Curcumin Embedded Electrospun Nanofibers for Wound Healing

Subjects: Surgery

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Chronic wounds impose a significant burden on individuals and healthcare systems all over the world. Through clinical and preclinical investigations, inflammation and oxidative damage have been established as the primary causes of chronic wounds. These skin sores are easily exposed to microorganisms, which in turn cause inflammation and hinder the healing process. Additionally, microorganisms may cause an infection that prevents collagen production and reepithelialization. Curcumin's antioxidant, anti-inflammatory, and anti-infectious characteristics, among others, have been identified as useful for diabetic wound healing management. However, curcumin has a few disadvantages, such as limited bioavailability, pH-dependent instability, water insolubility, slow cell absorption, and fast intracellular metabolism. These constraints necessitates the development of a suitable transporter to improve curcumin's stability, bioavailability, therapeutic efficacy, and solubility.

Keywords: curcumin ; electrospinning ; nanofibers

1. Potential of Curcumin in Skin Disorders

Acute skin infections may be caused by several microorganisms, such as bacteria, fungi, viruses, and parasites. *S. aureus* is responsible for many skin diseases, including folliculitis, impetigo, boils, and cellulitis. Propionibacterium acnes and *S. epidermidis* are both constituents of the microbiota of human skin, and both have a direct role in the formation of acne vulgaris. *Corynebacteria*, *Propionibacteria*, and *Staphylococci* are the most prevalent bacterial genera responsible for this sickness. These bacteria, which ordinarily reside on the skin as commensals and are essential for maintaining skin homeostasis, may also cause acute skin infections as opportunistic pathogens [1]. Immunocompetent people are not often afflicted with invasive primary skin infections.

However, as the number of germs resistant to numerous medications continues to increase, bacterial skin infections may continue to be challenging to treat. Some staphylococcal bacteria have evolved resistance to beta-lactamase-resistant penicillins that are both naturally occurring and semisynthetic, i.e., methicillin, dicloxacillin, and oxacillin. Propionibacterium acnes is naturally resistant to antibiotics such as sulfamides, aminoglycosides, mupirocin, and 5-nitroimidazole while being sensitive to many antibiotics. Propionibacterium acnes antibiotic resistance has progressively risen over the last decade, becoming a global concern, with erythromycin and clindamycin showing the most significant resistance and tetracycline resistance occurring less frequently, concurrent with the most common topical treatment of macrolides [2][3][4]. In addition to bacteria, several fungal species may cause superficial mycoses. Dermatophytes are the most prevalent fungal pathogens responsible for skin diseases. Trychophyton rubrum has become the most pervasive dermatophytic fungi globally, mainly causing *tinea pedis* and *tinea unguium* [5]. Like bacteria, fungi have resisted traditional antimycotic medications in recent years. In addition, the treatment of cutaneous mycotic infections is often complicated owing to the scarcity and toxicity of available antifungal medications. Treating these diseases by creating innovative antifungal agents capable of targeting particular cellular and molecular pathways implicated in fungal pathogenicity is vital [6]. *S. aureus* bacteria are sensitive to the inhibitory action of curcumin, according to in vitro investigations. In addition, the effectiveness of curcumin against Methicillin-resistant staphylococcus aureus (MRSA) has been shown either alone or in combination with conventional medicines [7].

This concern should restrict the long-term use of topical and systemic antibiotics in treating skin conditions such as acne vulgaris. Consequently, innovative therapeutic techniques are necessary to treat skin infectious illnesses. In recent years, scientists have prioritized the creation of natural products produced from plants as an alternative or supplement to conventional treatment. Indeed, it has been shown that the bioactive aromatic components extracted from several medicinal plants offer potential antimicrobial effects. In this context, the antimicrobial activity of curcumin has been

intensively studied owing to its wide range of applications and safety profile, even at the high dosages used in clinical studies [8][9][10].

Curcumin's effectiveness against skin infection illnesses has also been explored in vivo and in vitro [11][12][13][14]. Over the last three decades, extensive research has conclusively shown curcumin's efficacy against skin infections and diseases. Curcumin may be an effective option for treating bacterial and fungal skin disorders and conquering multidrug-resistant infections.

