

A Review on the Application of Electrospun Herbal Extract-Loaded Metallized Nanofiber Composites as Wound Healing Promoter: Fabrication, Efficacy, and Safety

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ABSTRACT

Electrospinning is a promising technique for wound healing applications, as it enables the fabrication of nanostructures that closely mimic the natural extracellular matrix. This review highlights the potential of electrospun nanofiber composites loaded with herbal extracts and metal nanoparticles as effective wound healing agents. Herbal extracts, known for their antioxidant, anti-inflammatory, and antibacterial properties, contribute significantly to therapeutic outcomes. The incorporation of metal nanoparticles further enhances antimicrobial activity and accelerates the healing process. This review provides a comprehensive overview of the fabrication methods, efficacy, and safety of electrospun herbal extract-loaded metallized nanofiber composites in wound healing applications.

Keywords: Nanofibers; electrospinning; Multimodal nanostructure; Wound healing.

1. INTRODUCTION

Wound dressing is essential for healing, providing a protective barrier and supporting recovery. The global demand for wound care is increasing, with millions suffering from burns and chronic skin ulcers. In the U.S. alone, records show 1.25 million burn patients and 6.5 million with chronic ulcers [1]. In 2021, A survey from 470 hospitals in the U.S. showed that 398,000 patients with burn injuries and 368,000 patients with other inflammatory conditions of skin and subcutaneous tissue received medical treatment [2]. The WHO forecasts 180,000 annual burn deaths and over 640 million diabetic ulcer cases by 2030 [3,4].

There isn't a single dressing that universally suits

every condition; instead, clinicians should evaluate each wound individually and choose the appropriate dressing accordingly. Plain gauze, despite its affordability, has limitations, leading to the development of various wound dressings such as films, foams, sponges, hydrogel, and nanofiber dressings. Ideally, a dressing for a specific wound should absorb fluid, protect against microbes, allow gas exchange, maintain a moist environment, be non-toxic, biocompatible, degradable, and promote angiogenesis and tissue regeneration while being easy to replace and remove without sticking to the wound [5,6].

Nanofiber dressings, particularly created through electrospinning, offer advantages over conventional options by mimicking tissue and providing an optimal wound repair environment. They excel in meeting diverse requirements and can incorporate therapeutic or antimicrobial agents for added functionality [1]. Wang et al. (2022) prepared a structurally stable Poly (DL-Lactic-co-caprolactone) (PLCL) scaffold as an

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"electronic skin" that transmits endogenous bioelectricity by absorbing wound exudates, thereby promoting the treatment of diabetic wounds [7]. Hu et al. (2023) designed an ultra-thin, breathable, and flexible Janus nanofiber dressing using polyvinylidene fluoride (PVDF) and polycaprolactone (PCL), which can unidirectionally drain excess exudate and kill local bacteria [8]. Lee et al. (2015) developed a nanofibrous membrane using collagen (Col) and Poly Lactic-co-Glycolic Acid (PLGA) to enhance diabetic wound healing. The PLGA/Col nanofiber membrane exhibited sustained release of high concentrations of glucophage for over three weeks, indicating its capacity for prolonged drug delivery. Experimental results showed that Col/PLGA membranes incorporated with glucophage were highly effective in promoting early-stage diabetic wound healing [9]. Anand et al. (2022) prepared multifunctional nanofiber scaffolds based on polyvinyl alcohol/sodium alginate/silk fibroin and loaded with *Centella asiatica*, demonstrating good antibacterial effects against *Pseudomonas aeruginosa* and *Staphylococcus aureus* and promoting wound healing in diabetic rats [10]. Poornima and Korrapati (2017) developed a nanofiber wound dressing consisting of chitosan (CS) and PCL using coaxial electrospinning technology. The dressing loaded with ferulic acid and resveratrol, exhibited antioxidant activity, high compatibility, with epidermal keratinocytes (HaCaT) *in vitro*, and accelerated wound cuts healing *in vivo* [11].

Electrospinning, a cost-effective and straightforward process, is employed to create nanofibers suitable for bandages. These nanofibers, with their extensive surface area and porous nature, can accommodate various substances, including medicines, vitamins, minerals, and

herbal extracts, allowing controlled drug release by adjusting fiber structure and morphology [12,13].

