by exploiting the self-segregation of emulsified immiscible phases during jet elongation and solvent evaporation, providing a simpler and less costly alternative to coaxial systems [35]. Side-by-side electrospinning produces Janus or bicomponent nanofibers from parallel spinnerets, enabling dual-drug delivery with independent release kinetics from each fiber compartment [35].

5.3 Non-Electrospinning Fabrication Methods

Self-assembly is a bottom-up technique in which amphiphilic molecules—typically peptides, proteins, or block copolymers—spontaneously organize into nanofiber structures driven by non-covalent interactions including hydrogen bonding, hydrophobic forces, and electrostatic interactions [9]. Self-assembled nanofibers offer excellent

biocompatibility and bioactivity due to their proteinaceous composition and ability to incorporate bioactive sequences, but the process is complex, production yields are low, and precise fiber dimension control is challenging [9]. Phase separation is a polymer processing technique in which thermodynamic instability is induced in a polymer solution by altering temperature or solvent composition, driving phase separation into polymer-rich and polymer-lean domains that, upon removal of solvent, yield a porous nanofibrous scaffold [9]. While producing highly porous structures with good mechanical properties, phase separation is limited to specific polymer–solvent systems and does not produce continuous fibers [9]. Centrifugal spinning generates nanofibers by utilizing high centrifugal forces to extrude polymer solutions through small orifices in a rapidly rotating spinneret, achieving production rates substantially higher than conventional electrospinning [9]. However, fiber uniformity and morphology control are less precise compared to electrospinning, limiting its current utility for pharmaceutical applications [9].

Fig.2. Fabrication Of Nanofibers: Electrospinning and Alternative Methods

6. POLYMERS USED IN NANOFIBERS FOR SKIN CANCER THERAPY

Polymer selection is a critical determinant of nanofiber performance in skin cancer drug delivery, governing drug loading capacity, release kinetics, mechanical properties, biocompatibility, biodegradability, and skin adhesion [13,14,15]. Polymers used in electrospun nanofibers are broadly classified as natural, semi-synthetic, and synthetic, and are typically employed individually or as blends to achieve the desired balance of properties [13].

Natural polymers employed in nanofibers for skin cancer applications include collagen, gelatin, hyaluronic acid (HA), chitosan (CS), silk fibroin, alginic acid, and keratin [13,15]. These materials offer excellent biocompatibility, biological activity, and inherent ECM-mimicking properties; however, they frequently exhibit poor mechanical strength, inconsistent batch-to-batch properties due to biological variability, and suboptimal spinnability when used alone [13,15]. Chitosan deserves particular mention owing to its inherent mucoadhesive properties, positive surface charge facilitating electrostatic interaction with negatively charged cell membranes, and documented antifungal and antimicrobial activities relevant to post-tumor wound management [30]. Semi-synthetic polymers such as cellulose acetate, hydroxyethylcellulose (HEC), and methylcellulose occupy an intermediate position, offering improved spinnability and more consistent properties compared to purely natural materials while retaining acceptable biocompatibility profiles [13,14].

Synthetic polymers constitute the most extensively investigated class of nanofiber materials for skin cancer drug delivery, primarily owing to their reproducible physicochemical properties, well-established biocompatibility and biodegradability profiles, and regulatory approval status for use in pharmaceutical and medical device products [13,14,15]. Polycaprolactone (PCL) has been the most widely studied synthetic polymer in this field due to its favorable hydrophobicity, excellent mechanical flexibility, and slow biodegradation rate (2–3 years under physiological conditions), which supports prolonged and sustained drug release [30,36]. PCL nanofibers loaded with anticancer agents have been shown to maintain cytotoxic drug release for over 21 days in vitro, achieving IC50 values significantly lower than free drug equivalents [30]. Poly(lactic-co-glycolic acid) (PLGA) offers a highly tunable biodegradation rate (weeks to months depending on the lactide:glycolide ratio) and FDA-approved status for parenteral and implantable applications, making it an attractive matrix for controlled-release nanofiber systems [14,30]. Polyvinylpyrrolidone (PVP) is a hydrophilic, water-soluble polymer that enhances drug solubility and dissolution rate through amorphous solid dispersion formation, and is commonly used as a shell polymer in coaxial nanofibers to modulate drug release [34]. Polyvinyl alcohol (PVA) offers excellent film-forming properties, hydrophilicity, and biocompatibility, and is widely employed in combination with other polymers to improve fiber spinnability and mechanical properties [37,38].