2. Biomedical Applications of Curcumin

The potent anti-microbial, anti-inflammatory, antioxidant, and other qualities of curcumin make it a particularly apt molecule for treating wounds and many inflammatory disorders, including diabetes, arthritis, inflammatory bowel disease, atherosclerosis, neurological disorders, and Alzheimer's disease [15][16]. Due to its excellent pharmacological qualities, Curcumin has a promising future in biological applications, such as cardiovascular disorders, chemotherapeutics, radiosensitizing, chemosensitizing, and wound healing, as shown by many in vitro and in vivo investigations [17][18]. Curcumin's antioxidant properties are demonstrated by its capacity to shield fibroblasts and keratinocytes from damage brought on by hydrogen peroxide and to lessen oxidative stress in Alzheimer's patients [19].

3. The Effects of Curcumin on Wound Healing

Curcumin has been demonstrated to heal dermal wounds by reducing reactive oxygen species (ROS), which are chemically reactive molecules containing oxygen and the leading cause of inflammation, including lipid peroxyl radicals (LOO•), superoxide radicals (O_2•), nitrogen dioxide radicals (NO_2•) and hydroxyl radicals (•OH). These forms are associated with the onset of oxidative stress, which limits granulation tissue development and remodelling as a crucial element in wound healing [20][21][22]. Curcumin therapy in diabetic mice increases granulation tissue growth, neovascularization, and the manufacture of collagen, a protein in the extracellular matrix. Additionally, it has been shown that curcumin may help wound healing in diabetic mice. Due to its ability to increase fibroblast and vascular density in wounds while also squelching free radicals, it has been extensively utilized to speed up wound healing and decrease healing timeframes. These qualities have established curcumin as a unique substance for treating diabetic wounds and inflammatory illnesses. Curcumin's remarkable antioxidant, anti-inflammatory, and anti-infectious properties, as shown in, have been discovered to be effective in treating diabetic wound healing [23][24][25].

3.1. Inflammation

Inflammation is often considered the first phase of optimum wound healing since it is one of the most crucial [26]. Because tissue injury induces acute inflammation early, reducing inflammation may enhance wound healing. Curcumin is well-known to contain anti-inflammatory properties, and various research efforts, including clinical trials, have shown that it interacts with various inflammatory cytokines in multiple disorders [27][28]. Curcumin's most significant effect in controlling inflammation is suppressing the generation of tumor necrosis factor (TNF) and interleukin1 (IL1), two essential cytokines that govern inflammatory responses generated by monocytes and macrophages [29]. Curcumin also inhibits the nuclear factor kappa light chain enhancer of activated B cells (NFB), a transcription factor that controls many genes implicated in inflammatory responses. Curcumin influences the pathways involved in the activation of NFB via several kinases. Notably, NFB is also implicated in response to oxidative stress; thus, curcumin may influence oxidative stress and inflammation [30]. According to the research, wound healing is enhanced by enhancing the natural inflammatory response generated by curcumin. By lowering the inflammation of the injured skin, the damaged skin can increase and rebuild more rapidly and advance to subsequent stages of healing [31].

Curcumin controls the levels of protein kinase C (PKC), protein kinase C-2 (PKC-2), and mitogen-activated protein kinase (MAPK) [32]. By suppressing vascular endothelial growth factor (VEGF), NF-B, and activator protein-1 (AP-1), it reduced the rapid buildup of advanced glycation end-products (AGE) and cross-linking of collagen in the tail tendons of diabetic rats [33]. In high glucose-induced microvascular endothelial cells of diabetic rat hearts, curcumin decreased both endothelial nitric oxide synthase (eNOS) and inducible nitric oxide synthase (iNOS) levels [34][35]. Its antioxidant activity alleviated endothelial cell dysfunction and PKC inhibition in Streptozotocin (STZ)-induced diabetic rats and mice [36]. It also reduced the vascular dysfunction brought on by diabetes in STZ rats by decreasing COX-2, NF-B, and PKC activity [37]. By lowering TNF and aortic Reactive Oxygen Species (ROS) and activating heme oxygenase (HO-1) in diabetic rats, curcumin improved dysregulated vascular contractility [38].

