



Review

# Emerging Trends in Curcumin Embedded Electrospun Nanofibers for Impaired Diabetic Wound Healing

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**Abstract:** 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 necessitate the development of a suitable transporter to improve curcumin's stability, bioavailability, therapeutic efficacy, and solubility. In recent years, Electrospun nanofiber mats have been an excellent choice for drug delivery because of their numerous advantages and inherent properties. Electrospun nanofibers have shown considerable promise as wound dressing materials. This review highlights the potential properties and recent advancements in using curcumin-loaded nanofibers for diabetic wound healing.

**Keywords:** curcumin; electrospinning; nanofibers; advanced delivery systems; skin tissue engineering; diabetic wound healing



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## 1. Introduction

The most prevalent metabolic illness, diabetic mellitus, is brought on by an inability to secrete insulin, which leads to hyperglycemia by accelerating the loss of pancreatic cells. This autoimmune condition causes several serious illnesses, resulting in lower extremity amputations, organ failure, and death. Lower extremity abnormalities are among the most prevalent and expensive consequences of diabetes [1,2]. These complications may account for up to one-third of the direct costs associated with diabetes treatment, including lower-limb amputations and diabetic foot ulcers. In the course of their condition, twenty-five percent of persons who have diabetes will develop a diabetic foot ulcer, which is the primary cause of hospital admission connected to diabetes. In addition, one in every five diabetic foot ulcers will result in the amputation of the lower leg [3]. Major lower limb amputation is a serious concern for patients who have diabetic foot ulceration and persistent limb-threatening ischemia. There has long been concern about how late presentation and delayed care might lead to higher amputation rates. Clinical risk factors for diabetic foot ulcers include a history of diabetic foot ulcers, diabetic peripheral neuropathy, high plantar

pressures, and foot deformities [4]. However, preventative interventions for first and recurrent diabetic foot ulcers remain elusive. After a person has a foot ulcer for the first time, their risk of a second one is forty percent in the first year and approximately one hundred percent after ten years. Even though there are several recommendations for managing both disorders, there is presently no agreed-upon window of time for implementing professional care and therapy [5]. Therefore, a prevention-based approach is required to ensure the remission of diabetic foot ulcers for sustainable and cost-effective diabetic foot treatment.

Curcumin was discovered in the root of the *curcumin longa* L. plant. In south and southeast Asia, turmeric has been used in traditional culinary and medicinal arts for generations. Curcumin is a polyphenol used extensively as a spice, food preservative, flavoring, and colouring ingredient in addition to its therapeutic use [6]. Traditional Indian medicine practitioners believe curcumin powder suppresses several ailments, including biliary disorders, diabetes, sinusitis, rheumatism, cough, anorexia, cancer, hepatic disorders, and Alzheimer’s [7,8]. In the traditional and herbal medicine of south and southeast Asia, turmeric has been used to cure several disorders for ages. Over the last three decades, curcumin’s biological and pharmacological usefulness has been amply shown by an extensive research [9,10]. 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 [11–13]. Curcumin has been the subject of numerous attempts to increase its stability and bioavailability. The topical use of curcumin may enhance its strength, pharmacological activity, solubility, and therapeutic efficacy [14]. Research has been conducted to enhance the bioavailability of curcumin utilising various drug carriers (Table 1) [15,16].

Current delivery systems, such as Electrospun nanofiber-based techniques made from natural and synthetic materials, or both, to deliver therapeutic agents, might herald a new era in which diabetes mellitus problems are avoided [17–19]. Both macromolecules and small molecules may be delivered successfully using such delivery fiber carriers. Nanofibers may also provide a perfect milieu for skin tissue engineering using nanofiber scaffolds [20–22]. Many research efforts have suggested the possible use of therapies, including nanofiber mats, to proliferate, regenerate, and remodel the structural and functional characteristics of diabetic skin ulcers [23–25]. This review aims to provide the reader with a comprehensive overview of the most recent discoveries in curcumin-loaded nanofibers, including studies and findings confirming their efficient involvement in diabetic wound healing and their huge potential for diabetic wound healing applications.