This review explores the wound healing process, the concept of electrospinning to produce nanofiber mats for wound dressing, and the potential role of herbal-loaded metallized electrospun nanofibers in promoting wound healing while ensuring safety.

2. WOUND HEALING

Wounds, classified as acute or chronic, disrupt normal skin structure and function. The ideal wound healing process involves organized cell migration and angiogenesis, progressing through hemostasis, inflammation, proliferation, and maturation phases. Local wound treatment aims to address pain, itching, infection, and bleeding, with chronic wounds presenting additional challenges like managing excess exudate and unpleasant odor. Figure 1 illustrates the different phases of wound healing.

The wound healing process begins with events focused on achieving hemostasis, involving a cascade of serine protease events preventing blood loss and leading to the formation of a fibrin clot. The inflammation phase, starting 72 hours post-injury, includes molecular signals facilitating immune cell infiltration and pathogen elimination. The proliferation phase, post-tissue injury, involves angiogenesis and re-epithelialization, driven by various signals. Remodeling, commencing two to three weeks after the injury, focuses on achieving maximum tensile strength through ECM reorganization, resulting in less vascular scar tissue and tissue structure recovery [1,14–16].

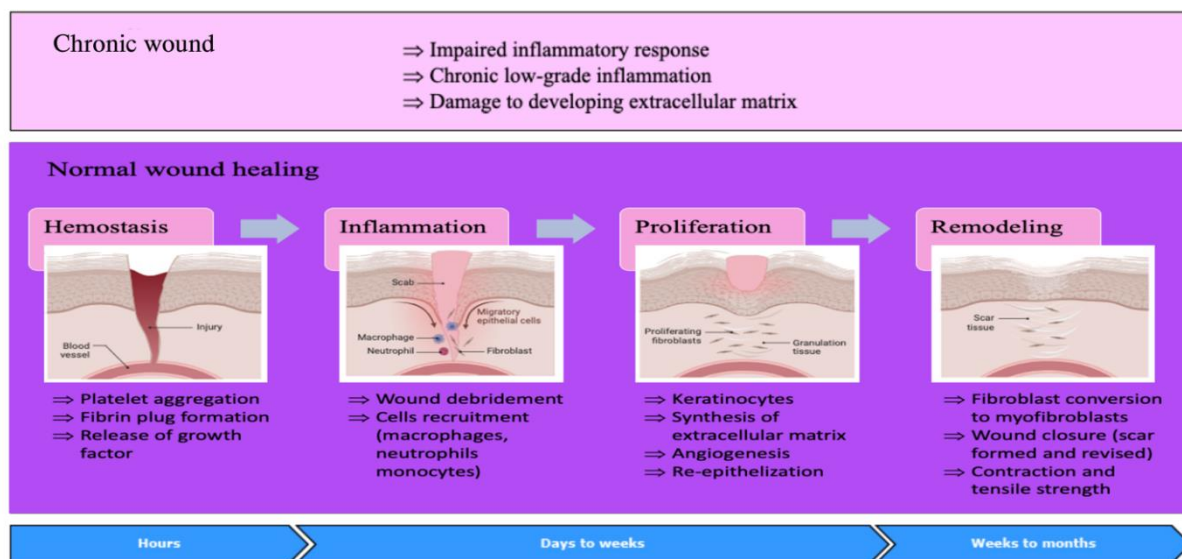


Figure 1. Wound healing phases

Therapeutic options such as coagulants, local anesthetics, anti-inflammatories, and antimicrobial agents can be employed to promote wound healing. However, it's important to note that no single treatment modality can address all aspects of the healing process [16].

The speed at which a wound heals, the strength and function of the healed skin, and the aesthetic appearance of the resulting scar can all be significantly influenced by the proper application and replacement of a dressing. While a moderately moist wound bed can facilitate healing, excessive moisture can lead to maceration. Ideally, a dressing for a specific wound should absorb excess drainage while maintaining an optimal level of moisture. In addition to these primary functions, certain dressings may also offer secondary benefits such as reduced pain during changes, odor control, anti-inflammatory or mild debridement properties, and local antibacterial actions [6,16].