3.2. Antioxidant

ROS are crucial for cellular and metabolic activities, such as intracellular communication, differentiation, immunity, and death. The immune system also employs reactive oxygen species (ROS) to defend against bacteria in a wound [39]. However, prolonged exposure to high amounts of ROS results in oxidative stress, which is harmful to cells. Oxidative stress is a crucial element in the wound healing process, often working to impede skin regeneration. Oxidative stress causes lipid peroxidation, DNA degradation, and enzyme inactivity and is the primary cause of wound inflammation. When applied topically, antioxidants can promote wound healing and neutralize free radicals [40][41]. Antioxidant effects of curcumin have been shown in clinical settings. In vitro, a collagen matrix embedded in curcumin showed radical-scavenging action against peroxy radicals [42]. In another investigation, the application of the curcumin in vivo rat model resulted in a considerable decrease of H_2O_2 induced damage to fibroblasts and keratinocytes. In similar research, curcumin was shown to eliminate H_2O_2 from keratinocytes and fibroblasts [43].

3.3. Fibroblast Proliferation

Fibroblast infiltration into the wound area is required to form granulation tissue and collagen synthesis and deposition [44] [45]. According to research, dermal wounds that do not heal within the expected time frame have reduced fibroblast migration and proliferation within the wound site [46]. Numerous research efforts have been conducted to assess fibroblast penetration in curcumin-treated wounds; it has been demonstrated that four days after the lesion was excised, myofibroblasts were seen at the location of the wound cured with the COP. It is essential to keep in mind, nevertheless, that curcumin's ability to increase fibroblast penetration in wounds treated with it is only possible at lethal doses. Curcumin promotes apoptosis in vitro fibroblast models at high concentrations (25 M), owing to oxidation and the formation of free radicals. Lower dosages (5 and 10 M) did not affect fibroblast shape, and no apoptosis has been seen in curcumin-treated fibroblasts [47].

3.4. Angiogenesis

Angiogenesis is a critical phase in wound healing; it is essential for oxygen and nutrients to be delivered to cells by forming new blood vessels at the wounds' locations [48]. Curcumin's topical application to burned wounds in rats has considerably enhanced angiogenesis and expedited wound healing [49]. Curcumin stimulated the neovascularization at the diabetic wound site directly by the increased expression of angiogenic factors such as VEGF, TGF-β1, and other factors such as HIF-1a, SDF-1α, and HO-1, as well as indirectly, by anti-inflammatory and antioxidant action [50].

3.5. Granulation Tissue Formation

Granulation tissue is distinguished by the creation of tiny capillaries, which occurs in tandem with fibroblast infiltration (about 4 days postinjury), allowing for the generation of ECM [51]. Granulation tissue promotes reepithelialization by providing a stable foundation for epithelial cell migration to the wound site. Excision injuries on the backs of treated rats with curcumin embedded with chitosan alginate formed more granulation tissue than wounds treated solely with sterile gauze reported that, compared to the control group, exposure with curcumin encapsulated into collagen matrix enhanced the amount of hydroxyproline in wounds [52][53]. During the creation of granular tissue, fibroblasts differentiate into myofibroblasts, and the presence of hydroxyproline indicates the existence of myofibroblasts.

3.6. Collagen Deposition

ECM is required for wound reorganization and remodeling. It is a supporting base for the injured area cells, containing various proteins and polysaccharides. However, collagen accounts for 70–80% of skin ECM [54]. A substantial portion of collagen should be generated and deposited on the injured area to promote wound healing and scar tissue formation [55]. In the curcumin-treated group, the collagen is denser and more aligned reported. When researchers covered wounds with curcumin-based bandages, they had more collagen than the control group; the suggestion that this group made collagen was strongly crosslinked [56][57].

3.7. Apoptosis

To proceed wound healing to the proliferative phase, apoptotic processes must occur to destroy inflammatory cells in the injured area [58]. Although the precise mechanism of apoptosis caused by curcumin is unknown, it has been proposed that curcumin could cause apoptosis because of its propensity to generate free radicals [59]. The amount of apoptosis rose on the 11th day following wound therapy in the reference group as opposed to wounds that had received curcumin treatment. This finding establishes wounds that haven't been treated are still in the first stage of healing, while wounds that have been treated with curcumin have moved on to the next stage, called proliferation [60].