**Table 1.** A summary of available curcumin-based wound dressing products and their benefits.

S. No	Wound Dressing Materials	Curcumin with Composition	Method of Formulation	Outcomes	Ref
1	Nanofibrous mats	Gelatin, Trifluoroethanol, Glutaraldehyde.	Electrospinning method	Curcumin has a prolonged release profile from the formulation. Curcumin/gelatin blended nanofibrous mats promoted faster and more effective wound healing in Sprague–Dawley rats. Compared to the control group, the epidermis layers in the group that had significant reepithelialization and differentiation were well-developed.	[26] March 2017

Table 1. Cont.

S. No	Wound Dressing Materials	Curcumin with Composition	Method of Formulation	Outcomes	Ref
2	Nanofibers	PCL	Electrospinning method	It has the potential to be biocompatible and cytoprotective, according to in vitro investigations. On the third day, a release analysis showed that fibres containing 3% and 17% curcumin released 35 mg and 20 mg of curcumin over an extended period. Studies on in vivo wound healing have shown significant wound closure capacity in addition to antioxidant and anti-inflammatory action.	[27] December 2009
3	Nanocrystal scaffolds containing curcumin-loaded microspheres	Bovine gelatin, Collagen	Emulsion solvent evaporation method	Curcumin release profile over time enhanced dermal regeneration and successfully reduced local inflammation in a rat full-thickness burn infection model.	[28] December 2017
4	Nanocomposite hydrogel	MPEG-PCL copolymer, Oxidized alginate, Chitosan	Thin-film evaporation method	Nanocomposite hydrogel regulates and sustains the release profile of curcumin. On day 14, an in vivo examination showed that the wound had fully healed. Improved collagen deposition, reepithelization, and granulation tissue development	[29] November 2012
5	Hydrogel film	Sacran, 2-hydroxypropyl $\beta$ -cyclodextrin	Solvent evaporation method	Curcumin release is slow and persistent. Enhanced curcumin antioxidant activity Faster healing of wounds relative to other groups	[30] May 2017
6	Hydrogel system containing micellar curcumin	PEG-PCL micellar curcumin, PEG-PCL-PEG copolymer hydrogel	Curcumin micelle by solid dispersion method and hydrogel by crosslinked methods	Wound dressing exhibited more significant cutaneous wound healing, increased collagen content, improved granulation, and increased wound maturity. 60% sustained release of curcumin during 14 days	[31] September 2013
7	Collagen films	Collagen from bovine achilles tendon	Crosslinking	The in vitro release kinetics demonstrated more than 60% curcumin release after 12 days of investigation. High expression of collagen and granulation tissue development with the application of collagen films containing curcumin	[32] May 2004

Table 1. Cont.

S. No	Wound Dressing Materials	Curcumin with Composition	Method of Formulation	Outcomes	Ref
8	Chitosan–alginate sponge	Curcumin, Alginate, Chitosan	Ionic interaction and crosslinking	The in vitro studies demonstrated enhanced water absorption and biodegradability. 40% to 80% sustained release of curcumin in vitro for up to 20 days. In vivo wound healing tests showed superior healing efficacy due to fast wound contraction and collagen deposition.	[33] September 2009
9	Nanostructured lipid carriers	Curcumin, Glycerol monostearate, Stearic acid, Caprylic/capric triglyceride, Soya lecithin	Emulsion evaporation–solidification method	Significant skin permeability ability in comparison to standard formulations. Significant anti-inflammatory efficacy accelerated skin regeneration and enhanced skin thickness.	[34] October 2016
10	Polymeric bandage	Curcumin, Oleic acid, Alginate, Chitosan	Ionic interaction and crosslinking	For a protracted period of 10 days, there was a release of curcumin that was more than 40%. 10 days after application, control, empty bandage, and curcumin bandage-treated wounds contracted 70%, 80%, and 94%.	[35] October 2012
11	Nanoparticle/hydrogel	Curcumin, Polyethylene glycol, Polyvinyl alcohol, PLA–10R5–PLA copolymer	w/o/w double emulsion solvent evaporation method	In vitro drug release behaviour with low cytotoxicity with an increase in granulation tissue development, collagen deposition, and angiogenesis demonstrated good wound healing efficacy in vivo.	[36] August 2016
12	Curcumin nanoparticles	Curcumin, Chitosan, Tetramethyl orthosilicate, Polyethylene glycol 400	Sol–gel-based	Curcumin releases slowly over time. Significantly improved collagen deposition, granulation tissue development, re-epithelization, and tissue regeneration	[37] January 2015
13	Polymeric bioadhesive emulsion	Neem and turmeric extract, Shellac, Casein and Polyvinyl alcohol and Maleic anhydride	Emulsion method	It has antibacterial qualities, is harmless, and degrades naturally.	[38] December 2005

Table 1. Cont.