7. ELECTROSPINNING PARAMETERS AND THEIR INFLUENCE ON DRUG DELIVERY PERFORMANCE

7.1 Solution Properties

Polymer solution concentration and viscosity are the most fundamental determinants of fiber diameter, morphology, and drug distribution [15,16]. At optimal concentrations, sufficient chain entanglement enables the formation of continuous, bead-free fibers; insufficient viscosity leads to the formation of electrosprayed droplets or fibers with pronounced bead defects, while excessive viscosity impedes jet formation and spinneret clogging [15,16]. From a drug delivery perspective, higher viscosity formulations generally produce thicker, more uniform fibers that support extended sustained drug release, whereas lower viscosity systems may generate structural irregularities contributing to accelerated burst release [15]. Electrical conductivity of the polymer solution, adjustable through the addition of ionic salts or conductive agents, directly influences jet charge density: higher conductivity generates finer

fibers with reduced bead formation and increased surface-to-volume ratio, which can accelerate drug release rates favorable for achieving rapid cytotoxic action [15,16]. The molecular weight of the polymer governs chain entanglement (quantified as the Berry number) and is inversely related to bead formation: higher molecular weight polymers produce larger fiber diameters with fewer defects, supporting structural integrity and controlled release [15].

7.2 Processing and Environmental Parameters

Applied voltage controls jet formation dynamics and fiber stretching: increasing voltage generally enhances jet elongation, potentially reducing fiber diameter, but excessively high voltages may cause multiple jets to form simultaneously, compromising fiber uniformity and drug distribution [15,16]. Working distance between the spinneret and collector must allow sufficient time for jet elongation and complete solvent evaporation before fiber deposition; inadequate working distances result in wet, fused fibers with irregular morphology and unpredictable drug release behavior [16]. Feeding (flow) rate influences the volume of solution available for jet formation: higher flow rates may yield larger fiber diameters with incomplete solvent evaporation and increased burst release, while lower rates favor uniform, thin fibers with more controlled drug release [15,16]. Environmental humidity significantly affects fiber morphology and surface texture, particularly for hydrophilic polymers: elevated humidity can induce phase separation at the fiber surface during jet elongation, generating porous fiber architectures with enhanced surface area and accelerated initial drug release [16]. Solvent selection, determined by boiling point and dielectric constant, critically influences jet stability, evaporation rate, and residual solvent content; high dielectric constant solvents such as dimethylformamide (DMF) promote finer fiber formation through enhanced jet charging [15,16].

8. MECHANISMS OF ANTICANCER ACTION OF NANOFIBERS IN SKIN CANCER

8.1 Localized and Sustained Drug Delivery

When applied topically as a flexible, patch-like construct directly over skin cancer lesions, electrospun nanofibers function as localized drug reservoirs that release incorporated anticancer agents in a controlled and sustained manner at the tumor site [30,36]. Drug release from polymeric nanofibers is governed by three primary mechanisms: diffusion of drug molecules through the polymer matrix, erosion and biodegradation of the polymer backbone, and swelling-mediated release in the presence of biological fluids [14,30]. An initial burst release phase, attributed to drug molecules localized near the fiber surface, provides rapid tumor debulking activity, followed by a sustained release phase governed by polymer degradation kinetics and diffusion-controlled mechanisms, which maintains therapeutic drug concentrations and reduces the risk of tumor regrowth between treatment cycles [14,30]. This biphasic release profile represents a mechanistic advantage over conventional topical formulations, which typically deliver drug over a few hours before removal or absorption [14,30,36].