3. ELECTROSPUN NANOFIBERS FOR WOUND HEALING

Nanofiber dressings have garnered attention for their

superior qualities compared to traditional options, offering improved anti-inflammatory and antimicrobial properties, better exudate absorption, prolonged dressing lifespan, and enhanced mechanical strength [14]. Nanotechnology advancements are crucial for overcoming the limitations of conventional dressings and enhancing wound healing outcomes. Nanofiber mats, with their high porosity and efficient gas permeation, address these limitations by promoting hemostasis, exudate management, moisture retention, skin regeneration, and cellular respiration [17]. Additionally, electrospun mats with added functionality can serve as personalized bandages [18]. These advantages not only improve patient comfort by reducing dressing changes but also contribute to cost-effective treatment [12]. This review discusses various approaches to achieving these benefits.

3.1. Basic Principles of Electrospinning

Electrospinning is an electrohydrodynamic process where electrically charged fluids are set in motion by applied electric fields. In this process, a liquid droplet is electrified to generate a jet, which then undergoes

stretching and elongation to form fibers. The electrospinning apparatus includes a high-voltage power supply, a collector, and a spinneret. As voltage is applied, the electrospinning fluid is injected into the spinneret, gradually changing its morphology until it reaches the

critical voltage. At this point, the droplet at the tip, supported by surface tension, forms a Taylor cone. The liquid jet must evaporate before fibers collect on the collector, reaching a specific distance and entering the bending and whiplash stage [1,5,12,14].

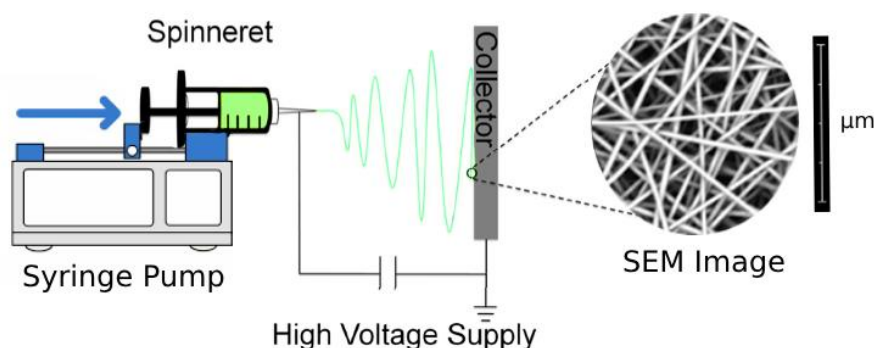


Figure 2. Elcctospinning basic principle

Several factors influence electrospinning and can be categorized into three main groups: apparatus, precursor solution, and environmental conditions. Apparatus-related variables include the setup type, collector type (stationary or rotating), and parameters such as voltage, spinneret-to-collector distance, and flow rate. The properties of the precursor solution—such as conductivity, surface tension, viscosity, and concentration—depend on the choice of polymer and solvent. The polymer concentration must be adjusted to a critical value to produce uniform nanofibers without beads. When the polymer concentration is too low, the entangled polymer chains may break into fragments before reaching the collector, resulting in bead formation. Conversely, if the polymer concentration exceeds a critical threshold, it may disrupt the solution flow through the needle tip, leading to defective or beaded nanofibers.

Environmental conditions, particularly temperature and humidity, also influence fiber synthesis and should be carefully controlled. Higher temperatures reduce solution viscosity, leading to a decrease in average fiber diameter. In contrast, high humidity can induce polymer swelling, which increases the average fiber diameter [19].

Precursor solution is usually made of polymer solutions or polymer melts. The polymer matrix can be synthetic, natural, or a sensible blend of polymers to produce the required properties of the nanofiber. The most commonly used polymers are summarized in Table 1.

To create wound healing scaffolds, biopolymers are often mixed with synthetic polymers to alter the porous fiber mat's degradative, mechanical, and/or morphological properties to meet the individual needs of each patient [5].