S. No	Wound Dressing Materials	Curcumin with Composition	Method of Formulation	Outcomes	Ref
14	Methoxy poly(ethylene glycol)-graft-chitosan composite film containing curcumin nanoformulation	Curcumin, Poly (ε-caprolactone)-Poly (ethylene glycol) methyl ether (MPEG-PCL) copolymer, Linoleic acid, Tween1 20, Chitosan	Casting/solvent evaporation method	8.4% of the curcumin was released early on day 1 and continued throughout the next five days. When the wound area was less than 10% at day 14, an in vivo wound healing research showed quicker healing. Rapid reepithelialization, collagen synthesis, and wound healing were seen after administration.	[39] March 2012
15	Hyalurosomes, a nanovesicle and liposomes	Curcumin, Soy Phosphatidylcholine, Sodium hyaluronate, ultrasonic disintegrator	Sonication	Human keratinocytes in vitro were shielded from oxidative stress damage by biocompatible materials. Compared to other groups, in vivo data demonstrated improved skin restoration activity in terms of decreased edema, myeloperoxidase activity, and early skin reepithelization.	[40] December 2015
16	Gel-core hyalurosomes (nanovesicle)	Curcumin, Lipoid1 S100, Tween1 80, Hyaluronic acid	Film hydration technique	After two hours of in vitro testing, there was a 50% release of curcumin. At day 10, the wound had healed properly and early with no scars. Compared to other groups, improved granulation tissue development, collagen fibre deposition, re-epithelization, and tissue regeneration	[41] May 2015
17	Nanovesicles	Curcumin, Lipoid1 S75, PEG400, Oramix1	Sonication method	It is spherical, multi- or oligolamellar, compact, and biocompatible. Application on skin injured by tissue plasminogen activator (TPA) revealed decreased oxidative inflammation. Data from histology showed significant re-epithelization with several thick epidermal layers.	[42] March 2014

Table 1. Cont.

S. No	Wound Dressing Materials	Curcumin with Composition	Method of Formulation	Outcomes	Ref
18	Curcumin-loaded poly (lactic-co-glycolic acid) (PLGA) nanoparticles	Curcumin, Poly (lactic-glycolic acid), Polyvinyl alcohol	Oil/water emulsion– solvent evaporation technique	Over the period of eight days, there was a steady release of curcumin, from 40.5% to 75.7%. Angiogenesis and wound healing were enhanced by lactate produced from PLGA. Studies using histology and RT-PCR showed that PLGA-curcumin had more potential for reepithelialization, granulation tissue development, and anti-inflammatory effects.	[43] October 2013