3.8. Wound Contraction

Wound contraction is one of the final steps of wound healing. It needs communication between cells, the extracellular matrix, and cytokines. When fibroblasts differentiate into myofibroblasts two weeks after wound surgery, wound contraction begins. Myofibroblasts promote wound contraction by increasing smooth muscle actin expression in granulation tissue [61]. By means of planimetric wound measurement, it was discovered that administering curcumin to the wounds considerably accelerated wound closure (by 20%) as compared to the control; researchers found that wounds in rats treated with curcumin-loaded sponges healed at a rate of 90% after 12 days, compared to 74% in the control group. TGF is a type of cytokine that is released by many cells, including fibroblasts. It helps heal wounds and build up collagen [62][63]. Curcumin-treated wounds had more TGF than the control, which provided a higher number of fibroblasts [64]. Furthermore, the soft tissue in diabetic mouse wounds showed increased TGF expression in the curcumin-treated group [65].

3.9. Re-Epithelialization and Remodeling

The epidermis is the skin's outer layer and is a protective barrier against physical, chemical, and microbiological penetration and harm [66]. Epithelialization is the process by which keratinocytes move up from the bottom layers of the skin and multiply. As the last steps in healing a wound, reepithelialization and remodeling are essential for the epidermis to form a strong barrier. Compared to the control group, curcumin-treated wounds in a rat model were epithelialized, and the epithelialization period was decreased from 23 to 11 days [56]. Curcumin exhibits multiple biological activities in treating various aspects of diabetic wound complications.

4. Curcumin Embedded Electrospun Nanofibers for Wound Healing

Merrell et al. developed Polycaprolactone (PCL) nanofibrous scaffolds incorporated with curcumin to treat diabetic wounds.The amount of PCL employed in the nanofiber preparation process impacted how beads developed along the nanofibers. Nanofibrous scaffolds with an average diameter of between 300 and 400 nm were produced utilizing the electrospinning technique incorporating 15% (*w*/*v*) PCL. The in vitro drug release characteristics of curcumin from the nanofibers were maintained for 3 days under physiological circumstances and could be designed to transport a quantity considerably lower than the reported cytotoxic concentration while still being therapeutically effective. The human foreskin fibroblast (HFF-1) cells in vitro cytotoxicity experiments showed a cell viability of more than 70%, supporting the idea that curcumin-loaded PCL nanofiber scaffolds are not cytotoxic. In contrast to plain PCL, which showed only 60% wound closure in the in vivo wound healing experiment, the curcumin-loaded nanofibrous scaffolds demonstrated an accelerated 80% wound closure in the STZ-induced diabetic rats [67].

Ramalingam et al. developed curcumin-loaded Electrospun poly(2-hydroxyethyl methacrylate)p(HEMA) nanofibrous mats. The in vitro drug release profile of curcumin-embedded nanofibrous mats revealed regulated and controlled curcumin release, proving effective against wound microbial infections. Curcumin-loaded nanofibrous mats inhibited the growth of MRSA and ESBL in vitro [68].

Nguyen et al. developed poly (lactic acid) (PLA) nanofiber scaffolds infused with curcumin for wound treatment. Curcumin encapsulation inside nanofibers scaffolds resulted in a considerable improvement in tensile strength of up to 3.5 MPa, making them acceptable for wound dressing. In vivo wound healing investigations on rats and dorsal wounds indicated 87% and 99% of wound closure on days 7 and 15, respectively [69].

Ravikumar et al. generated curcumin-loaded cellulose acetate (CA) phthalate Electrospun nanofibrous scaffolds. Between 1 and 12 h, the nanofibers loaded with curcumin and the nanofibers without curcumin exhibited a 400% swelling capability, as determined by the swelling analysis. The in vitro diffusion investigation revealed a delayed and prolonged release of the wound-healing agent curcumin [70].

Ranjbar-Mohammadi et al. created PCL and gum tragacanth Electrospun nanofibers embedded with curcumin. The fact that the curcumin-embedded nanofibrous scaffolds were 99.9% and 85.14% effective against MRSA and extended spectrum beta-lactamase (ESBL), respectively, demonstrates their use in the treatment of bacterially infected wounds. In vivo wound healing investigations with injured diabetic Sprague Dawley rats revealed that wound regions healed covered with curcumin-embedded nanofibrous scaffolds on day 15 compared to the control group, in which the wound area decreased by 20.96% [71].

Ranjbar-Mohammadi et al. developed curcumin-embedded nanofibrous scaffolds with outstanding biological characteristics. The nanofibrous scaffolds were free of beads, and the addition of curcumin created a hydrophilic surface

for cell adhesion and growth. In addition, the nanofibers' tensile strength was enhanced by a factor of two- to three-fold, enhancing their mechanical qualities. Curcumin also improved the nanofibers' stability. Over the course of 15 days, the nanofibers stimulated considerable cell growth and proliferation while preserving the cellular shape. The nanofibers' in vitro drug release of curcumin was maintained [72].