Table 1: Most commonly used polymers' types and applications [5,20,21]

Category		Polymer Examples		Applications
Synthetic	Biocompatible	• Poly(vinyl alcohol) (PVA) • Poly(lactic acid) (PLA) • Poly(glycolic acid) (PGA) • Poly(lactic-co-glycolic acid) (PLGA) • Poly(ethylene oxide) (PEO) • Polycaprolactone (PCL) • Poly(hydroxybutyrate) (PHB)		• Tissue engineering • Drug delivery • Wound healing • Scaffolds for cell growth • Filtration
		Natural	Polysaccharide	Plant
Animal	• Chitosan (CS) • Hyaluronic acid			
Protein	• Gelatine • Collagen • Silk fibroin			

3.1.2. Incorporation of bioactive agent into electrospun nanofibers

Loading an active agent into nanofiber mats can be achieved through various methods, depending on the desired properties of the final product [5]. For burst release, the active agent is suspended in the electrospinning blend to distribute it throughout or on the fiber's surface. Coaxial electrospinning is employed when abrupt release is undesirable or when the active agent is solvent-labile, forming core/shell fibers using a concentric needle configuration. Another approach involves using an emulsion as the feeding solution, with a surfactant added during electrospinning to create a core/shell structure. This technique protects proteins, DNA, and peptides from harsh solvents, enabling their incorporation. Finally, dip-coating imparts desired qualities to electrospun mats by immersing them in a solution [17].

Loading efficacy and release profiles can be assessed using appropriate analytical methods, such as spectroscopy or high-performance liquid chromatography [22]. Various active agents—including antibacterial particles, growth factors, stem cells, vitamins, and other effective wound-healing factors—can be incorporated into electrospun nanofibers.

In one study, lemon oil was used as a highly antibacterial active agent to create cellulose acetate nanofiber membranes. The investigation examined various properties and demonstrated that lemon oil-loaded cellulose acetate nanofibers maintained antibacterial efficacy, eliminating *Escherichia coli* and *Staphylococcus aureus* even at low lemon oil concentrations. The nanofiber structure retained its antibacterial properties after two months, suggesting its potential as a long-lasting bioactive wound dressing [23].

4. MEDICINAL PLANTS IN WOUND HEALING

Throughout history, herbal remedies have been valued for their healing properties, with many plants used in traditional medicine for treating burns, wounds, and cuts. These remedies often offer antioxidant, antibacterial, and anti-inflammatory benefits. Illustrative examples include *Sphagneticola trilobata*, *Aloe vera*, *Panax ginseng*, and *Hypericum perforatum*. Extracts from plants like *Centella asiatica* and *Curcuma longa* have shown support for key wound healing processes like angiogenesis and collagen formation [24,25]. Researchers are now exploring new formulations and dressings to create stable, sustainable,

and cost-effective wound care treatments. The use of innovative materials and advancements in nanotechnology have led to improved wound management, focusing more on patients' needs [26].

5. METALLIC AND INORGANIC NANOPARTICLES IN WOUND HEALING

Metallized nanomaterials, featuring unique physicochemical characteristics like a large specific surface area and excellent surface properties, play a crucial role in biomedicine. Nanoparticles like gold, silver, iron, silicon, germanium, and cadmium selenide possess antibacterial properties, aiding wound healing and combating antibiotic resistance. These nanoparticles are increasingly utilized in medical applications for drug delivery, imaging, diagnostics, and tissue engineering [27,28]. In addition, incorporating inorganic nanoparticles into nanofibers offers a promising approach to regulate release kinetics from biomaterials.

Gold nanoparticles applied topically speed up wound healing by boosting the production of growth factors, cytokines, and collagen [29]. Silver nanoparticles fight bacteria and are useful for treating wounds [30]. Zinc oxide nanoparticles help tissues regenerate by promoting processes like tissue granulation and collagen deposition [31]. Mesoporous silica nanoparticles (MSNs) are versatile in medical applications and aid wound healing by helping blood clot [32–34].