## 2. Potential of Curcumin in Skin Disorders

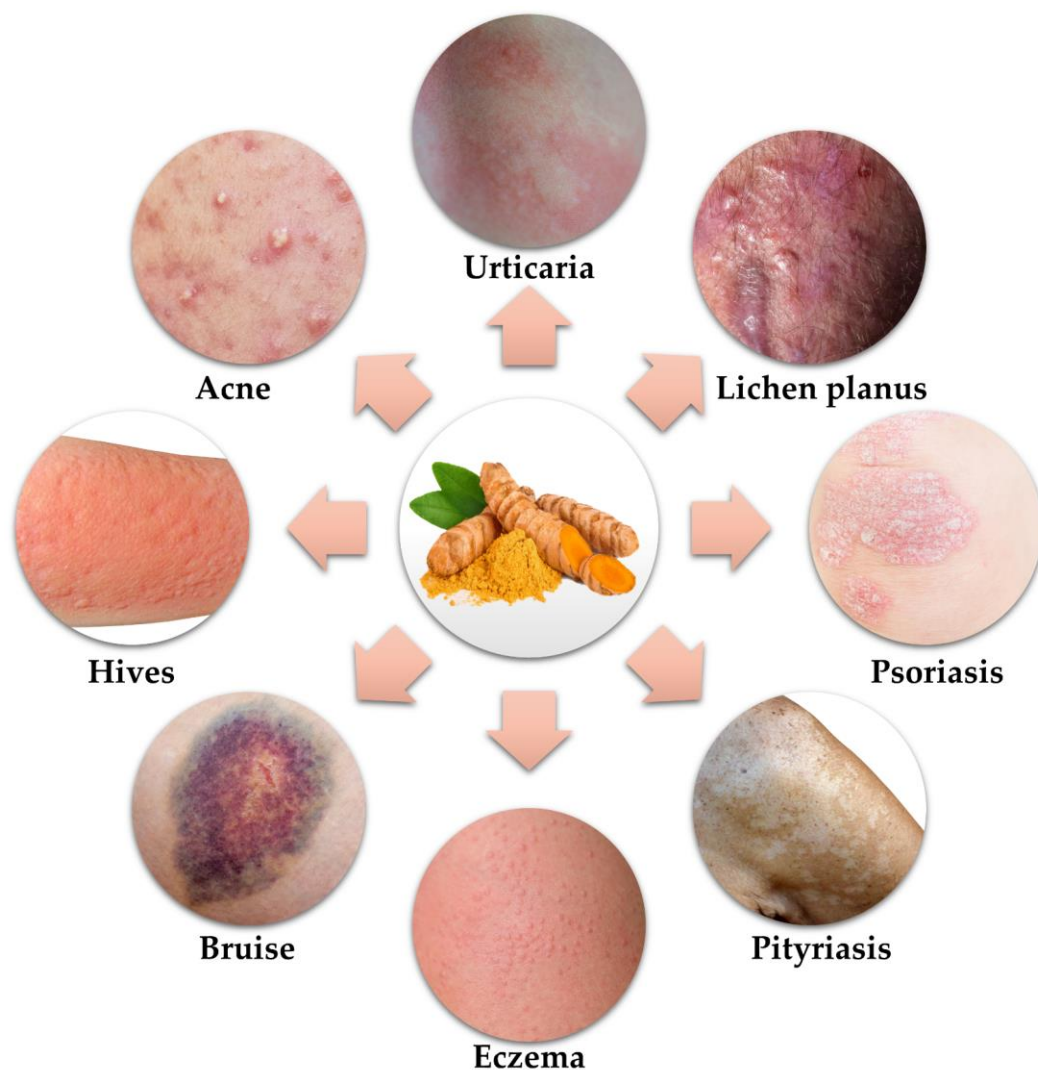
Acute skin infections may be caused by several microorganisms, such as bacteria, fungi, viruses, and parasites. *S. aureus* is responsible for many skin diseases, including folliculitis, impetigo, boils, and cellulitis. *Propionibacterium acnes* and *S. epidermidis* are both constituents of the microbiota 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 [44]. 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 [45–47]. In addition to bacteria, several fungal species may cause superficial mycoses. Dermatophytes are the most prevalent fungal pathogens responsible for skin diseases. *Trichophyton rubrum* has become the most pervasive dermatophytic fungi globally, mainly causing *tinea pedis* and *tinea unguium* [48]. 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 [49]. *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 [50].

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 [51–53].

Curcumin's effectiveness against skin infection illnesses (Figure 1) has also been explored in vivo and in vitro [54–57]. 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.



**Figure 1.** Potential of Curcumin in Skin Disorders. Created with [BioRender.com](https://www.biorender.com) (BioRender, Toronto, ON, Canada, accessed on 11 September 2022).