Physicochemically, the patch-like architecture of nanofiber mats creates an occlusive microenvironment at the skin surface that reduces transepidermal water loss and establishes a hydration gradient within the stratum corneum. This hydration effect increases the fluidity of intercellular lipid bilayers within the stratum corneum, lowering barrier resistance and facilitating passive drug diffusion into deeper epidermal and dermal layers where cancer cells reside [11,12]. The intimate nanoscale contact between the fibers and the skin surface maximizes the drug–skin interface area, generating a steep local concentration gradient that drives drug partitioning into the epidermis according to Fickian diffusion principles [14,15]. Amorphous dispersion of drug within the polymer matrix, a hallmark of electrospun nanofibers, increases the apparent thermodynamic activity of the drug compared to crystalline forms, further augmenting the transdermal permeation driving force [15,16].

8.2 Improved Skin Penetration and Tumor Retention

Nanofiber-based systems demonstrate distinct advantages over conventional topical vehicles in terms of drug penetration into the epidermis and dermis, and retention at the tumor site [30,31,32]. Unlike semisolid formulations susceptible to removal by physical contact, perspiration, or washing, nanofiber mats adhere firmly to the skin surface and resist displacement, ensuring prolonged drug contact with the lesion [11,12]. The solid fibrous matrix physically retains drug within the scaffold and releases it through combination of polymer degradation and diffusion-controlled mechanisms, maintaining local therapeutic drug concentrations over days to weeks compared to hours for most topical creams and gels [14,15,30]. For coaxial and core–shell nanofibers, the shell polymer acts as a rate-controlling membrane, preventing rapid release and maintaining a steady-state concentration gradient over extended periods that prolongs drug accumulation within tumor tissue [33,34]. The superior skin retention and penetration characteristics of nanofiber-based systems compared to conventional topical vehicles have been confirmed in multiple ex vivo skin permeation studies, with nanofibers achieving significantly higher drug concentrations in the viable epidermis and dermis at equivalent doses [30,31,36].

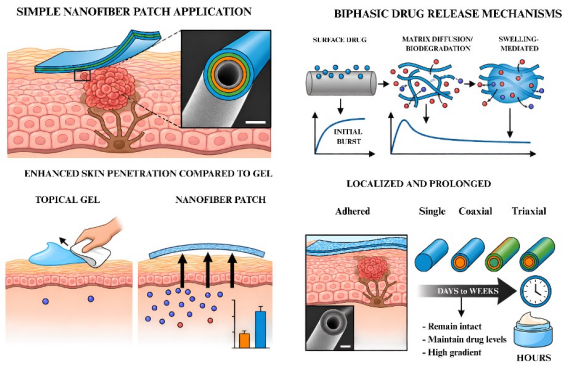

Fig.3. Mechanism of nanofiber in skin cancer (Localized and Sustained Drug Delivery and Improved Skin Penetration and Tumor Retention.

8.3 Hyperthermia-Assisted Chemo-Synergism

A subset of advanced nanofiber constructs incorporates magnetic nanoparticles predominantly superparamagnetic iron oxide nanoparticles (Fe_3O_4) within the polymer matrix, enabling hyperthermia-based tumor ablation therapy as a complementary modality to conventional chemotherapy [39]. Upon exposure of the applied nanofiber patch to an external alternating magnetic field (AMF) in the frequency range of 100–500 kHz, the embedded magnetic nanoparticles dissipate electromagnetic energy as heat through Néel relaxation and Brownian relaxation mechanisms, generating localized temperatures of 42–45°C within the tumor microenvironment [39]. This temperature elevation directly induces cancer cell death through protein denaturation, membrane disruption, and mitochondrial damage, while simultaneously sensitizing tumor cells to concurrently released chemotherapeutic agents through enhanced membrane permeability and upregulation of heat shock protein-mediated apoptotic pathways [39]. This chemo-hyperthermic synergism has been demonstrated to achieve significantly greater tumor regression than either hyperthermia or chemotherapy alone in preclinical models, with the nanofiber platform enabling spatial co-localization of heat generation and drug release within the same tumor lesion [39].