6. COMBINATION OF HERBAL EXTRACT AND METALLIC/INORGANIC NANOPARTICLES IN THE FABRICATION OF NANOFIBROUS WOUND DRESSING

There are several parameters depending on the application of nanofibers. The water absorption capacity of electrospun nanofibers plays an important role in wound healing. Nanofibers can retain moisture and nutrients in the wound area and also increase cell adhesion and proliferation with a higher swelling ratio. Adequate mechanical

properties of engineered electrospun nanofibers are another important parameter for the formation of new skin tissue and resistance to biological degradation during the wound healing process. Plant extracts may act as a reinforcing agent and increase the tensile strength of nanofibers, leading to enhanced wound healing. On the other hand, the solubility of plant extracts is important in choosing the type of nanofibers, and depending on the type of plant extract, suitable biomaterials are selected for making nanofibers[26]. Utilizing nanotechnology for improved phytochemical delivery involves incorporating plant-derived substances into nanomaterials like nanoparticles and nanofibers. These environmentally friendly and non-toxic nanocarriers provide controlled release of active plant materials in wound treatment. Plant extract-loaded nanofibers, with unique properties, exhibit antimicrobial, anti-inflammatory, antioxidant, antiseptic, and antiviral effects, showcasing their potential in wound healing [35,36].

In a study, St. John's Wort infused oil was incorporated into a CS cryogel for use as a wound dressing material. The investigation revealed antimicrobial activity, particularly against *E. coli* and *L. pneumophila*. Additionally, the presence of free radical scavenging activity makes it a promising candidate for wound healing [37].

Another study introduced a silk fibroin-curcumin-based nanofiber in combination with PCL and PVA for sustained drug release and oxygen delivery to diabetic wounds. *In vivo* studies on diabetes-induced mice demonstrated a higher wound healing rate compared to the control group, highlighting the potential of the nanofibrous tissue formulation with no dermal irritation [38]

Metal nanoparticles can be immobilized on nanofibers, which brings a new generation of nanomaterials that have potential applications in a wide range of fields such as electronics, medicine, sensors. As a result, many efforts have been made to synthesize, identify and use metal nanofiber composites with well-controlled dimensions and properties. this modified fiber can be called metallized nanofibers or composite nanofibers with metallic nanoparticles.

Metallic nanofiber-based composites, created through electrospinning, involve the integration of metal nanoparticles into polymer nanofibers. This combination, known as metallized nanofibers, can be achieved through *in situ* reactions of metallic precursors during electrospinning. Alternatively, precursor metal nanoparticles can be added to the polymer solution, and their nanofibers can be prepared through electrospinning [39]. These nanocomposites offer a unique combination of nanofiber qualities and metallic nanoparticle properties, including formability, stability, and conductivity. Metallized nanofibers find applications in tissue engineering due to their exceptional antimicrobial properties and plasticity [40–43]. They boast strong mechanical properties, providing a non-toxic and antibacterial foundation for constructing drug-loaded wound healing platforms. Metallized nanofibers are new biomaterials obtained by combining metals or metal nanoparticles with nanofibers. Due to their unique physical and chemical properties, metallized nanofibers are rapidly developing in the fields of physical chemistry, materials science, and biomedical applications.

Silver nanoparticles dispersed in a CS matrix are electrospun, resulting in immobilized cubic-structured silver nanofibers [44]. Researchers incorporated MSNs into CS, forming porous CS-silica composite microspheres with hemostatic properties for controlling traumatic hemorrhaging. Positive results were observed in a rat liver laceration model, with no adverse effects in cytotoxicity and histological analysis [45]. Additionally, gentamicin-loaded MSNs-PCL nanofibers were produced, demonstrating sustained antibiotic release to prevent post-surgery wound infections. MSNs played a crucial role in drug delivery, acting as release modifiers and bioactivity protectors. The antimicrobial activity of the fibers was confirmed, with 50% drug release after 40 hours and complete release after 136 hours [22].

Herbal extract-loaded metallized nanofibers have garnered research attention. In a study, MSNs were

incorporated into PCL/Curcumin nanofibers. Antibacterial studies encompassing both gram-positive and gram-negative bacteria, *in vitro* experiments with Swiss 3T6 cell lines, and *in vivo* studies on female Wister rats were conducted. Results indicated enhancements in the zone of inhibition, tissue re-epithelization, collagen deposition, and granulation tissue formation. Using the fabricated nanofibers on rats demonstrated 99% scar-less wound healing within 3 weeks [46].