Ghaee et al. created PCL-based nanofibrous scaffolds incorporated with curcumin and integrated with gelatin, and chitosan. The nanofibers' porosity ranged from 90.43% and 71.48%, and their pore size was between 101 and 256 μm, making them appropriate for skin tissue regeneration. The nanofibrous scaffolds were cytocompatible with L929 cells and enhanced cell adhesion [73].

Moradkhannejhad et al. created PLA/PEG nanofibrous mats with infused curcumin with a porous nanostructure shape suitable for gas exchange. The average fiber diameter increased from 430 to 750 nm when the PEG1500 concentration rose from 0 to 20 wt%. A regulated release of curcumin was seen in the nanofibers [74].

Mutlu et al. developed curcumin-loaded poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV) nanofibrous mats. Depending on the amount of curcumin present, the mean fiber diameter of the nanofibrous mats ranged from 207 to 519 nm. The modules' elastic and tensile strengths were 5.80 MPa and 6.10 Mpa, respectively. Following the introduction of curcumin, the nanofibers' swelling rate has risen from 50% to 320%. It supported cell adhesion and proliferation in vitro and was biocompatible with L929 murine fibroblasts [75].

Bui et al. created PCL-PEG nanofibrous mats encapsulating curcumin. The manufactured nanofibrous mats had a porous surface, which is essential for cell growth. Compared to ordinary nanofibers, the curcumin-incorporating nanofibers inhibited S. aureus growth better. On day 10, the curcumin-loaded nanofibers accelerated wound healing by 99% compared to the plain PCL-PEG nanofibrous mats, which accelerated wound closure by 59% [76].

Mohammadi et al. created PCL-PEG nanofibrous scaffold encapsulating chrysin-curcumin. In vivo investigations on injured male rats revealed that the wound-healing process was dose-dependent and substantially impacted the inflammatory phase compared to the other phases of wound healing. After 10 days in vivo, there was an increase in IL-6 gene expression, which plays a crucial role in inflammation. iNOS was downregulated, and MMP-2 expression was decreased [77].

Perumal et al. created a curcumin-loaded PLA-hyperbranched polyglycerol nanofibrous scaffold. The fiber had a diameter of 601 nm, and the encapsulation of curcumin into the nanofiber scaffolds caused an increase in the mean diameter of the nanofibers. Compared to the nanofibers PLA alone, the hydrophilic nature of the nanofibers improved regulated drug release, cell proliferation, and adherence. Within 24 h, the nanofibers' swelling ratio increased to 108%. A regulated release pattern followed an early burst release in the in vitro drug release profile under physiological settings. Swiss 3T3 fibroblast cells were used for the in vitro cell viability investigation. The curcumin-loaded nanofibers showed a considerably increased cell vitality of 109% compared to the control's 96% and the plain nanofibers' 100%. Compared to curcumin-loaded PLA nanofibers, the curcumin-infused PLA-hyperbranched polyglycerol nanofibrous scaffold showed a 100% wound closure after 36 h of use [78].

Ramaswamy et al. created tetrahydro curcumin-embedded PCL-PEG Electrospun nanofibers. Because of the enormous surface area, these nanofiber mats displayed high loading effectiveness of 95% curcumin encapsulation into the nanofibers. The swelling capacity of curcumin-embedded nanofiber mats was 205% and 215% for blank nanofibers, indicating a reduction in swelling ability following the addition of curcumin. In vitro, nanofibers maintained drug release profiles from nanofiber mats [79].

Shababdoust et al. created the regulated release of curcumin, an amphiphilic-block segmented polyurethane nanofiber. The average diameter varied between 651 nm and 663 nm, while the porosity ranged between 80.1 ± 0.5% and 91.6 ± 0.4%. The quantity of loaded curcumin influenced the diameter and porosity of the nanofibers. The nanofibers' intense antibacterial activity against *E. coli* and *S. aureus* was shown by the in vitro antibacterial tests. The L929 fibroblast cells treated with the curcumin-embedded nanofibers showed cell vitality ranging from 89% to 92%, demonstrating their cytocompatibility for the wound area. Temperature, pH, and pressure all impacted the in vitro drug release profile of curcumin from the nanofiber mats [80].