Similarly, photoresponsive nanofibers incorporating photosensitizers such as indocyanine green (ICG) or porphyrin derivatives enable photothermal and photodynamic therapy upon irradiation with near-infrared (NIR) light [40]. ICG-loaded nanofibers irradiated at 808 nm have been shown to elevate local tumor temperatures to 50–55°C in murine melanoma models, achieving complete tumor regression in conjunction with co-delivered chemotherapeutic agents [40]. The generation of reactive oxygen species (ROS) by photosensitizers under NIR excitation provides an additional mechanism of photodynamic cytotoxicity, directly oxidizing critical cellular macromolecules and inducing apoptosis through intrinsic mitochondrial pathways [33,40].

Fig.4. Mechanism of action of nanofiber in skin cancer (Hyperthermia-Assisted Chemo-Synergism)

8.4 Overall Cellular Mechanisms of Anticancer Activity

At the cellular level, anticancer drugs released from the nanofiber matrix—including 5-fluorouracil, doxorubicin, paclitaxel, and curcumin—exert cytotoxic effects through well-established mechanisms: 5-FU inhibits thymidylate synthase, blocking DNA synthesis and inducing cell cycle arrest at the G1/S checkpoint; doxorubicin intercalates into DNA and inhibits topoisomerase II, inducing double-strand breaks and triggering apoptosis via the p53 pathway; paclitaxel stabilizes polymerized tubulin, disrupting microtubule dynamics and arresting mitosis at the G2/M checkpoint; and curcumin inhibits NF-κB signaling, suppressing inflammatory cytokine production and sensitizing tumor cells to chemotherapy [41,42,43]. The nanofiber scaffold creates a sustained cytotoxic microenvironment at the tumor site, ensuring continuous exposure of cancer cells to therapeutic drug concentrations and minimizing the regrowth of partially drug-exposed subpopulations that contribute to acquired resistance [30,36,44]. This mechanistic versatility, combined with localized delivery and minimal systemic absorption, constitutes the fundamental therapeutic rationale for nanofiber-based skin cancer treatment platforms.

9. APPLICATIONS OF NANOFIBERS IN SKIN CANCER THERAPY

9.1 Allopathic Drug-Loaded Nanofiber Systems

Nanofibers loaded with conventional chemotherapeutic agents have been the most extensively investigated platforms for skin cancer therapy, with 5-fluorouracil representing the most commonly studied drug owing to its established topical activity against superficial BCC and SCC [32,36]. Patel and Yadav (2019) developed PCL-based blend nanofibers loaded with 5-FU with fiber diameters of 300–700 nm and demonstrated significantly lower IC50 values against A431 human epidermoid carcinoma cells compared to free 5-FU solution, confirming the advantage of sustained local drug delivery from the nanofiber matrix. Drug release followed diffusion-controlled Higuchi kinetics, indicating matrix-dominated release over 10–14 days [36]. Yadav et al. (2025) extended this approach by loading PLGA nanoparticles containing 5-FU into PCL nanofibers, creating a nano-in-nano topical patch system that demonstrated superior skin penetration,

sustained drug release over 21 days, and significant antitumor activity in preclinical SKH-1 hairless mouse models [45]. Vishwakarma et al. (2025) employed cellulose-based nanofibers to stabilize cationic ethosomes containing bleomycin sulfate, achieving enhanced skin permeation and tumor cell cytotoxicity against melanoma cell lines through vesicle–fiber synergism [38].