7. SAFETY OF HERBAL EXTRACT-LOADED MULTIMODAL NANOFIBERS

Ensuring the safety of nanofibers loaded with various active ingredients requires comprehensive toxicity testing. Key assessments, such as *in vitro* cytotoxicity, irritation, and sensitization, form the forefront of toxicity evaluations. Additionally, genotoxicity serves as a crucial endpoint, underscoring the necessity of its application to novel materials.

7.1. Genotoxicity evaluation of nanomaterials

Genotoxicity from nanomaterial exposure can induce transient or permanent genetic changes through direct or indirect mechanisms. Direct mechanisms involve physical contact between nanomaterials and the nucleus, leading to DNA damage like chromosomal breaks. Indirect mechanisms occur when nanomaterials dissolve, releasing harmful ions or reactive oxygen species (ROS), inducing oxidative stress. Additionally, molecules released by nanomaterials can interfere with DNA replication and cell division, further contributing to genotoxic effects.

The genotoxicity of nanomaterials depend on factors like dose, exposure duration, size, surface characteristics, chemical composition, and shape. The genotoxicity mechanism is primarily influenced by the uptake method. Smaller nanomaterials (<10nm) have a higher chance of entering the nucleus directly through nuclear pores, while larger ones (>10nm) may enter through endocytosis or during mitosis when the nuclear membrane dissolves. Indirect damage is more common, triggering inflammation

and chronic immune cell responses [47–49].

Genotoxicity biomarkers include gene mutations, chromosomal damage, and DNA damage. In the genotoxic risk assessment of nanomaterials, three commonly employed *in vitro* methodologies are: (a) Tests for mammalian gene mutation, utilizing Thymidine kinase (Tk) and hypoxanthine phosphoribosyltransferase (Hprt) as a basis for gene mutation, (b) Chromosomal damage tests, with clastogenicity (structural chromosome damage) and aneugenicity (numerical chromosome alterations) as key endpoints, employing assays such as the micronucleus test, and (c) the comet test for assessing DNA damage, serving as the preferred technique for evaluating DNA strand breakage and quantifying damage to cellular DNA [47,48].

It is worthy to note that, before introducing nanomaterial stock solutions to cultured cells in *in vitro* genotoxicity testing systems, they are typically diluted in a cell culture medium. The interactions of nanomaterials, whether particle-particle or particle-cell, undergo alterations when suspended in cell culture medium or other biological fluids. These changes may affect the nanomaterials size, shape, composition, surface chemistry, as well as the temperature, pH, ionic strength, and protein content of the surrounding fluid. Techniques such as dynamic light scattering (DLS) and nanoparticle tracking analysis (NTA) determine nanomaterial size and distribution, while microscopic methods like atomic force microscopy (AFM), scanning electron microscopy (SEM), and transmission electron microscopy (TEM) directly observe nanomaterials. Zeta potential, measuring the electrostatic potential of the electrical double layer where nanomaterials are suspended and describing their surface charge.

7.2. Cytotoxicity testing

Various cytotoxicity assessment techniques exist, with viability tests being common. These tests, following OECD Test Guidelines 476 and 490, measure cell proliferation, survival, and colony formation. Methods like Trypan blue exclusion or dual staining with fluorescent dyes indicate damaged cell membranes. Intracellular

material leakage, detected by LDH assays like Alamar Blue or MTT tests, identifies dead cells. Studies evaluating nanofiber safety include one examining composite CS microspheres loaded with mesoporous silica. Using the MTT method on mouse embryonic fibroblast cells, it demonstrated good biocompatibility and non-cytotoxicity, suggesting their safety for medical use [47,48].