### 3. Biomedical Applications of Curcumin

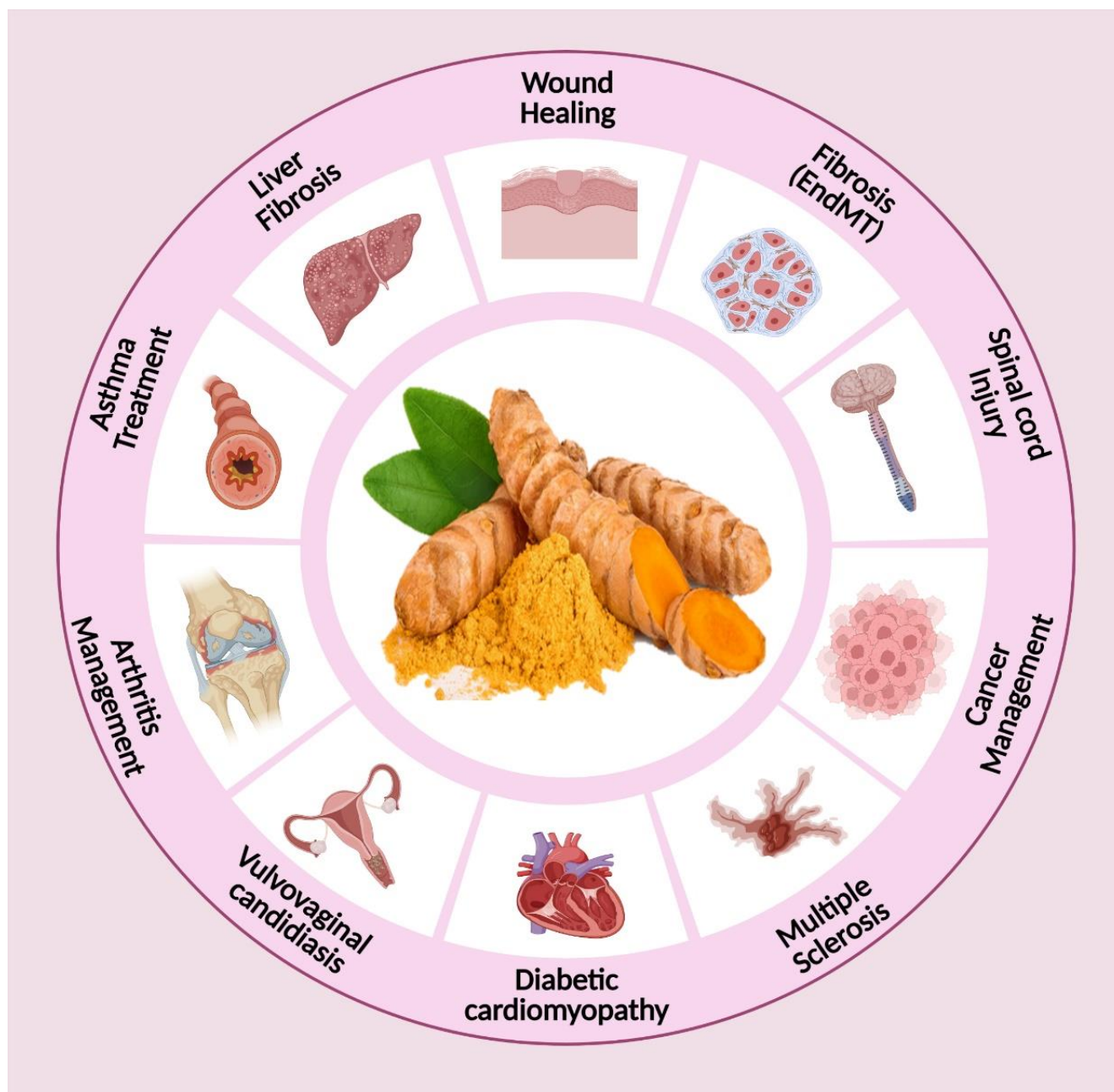
The potent anti-microbial, anti-inflammatory, antioxidant, and other qualities of curcumin make it a particularly apt molecule for treating wounds and many inflammatory disorders, including diabetes, arthritis, inflammatory bowel disease, atherosclerosis, neurological disorders, and Alzheimer's disease (Table 2) [58,59]. Due to its excellent pharmacological qualities, Curcumin has a promising future in biological applications (Figure 2), such as cardiovascular disorders, chemotherapeutics, radiosensitizing, chemosensitizing, and wound healing, as shown by many in vitro and in vivo investigations [60,61]. 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 [62].