Fu et al. developed curcumin-loaded PCL-PEG nanofibers for cutaneous wound healing management. Their sizes ranged from a few hundred nanometers to a few microns. The nanofibrous scaffold demonstrated good cell viability when cultured with rat fibroblast cells, indicating minimal toxicity. Curcumin has an early burst release characteristic followed by a persistent drug release profile in vitro. The curcumin-loaded nanofibrous mats showed a considerable wound closure rate

of 93.3% on day 21 compared to 80.4% and 76.9% wound closure rates for the plain and control nanofiber mats, respectively [81].

Lian et al. created nanofibrous scaffolds made of Silk fibroin (SF) and PLA-PCL incorporated with curcumin. Following the addition of curcumin, the mean nanofiber diameter, initially 461 ± 215 nm, subsequently shrank to 293 ± 110 nm with an average elongation at a break of 117.4 ± 4 1.35% and tensile strength of 5.27 ± 0.34 MPa. An initial 12-h burst of curcumin from the scaffolds was seen in the in vitro drug release studies, followed by a continuous release over the next 72 h. The DPPH-free radical scavenging assay was used in invitro antioxidant experiments of curcumin-incorporated nanofiber scaffolds, and the results confirmed the scaffolds' excellent antioxidant activity. Scavenging efficacy increased gradually with increasing curcumin concentrations, ranging from 2.0% to 6.0% (*w*/*w*). Compared to plain nanofibrous, which had a growth inhibition of 15.8% against S. aureus, the curcumin-infused nanofibers scaffolds had a high growth inhibition of 99.7 ± 0.85% [82].

Tsekova et al. developed Electrospun fibrous materials made of cellulose acetate and polyvinylpyrrolidone (PVP) embedded with curcumin for wounds affected by bacteria. Researchers added the curcumin to cellulose acetate and PVP, and the viscosity study revealed a significantly higher viscosity of 142 cP due to hydrogen bonding between the polymers and curcumin. The curcumin-embedded nanofibers mats had a 121.8 ± 3.4 degrees water contact angle. In vitro microbiological investigation of curcumin-loaded nanofibrous materials showed potent antimicrobial activity against S. aureus, indicating that these scaffolds help treat bacterially infected wounds [83].

Celebioglu et al. created nanofibrous scaffolds based on hydroxypropyl-γ-cyclodextrin and hydroxypropyl-β-cyclodextrin embedded with curcumin. The nanofibrous scaffolds had a homogeneous fibrous structure without beads. The nanofibrous scaffolds were 165 ± 65 nm in diameter on average. In the nanofibrous scaffolds, the curcumin encapsulation effectiveness (%) was 98.8 ± 1.6% and 99.3 ± 1.0%, respectively. When curcumin-loaded nanofibrous material was subjected to an antioxidant study utilizing the DPPH scavenging test, the curcumin-loaded hydroxypropyl-gamma-cyclodextrin webs demonstrated significantly higher antioxidant effectiveness of 100% when compared to the hydroxypropyl-β-cyclodextrin. The hydroxypropyl-γ-cyclodextrin nanofibrous webs coated with curcumin have promise as wound dressings [84].

Saeed et al. created a curcumin-loaded PCL and PVA Electrospun three-layer nanofibers scaffold. The water vapor transmission and water contact angle tests showed that the three-layer nanofibrous mats had a greater water vapor transmission rate than the monolayer mat owing to the hydrophilicity of the polyvinyl alcohol (PVA) layers (control). After two days of incubation, the antimicrobial assessment of the multi-layer Electrospun nanofibers revealed a more significant percentage inhibition against *E. coli* and *S. aureus*. Curcumin-loaded three-layer nanofibrous mats have potential wound-healing applications [85].

Esmaeili et al. developed Polyurethane (PU) and cellulose nanofibers for treating wounds co-entrapped with curcumin, silver nanocomposites, and graphene oxide. Compared to drug-loaded nanofibrous mats, The co-loaded nanofibers showed a synergistic solid antibacterial activity against Pseudomonas bacteria and S. aureus. Dual drug-loaded nanofibers were used in in vivo wound closure tests. The results showed a significantly accelerated rate of wound healing, with 100% compared to 78% for the plain nanofibers, 90% for GO embedded nanofibers, and 93% for Ag-embedded nanofibers [86].