7.3. Irritation

Historically, skin irritation and corrosion experiments often relied on animal testing, specifically involving rabbits following OECD Test Guideline (TG 404). Ethical considerations have led to the exploration of alternative *in vitro* methods to assess skin irritation and corrosion, seeking to replace animal-based approaches [50]. Several three-dimensional (3D) human skin models, such as SkinEthic™, EpiDerm™, and EpiSkin™, serve as substitutes for *in vivo* tests, utilizing reconstructed human epidermis closely mimicking histological, morphological, biochemical, and physiological characteristics of human skin [51,52]. *In vitro* testing with cultivated skin-derived cell lines has assessed the skin irritation potential of nanomaterials. For instance, titanium nanoparticles and quantum dot nanoparticles exhibited reduced viability in cultured HaCaT human keratinocytes but showed no effect on a human skin equivalent model [53,54]. Conversely, nano silica nanoparticles induced cell death in cultured human keratinocytes but demonstrated no cytotoxicity in a human skin equivalent model [55]. Exposure of EpiDerm™ to TiO₂ nanoparticles did not cause skin irritation symptoms in one study [56]. Furthermore, the application of TiO₂ nanoparticles and ZnO nanoparticles, either alone or in combination, did not induce irritation or corrosion on undamaged rabbit skin or KeraSkin, a 3D human skin model [57].

7.4. Sensitization

While many studies have explored skin sensitization caused by certain chemicals, limited research exists on the potential sensitization effects of nanomaterials. The skin sensitization process involves the covalent interaction of

electrophilic substances with primary amines in skin proteins and nucleophilic thiol as the initial step. Subsequently, inflammatory reactions and modifications in gene expression occur in keratinocytes, involving cell signaling pathways like the antioxidant/electrophile response element (ARE) [58]. The ARE-Nrf₂ Luciferase KeratinoSensTM test is a tool representative of these events, capable of distinguishing between skin sensitizers and non-sensitizers in line with the United Nations Globally Harmonized System of Classification and Labelling of Chemicals standards [53].

In a study by Kim et al., the ARE-Nrf2 Luciferase KeratinoSensTM test assessed skin sensitization induced by seven different metal oxide nanoparticles, including nickel oxide, titanium oxide, copper oxide, cobalt oxide, zinc oxide, iron oxide, and cerium oxide on KeratinoSensTM cells. Notably, copper oxide nanoparticles produced a positive response, while the other nanoparticles exhibited

no response [59].

8. CONCLUSION

Electrospinning technology finds applications in medicine, including tissue engineering scaffolds, drug delivery, and wound dressings. Simultaneous production of nanofibers with natural and mixed polymers enhances biocompatibility, biodegradability, and physical characteristics. The nanofibers, with high surface area and extracellular matrix -like properties, offer a unique delivery method for herbal medicine extracts and bioactive components. As genotoxicity is a main concern of nanomaterials, more studies for a better understanding of the mechanism of toxicity and the development of more robust *in vitro* toxicity assay methods. Further studies are needed to explore herbal loaded metallized nanofiber efficacy, safety, co-encapsulation with inorganic materials, synergistic activity, controlled release, and scalability.

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مراجعة لتطبيق مركبات الألياف النانوية المعدنية المحملة بمستخلصات الأعشاب المغزولة كهربائياً كمحفز لالتئام الجروح: التصنيع، الفعالية، والسلامة

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ملخص

يُعد الغزل الكهربائي تقنية واحدة لتطبيقات التئام الجروح، حيث يُنتج هياكل نانوية تُشبه النسيج خارج الخلية الطبيعية. تُركز هذه المراجعة على مركبات الألياف النانوية المعدنية المُحمَّلة بمستخلصات عشبية مُغزولة كهربائياً كمُحفِّزات لالتئام الجروح. تُعزز المستخلصات العشبية، المعروفة بخصائصها العلاجية كمضادات الأكسدة والعوامل المضادة للبكتيريا، العناية بالجروح. كما يُعزز دمج الجسيمات النانوية المعدنية الوقاية من العدوى وتعزيز التئام الجروح. تهدف هذه المراجعة إلى تقديم لمحة عامة عن مركبات الألياف النانوية المعدنية المُحمَّلة بمستخلصات عشبية مُغزولة كهربائياً، وتصنيعها، وفعاليتها، وسلامتها في تطبيقات التئام الجروح.

الكلمات الدالة: الألياف النانوية؛ الغزل الكهربائي؛ بنية نانوية متعددة الوسائط؛ التئام الجروح.

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