**Table 2.** Curcumin's potential for biomedical applications.

S. No	Target Disease	Mechanism of Action	Ref
1	Liver Diseases	Curcumin down-regulates expression of TGF- $\beta$ 1 to enhance VE-cadherin, DDAH1 and Nrf2 levels, and diminish MMP-9 and ERK1/2 levels. Consequently, TGF-b-mediated EndMT is inhibited to suppress endothelial cell fibrosis	[63]
2	Skin cancer	Inhibits pAKT, pS6, p-4EBP1, pSTAT3 and pERK1/2 Improved skin penetration, deposition and antimelanoma activity of curcumin	[64]
3	Osteoarthritis	Decreases Visual Analog Score (VAS), CRP, CD4+ and CD8+ T cells, Th17 cells and B cells frequency	[65]
4	Multiple sclerosis	Enhancing expression of anti-inflammatory factors such as IL-4, IL-5 and TGF- $\beta$ is a promising strategy in multiple sclerosis therapy	[66]
5	Asthma	The inhibitory effect on the expression and level of TGF- $\beta$ is critical in asthma therapy.	[67]
6	Vulvovaginal candidiasis	By lowering the level of IL-1 $\beta$ (a pro-inflammatory factor) in comparison to TGF- $\beta$ (an anti-inflammatory factor), Vulvovaginal candidiasis improves, paving the way for effective treatment of this infection.	[68]
7	Diabetic cardiomyopathy	Curcumin down-regulates the expression of TGF- $\beta$ 1 via inhibition of JAK/STAT signaling pathway, leading to reducing inflammation and improving diabetic cardiomyopathy.	[69]
8	Psoriasis	Inhibits phosphorylase kinase activity and decreases the epidermal CD8+ T-cell density resulting in reduced autoimmune-mediated cell damage and resolution of psoriasis	[70]
9	Scleroderma	Inhibits the TGF- $\beta$ -mediated phosphorylation of smad2 by upregulation of TGF- $\beta$ -induced factor (TGIF) which is a negative regulator of TGF- $\beta$ signalling	[71]
10	Antihypertensive	Inhibits ACE thereby preventing overexpression of RAAS, curcumin scavenges superoxide anion (O <sub>2</sub> <sup>-</sup> ) generated under the diabetic conditions, thereby preventing its reaction with potent vasodilator nitric oxide (NO) to form the much more powerful oxidant peroxynitrite (ONOO <sup>-</sup> ); curcumin prevents cadmium-mediated inhibition of catechol-O-methyltransferase by its chelating effect which decreases adrenaline and noradrenaline level.	[72]
11	Antidiabetic	Decreases hepatic glucose level, increases glucose uptake by upregulating GLUT2, GLUT3 and GLUT4 gene expressions, enhancing secretion of insulin from pancreatic cells, decreases insulin resistance.	[73]
12	Diabetic foot ulcer	Inhibits the growth of bacteria that are associated with the onset of foot infections in patients with diabetes	[74]
14	Alzheimer	Improves memory due to its antioxidant effect which decreases degradation of neurons, beta-amyloid plaques and microglia formation	[75]
15	Ulcerative colitis	Decreases TNF- $\alpha$ , IL-6	[76]





**Figure 2.** Biomedical applications of curcumin. Created with [BioRender.com](https://www.biorender.com) (accessed on 11 September 2022).

#### 4. Safety Profile of Curcumin

The Food and Drug Administration (FDA) has acknowledged curcumin as a safe substance. Researchers evaluated this drug's safety in several preclinical and clinical trials (Table 3) [77–79]. In a clinical investigation, curcumin was not found in the serum of healthy volunteers given up to 8000 mg per day. Only meager quantities were found in two subjects given 10,000 or 12,000 mg. Daily consumption of 12,000 mg is considered safe in healthy persons since no adverse effects were seen in participants [13]. Patients with internal organ pre-malignant lesions and cardiovascular risk who took curcumin at doses ranging from 500 to 8000 mg per day for three months also had a favorable safety profile [80]. This safety has also been shown in advanced pancreatic malignancy patients receiving 8000 mg per day of curcumin for two months and advanced breast cancer patients receiving radiation while taking up to 6000 mg per day of curcumin [81–83].

Other trials in healthy participants and patients with various illnesses, including ulcerative colitis, cholangitis, and advanced colorectal cancer, showed moderate and controllable gastrointestinal complications with daily consumption of up to 8000 mg of curcumin [14,84–86]. In addition to these findings, a small proportion of individuals with sclerosing cholangitis receiving up to 1400 mg per day of curcumin experienced only moderate effects like headache or nausea [87]. Intriguingly, individuals with advanced pancreatic cancer receiving gemcitabine have also reported experiencing severe stomach discomfort after starting curcumin at a dosage of 8000 mg daily [88]. A clinical investigation of healthy volunteers found that short-term IV administration of liposomal curcumin was safe up to a dose of 120 mg/m. In contrast, a dose escalation study on patients with metastatic cancer found that the highest tolerable amount was 300 mg/m<sup>2</sup> over 6 h [89,90].