For doxorubicin delivery, coaxial chitosan/PEO nanofibers incorporating graphene oxide demonstrated pH-responsive drug release under mildly acidic conditions (pH 6.5) simulating the tumor microenvironment, achieving enhanced intracellular drug uptake and apoptotic activity in A431 cells with encapsulation efficiency exceeding 85% [30]. Paclitaxel-loaded PHA/PLGA coaxial nanofibers demonstrated sustained drug release and effective inhibition of melanoma cell viability by disrupting microtubule dynamics, with the coaxial architecture reducing burst release compared to blend systems [30]. Altharawi et al. (2025) synthesized rhodium metal-organic framework (Rh-MOF)/PVA-PVP nanofibers and evaluated their cytotoxicity against A431 cells, demonstrating approximately 30–35% reduction in cell viability mediated by ROS-driven oxidative stress mechanisms [37]. Wang et al. (2025) demonstrated sustained release of 5-FU from poly(trimethylene carbonate) nanofiber membranes over 28 days with enhanced antitumor efficacy in squamous cell carcinoma models [45]. El-Habashy et al. (2023) engineered tanshinone IIA-loaded, levan-functionalized PCL nanofibers for skin cancer treatment, achieving controlled release, improved bioavailability, and significant in vitro cytotoxicity against A431 cells, with the levan surface functionalization providing mucoadhesive properties enhancing skin contact [46].

9.2 Herbal and Phytochemical-Loaded Nanofiber Systems

Herbal compounds have attracted increasing interest as anticancer agents in nanofiber formulations owing to their multi-target pharmacological activity, favorable safety profiles, and potential to synergize with conventional chemotherapeutic agents [41,42,47]. Curcumin has been the most extensively studied phytochemical in this context, with multiple studies demonstrating its ability to inhibit melanoma and SCC cell proliferation through NF-κB pathway suppression, induction of apoptosis, and antioxidant mechanisms [42,47]. Ajalloueian et al. (2025) fabricated coaxial cellulose acetate nanofibers loaded with curcumin and evaluated drug release on ex vivo pig skin models and melanoma cell lines, achieving encapsulation efficiency of 90–95% with sustained drug release over 10–14 days and significant antioxidant and antiproliferative activity [47]. Goonoo et al. (2024) developed bilayer polyurethane/PCL and gelatin/PCL nanofibers loaded with propolis extract, demonstrating controlled release of approximately 40% extract over 48 hours, potent antibacterial activity, and promotion of wound healing in murine post-resection wound models, establishing the utility of phytochemical nanofibers as adjunct therapy following tumor excision [48]. Silk fibroin nanofibers loaded with dual curcumin formulations—incorporating curcumin-loaded RSF nanospheres within the fiber matrix—demonstrated biphasic release kinetics with enhanced cellular uptake and NF-κB inhibitory activity in melanoma cells [43].

9.3 Combination Drug-Loaded Nanofiber Systems

Combination nanofiber systems that co-deliver multiple therapeutic agents have emerged as particularly promising strategies for skin cancer therapy, exploiting synergistic drug interactions to achieve superior efficacy compared to either agent administered alone [41,42]. Guo et al. (2020) co-delivered doxorubicin and curcumin in triaxial PLGA/gelatin nanofibers, designing the system to release doxorubicin rapidly from the outer shell layer within the first 24 hours to provide immediate cytotoxic action, followed by sustained curcumin release from the inner core over 7 days for persistent NF-κB inhibition and anti-inflammatory activity against A431 and SCC cells. Encapsulation efficiency exceeded 90% for both agents, and the combination system demonstrated significantly greater cytotoxicity than either drug alone, confirming synergistic anticancer activity [41]. Srivastava et al. (2018) co-loaded 5-FU and curcumin in PLGA-based blend nanofibers and demonstrated a combination index below 1 against A431 cells, confirming synergism, with curcumin's NF-κB inhibitory activity complementing 5-FU's DNA synthesis blockade to suppress tumor recurrence-associated inflammatory signaling [42]. These studies collectively establish the mechanistic and therapeutic rationale for multi-drug nanofiber co-delivery as an advanced strategy in skin cancer management.