Pankongadisak et al. created a nanofibrous scaffold made of PLA that is incorporated with curcumin. According to the TEM examination, incorporating curcumin in the fibrous scaffold caused the average diameter of the plain scaffold to shrink from 386 ± 121 nm to a diameter that ranged between 333 ± 124 and 380 ± 113 nm. The examination of the mechanical properties showed that the curcumin-encapsulated fibrous scaffold had tensile strengths of 2–3 MPa, Young's modulus of 57–111 MPa, and elongation at break of 40–49%. Curcumin was first released from the fibrous scaffold in a controlled manner after an hour, according to the in vitro drug release profile physiological conditions. The antioxidant assessment using the DPPH test revealed the antioxidant effects that varied between 42.50% and 52.96% for fibrous scaffolds embedded with curcumin, indicating their excellent antioxidant impact on wound management [87].

Mahmud et al. developed antimicrobial wound dressings comprised of Electrospun fiber mats infused with curcumin. The nanofibrous mats-controlled temperature-dependent curcumin drug release. Examining the mats' potential to swell revealed a 332% expansion rate. After six hours of incubation, the antibacterial tests against *E. coli* and *S. aureus* bacteria demonstrated a decrease of 100 percent [88].

Suwantong et al. formulation of cellulose acetate nanofibers scaffold embedded with curcumin demonstrated antioxidant activity ranging from 64 to 92% and cell viability of 97% on Human Dermal Fibroblasts (HDF), demonstrating outstanding

cytocompatibility of curcumin-embedded nanofibers scaffold [89].

Liu et al. created curcumin-infused PEG-SF nanofibrous mats. Compound curcumin release was constant for 350 h, and drug release improved as fiber diameter decreased [90].

Zahiri et al. developed a PCL and gelatin nanofibrous scaffold incorporated with curcumin-infused chitosan nanoparticles. When curcumin nanoparticles were added, the plain nanofibrous scaffolds' high tensile strength of 3.78 ± 0.17 MPa dropped to 1.84 ± 0.12 MPa. Curcumin-loaded nanofibrous scaffold's water contact angle investigations revealed that they were hydrophilic, with a contact angle of 48.9 ± 5.4. Once compared to ordinary scaffolds and scaffolds with curcumin, the nanofibers had a low rate of deterioration. Nanofibers showed high levels of wound closure in vivo wound healing investigations using a PCL-gelatin scaffold coated with curcumin-infused chitosan nanoparticles. On day 14, 82% of wounds were closed using the curcumin-infused scaffold, but only 73.4% were closed using the plain nanofibrous scaffold [91].

Jonathan G. Merrell investigated the feasibility and potential of PCL nanofibres as a vehicle for curcumin delivery in diabetic wound healing applications. The antioxidant activity of curcumin-loaded nanofibers was demonstrated using an oxygen radical absorbance capacity assay and by the ability of the nanofibers to maintain the viability of HFF-1 cells under conditions of oxidative stress. The nanofibers also reduced inflammatory induction, as evidenced by low levels of interleukin-6 release from mouse monocyte–macrophages seeded onto the nanofibers following stimulation by E. coli-derived lipopolysaccharide. In a diabetic mouse model induced by streptozotocin, an increased rate of wound closure demonstrated the in vivo wound healing capability of the nanofibers [67].

Han Tsung Liao et al. reported that in vitro, PLGA/curcumin provides additional benefits, such as increased migration ability and induced oxidative stress protection in HS68 fibroblast cells. An in vivo study indicated the PLGA/curcumin nanofibers exhibit the fastest wound closure rate with accelerated re-epithelialization, higher angiogenesis, and higher collagen deposition at the wound site [92].

Wounds treated with gelatin-infused curcumin nanofibers recovered faster and had higher levels of transforming growth factor-beta (TGF-) expression in Western blot tests. The reduced levels of pro-inflammatory markers interleukin-6 (IL-6) and tumour necrosis factor- (TNF-) provided evidence for nanofiber treatment's anti-inflammatory effects. Chronic wounds treated with curcumin-based nanofibers achieved better performance, with a 58 ± 7% increase in recovery rate on the seventh day. Based on their anti-inflammatory and wound-healing effects, the nanofibrous scaffolds can be potential materials for chronic wound treatment [93].

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