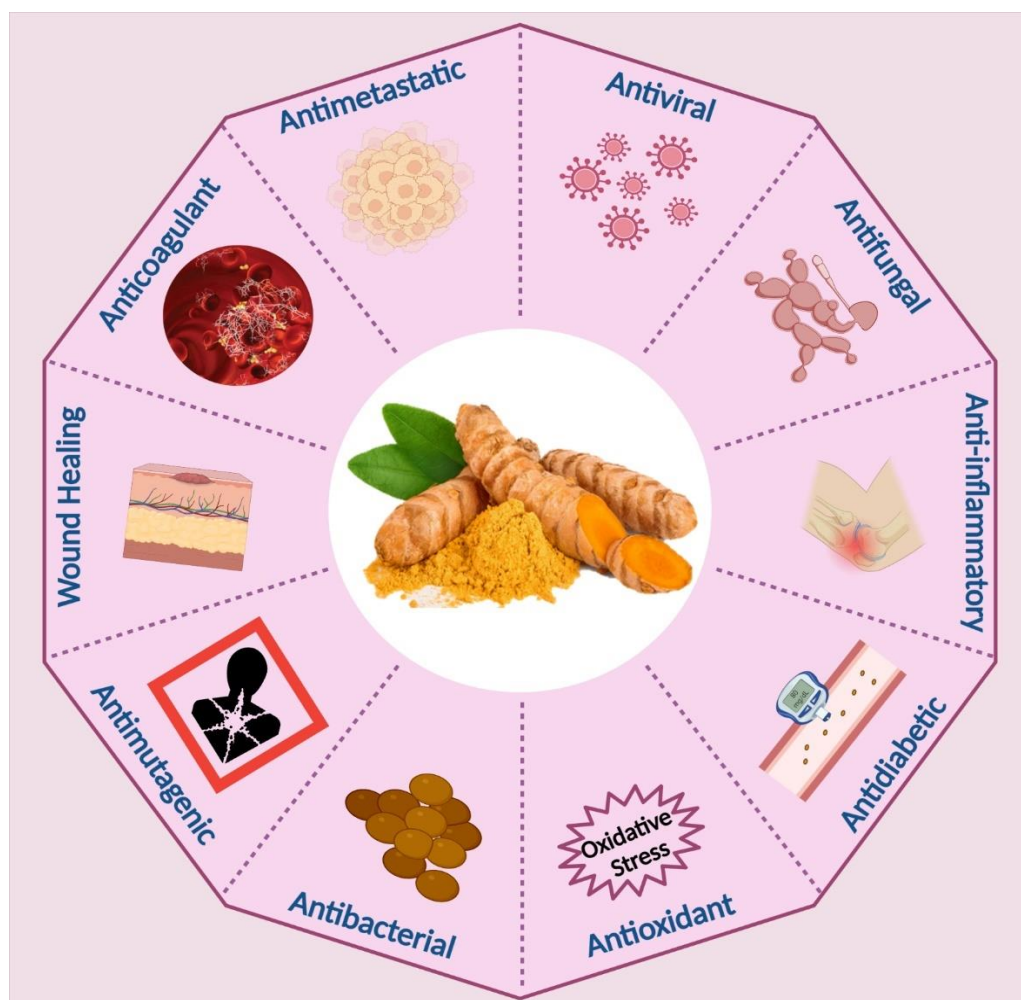
It is important to note that researchers carried out the bulk of research evaluating the safety profile of curcumin over brief periods. No reliable data is currently available concerning the effects of long-term usage of this compound. Although the quantities suggested for over-the-counter curcumin are often smaller than those in the clinical research listed above, supplements containing this substance are readily accessible to the general population and are growing in popularity. Curcumin may be harmful to the liver, as shown by new cases of liver disorders [91]. Curcumin's precise contribution to the emergence of these illnesses is still unclear, and lead contamination of supplements has been theorized. Until further information is available, monitoring is necessary, particularly for long-term usage, over-the-counter medications, and in patients with liver disorders. Topically, curcumin may alleviate these problems associated with long-term use, over-the-counter drugs, and liver disease patients. This limitation would require the creation of a suitable transporter to enhance curcumin's bioactivity.