10. COMPARISON OF NANOFIBERS WITH OTHER NANOCARRIER PLATFORMS

Electrospun nanofibers occupy a unique position among drug nanocarrier platforms by virtue of their one-dimensional fibrous architecture, which imparts distinctive advantages for topical and localized drug delivery applications compared to zero-dimensional particulate systems [49,50]. Polymeric nanoparticles and liposomes, while achieving significant clinical translation for systemic delivery, require secondary incorporation into gels, films, or dressings for effective topical application and are associated with rapid clearance from the application site [49,50]. In contrast, nanofiber mats inherently

function as self-sustaining topical patches that adhere directly to skin or wound surfaces, providing site-specific drug delivery without the need for a secondary vehicle [51,52]. Metal-organic frameworks (MOFs) have emerged as novel nanocarriers with exceptionally high surface areas and tunable pore structures enabling high drug loading, but standalone MOF particles suffer from instability in physiological environments and poor handling characteristics for topical applications; incorporation of MOFs within electrospun nanofibers, as demonstrated by Altharawi et al. (2025) with Rh-MOF/PVA-PVP nanofibers, provides a synergistic approach combining the loading capacity of MOFs with the sustained release and adhesion properties of fibrous scaffolds [37,50]. Hybrid 'nano-in-nano' systems embedding nanoparticles or liposomes within nanofibers represent a convergence strategy that combines the targeting advantages of nanoscale particles with the localization and sustained release characteristics of fibrous matrices, exemplified by the nanoparticle-embedded 5-FU nanofiber patch system reported by Yadav et al. (2025) [45,53].

11. CLINICAL APPLICATION, REGULATORY CONSIDERATIONS, AND TRANSLATION CHALLENGES

11.1 Clinical Application and Handling

In the clinical setting, electrospun nanofibers for skin cancer are most commonly formulated as flexible, self-adhesive patches or transdermal films applied directly over tumor lesions or affected skin surfaces [31,32]. The application protocol mirrors that of conventional wound dressings: the sterile nanofiber patch is removed from sealed packaging, positioned over the lesion with gentle pressure to ensure conformal skin contact, and secured with a secondary dressing or medical tape if required. Replacement frequency depends on the drug release profile of the specific formulation, ranging from daily to every 3–7 days for sustained-release systems [31,32,51]. Nanofiber mats are typically fabricated as free-standing matrices, cut to precise dimensions tailored to lesion size, sterilized by gamma irradiation or ethylene oxide treatment, and packaged in sealed sterile pouches [32,51]. For photothermal or magnetic hyperthermia-integrated nanofiber systems, the applied patch is subsequently activated by NIR light irradiation or alternating magnetic field exposure using a clinical device, enabling non-invasive synergistic therapy without the need for surgical intervention [39,40]. The scale-up of electrospinning from laboratory to industrial GMP manufacturing represents a particularly formidable challenge, as conventional single-needle systems produce nanofibers at rates of only 0.01–0.1 g/h—wholly inadequate for commercial production. Multi-jet electrospinning arrays, needleless electrospinning configurations, and centrifugal electrospinning technologies offer substantially higher production rates while maintaining fiber quality; however, each introduces unique process validation challenges [31,52]. Despite these hurdles, the growing body of preclinical evidence, increasing number of nanofiber-related patents, and expanding regulatory experience with nanomedicine products provide a supportive foundation for the progressive clinical translation of electrospun nanofiber systems for skin cancer therapy [51,52].

12. FUTURE PERSPECTIVES

The successful clinical translation of nanofiber-based platforms for skin cancer therapy will require addressing several key scientific, technological, and regulatory challenges over the coming decade [33,34,52]. From a materials science perspective, the development of novel biodegradable and bioresponsive polymer systems with precisely engineered degradation profiles, combined with advanced surface functionalization strategies incorporating targeting ligands, peptides, antibodies, and aptamers, holds considerable promise for improving tumor selectivity and reducing off-target effects [33,54]. Stimuli-responsive nanofibers capable of releasing their drug payload on demand in response to tumor microenvironment triggers such as acidic pH, elevated ROS levels, elevated temperature (hyperthermia), enzymatic activity, or externally applied NIR light or ultrasound represent a particularly exciting frontier, offering spatiotemporal precision in drug delivery that is unachievable with passive release systems [33,34].

The incorporation of immunotherapeutic agents, including checkpoint inhibitors, cytokines, and cancer neoantigens, into nanofiber systems for localized immunotherapy represents a conceptually transformative approach that could harness the cytotoxic effects of localized drug delivery while simultaneously re-educating the tumor immune microenvironment toward sustained antitumor immunity [27,28,54]. Co-delivery of phytochemicals with conventional chemotherapeutics in precisely engineered combination nanofibers, combined with a deeper mechanistic understanding of synergistic drug interactions at the molecular level, will further expand therapeutic possibilities [41,42,47]. Advances in computational modeling of electrospinning process parameters and drug release kinetics, combined with artificial intelligence-guided formulation optimization, offer the prospect of accelerating nanofiber product development and reducing the iterative experimental burden currently associated with formulation screening [34,44].

From a translational perspective, the establishment of standardized characterization

protocols, validated in vitro drug release models predictive of in vivo performance, and relevant preclinical animal models that more accurately recapitulate human skin cancer biology will be essential for generating the high-quality efficacy and safety data required by regulatory agencies [31,32,51]. Well-designed, randomized controlled clinical trials evaluating nanofiber-based topical formulations for both melanoma and non-melanoma skin cancers are urgently needed to establish clinical efficacy, tolerability, and patient acceptability [51,52]. The integration of patient-centric design principles, including skin-compatible adhesive properties, cosmetically acceptable appearance, ease of self-application, and flexible individualized dosing formats, will be critical for ensuring clinical adoption and patient compliance [31,32,44].

13. CONCLUSION

Electrospun nanofibers represent a scientifically rigorous, technically versatile, and clinically promising platform for overcoming the fundamental limitations associated with current topical and systemic therapies for skin cancer. The convergence of advanced polymer science, electrospinning technology, and pharmaceutical drug delivery principles has enabled the design of nanofiber-based constructs that offer superior skin adhesion, high and efficient drug loading, controlled and sustained release at the tumor site, enhanced epidermal penetration, and the capacity for multi-modal therapeutic strategies combining chemotherapy, phototherapy, and hyperthermia. The extensive preclinical evidence reviewed herein demonstrates that nanofiber-based systems consistently outperform conventional topical formulations in terms of local drug concentrations, tumor cell cytotoxicity, and antitumor efficacy across both melanoma and non-melanoma skin cancer models. Combination nanofiber systems co-delivering chemotherapeutic agents with phytochemicals or photosensitizers have further demonstrated synergistic anticancer activity, offering compelling mechanistic rationale for multi-drug approaches in clinical practice. Through sustained multidisciplinary innovation and rigorous clinical validation, electrospun nanofibers hold the realistic potential to emerge as next-generation, patient-friendly, and effective platforms for localized skin cancer therapy in the near-to-medium clinical future.

Author Contributions

Priya. p concepted the review framework, conducted the literature survey, and prepared the initial manuscript draft and Allimalarkodi. s contributed to the conception and critical review of the content. Sambathkumar. R supervised the study and contributed critical revisions. All authors reviewed, read, and approved the final version of the manuscript. The authors declare that no paper mill was used and that all data presented in this work were prepared by the authors.

Funding: The authors declare that this research received no external funding.

Conflict of Interest: The authors declare no conflict of interest.

Ethical Approval: This article does not contain any studies involving human participants or animals.

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