**Table 3.** Safety Profile of Curcumin.

S. No	Safety Profile of Curcumin	Ref
1	The Food and Drug Administration has acknowledged curcumin as a safe substance.	[77–79]
2	Daily consumption of 12,000 mg is considered safe in healthy persons since no adverse effects were seen in participants.	[13]
3	Healthy patients given up to 8000 mg per day did not have curcumin in their blood serum. Two persons given 10,000 or 12,000 mg had low levels.	[13]
4	Curcumin at 500 to 8000 mg per day for three months was safe for patients with internal organ pre-malignant lesions and cardiovascular risk.	[80]
5	Advanced pancreatic cancer patients taking 8000 mg per day of curcumin for two months and advanced breast cancer patients receiving radiation while taking up to 6000 mg per day of curcumin have also shown this safety.	[81–83]
6	In healthy participants and patients with ulcerative colitis, cholangitis, and advanced colorectal cancer, up to 8000 mg of curcumin daily caused moderate and controllable gastrointestinal complications.	[14,84–86]
7	A tiny proportion of sclerosing cholangitis patients receiving up to 1400 mg per day of curcumin experienced headache or nausea.	[87]
8	Individuals with advanced pancreatic cancer taking gemcitabine reported severe stomach discomfort after starting 8000 mg of curcumin daily.	[88]
9	Short-term IV liposomal curcumin administration to healthy volunteers was safe up to 120 mg/m.	[89]

## 5. 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 peroxy radicals ( $\text{LOO}\bullet$ ), superoxide radicals ( $\text{O}_2\bullet$ ), nitrogen dioxide radicals ( $\text{NO}_2\bullet$ ) and hydroxyl radicals ( $\bullet\text{OH}$ ). These forms are associated with the onset of oxidative stress, which limits granulation tissue development and remodelling as a crucial element in wound healing [92–94]. 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 (Figure 3), have been discovered to be effective in treating diabetic wound healing [95–97].



**Figure 3.** The Potential of Curcumin in Wound Healing. Created with [BioRender.com](https://www.biorender.com) (11 September 2022).

### 5.1. Inflammation

Inflammation is often considered the first phase of optimum wound healing since it is one of the most crucial [98]. 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 [99,100]. 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 [101]. 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 [102]. 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 [103].

Curcumin controls the levels of protein kinase C (PKC), protein kinase C-2 (PKC-2), and mitogen-activated protein kinase (MAPK) [104]. 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 [105]. 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 [106,107]. Its antioxidant activity alleviated endothelial cell dysfunction and PKC inhibition in Streptozotocin (STZ)-induced diabetic rats and mice [108]. It also reduced the vascular dysfunction brought on by diabetes in STZ rats by decreasing COX-2, NF-B, and PKC activity [109]. By lowering TNF and aortic Reactive Oxygen Species (ROS) and activating heme oxygenase (HO-1) in diabetic rats, curcumin improved dysregulated vascular contractility [110].

### 5.2. 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 [111]. 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 [112,113]. 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 [114]. In another investigation, the application of the curcumin in vivo rat model resulted in a considerable decrease of H<sub>2</sub>O<sub>2</sub> induced damage to fibroblasts and keratinocytes. In similar research, curcumin was shown to eliminate H<sub>2</sub>O<sub>2</sub> from keratinocytes and fibroblasts [115].

### 5.3. Fibroblast Proliferation

Fibroblast infiltration into the wound area is required to form granulation tissue and collagen synthesis and deposition [116,117]. According to research, dermal wounds that do not heal within the expected time frame have reduced fibroblast migration and proliferation within the wound site [118]. 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 [119].

#### 5.4. 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 [120]. Curcumin's topical application to burned wounds in rats has considerably enhanced angiogenesis and expedited wound healing [121]. Curcumin stimulated the neovascularization at the diabetic wound site directly by the increased expression of angiogenic factors such as VEGF, TGF- $\beta$ 1, and other factors such as HIF-1 $\alpha$ , SDF-1 $\alpha$ , and HO-1, as well as indirectly, by anti-inflammatory and antioxidant action [122].

#### 5.5. 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 [123]. 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 [32,33]. During the creation of granular tissue, fibroblasts differentiate into myofibroblasts, and the presence of hydroxyproline indicates the existence of myofibroblasts.

#### 5.6. 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 [124]. A substantial portion of collagen should be generated and deposited on the injured area to promote wound healing and scar tissue formation [125]. 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 [126,127].

#### 5.7. Apoptosis

To proceed wound healing to the proliferative phase, apoptotic processes must occur to destroy inflammatory cells in the injured area [128]. 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 [129]. 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 [35].

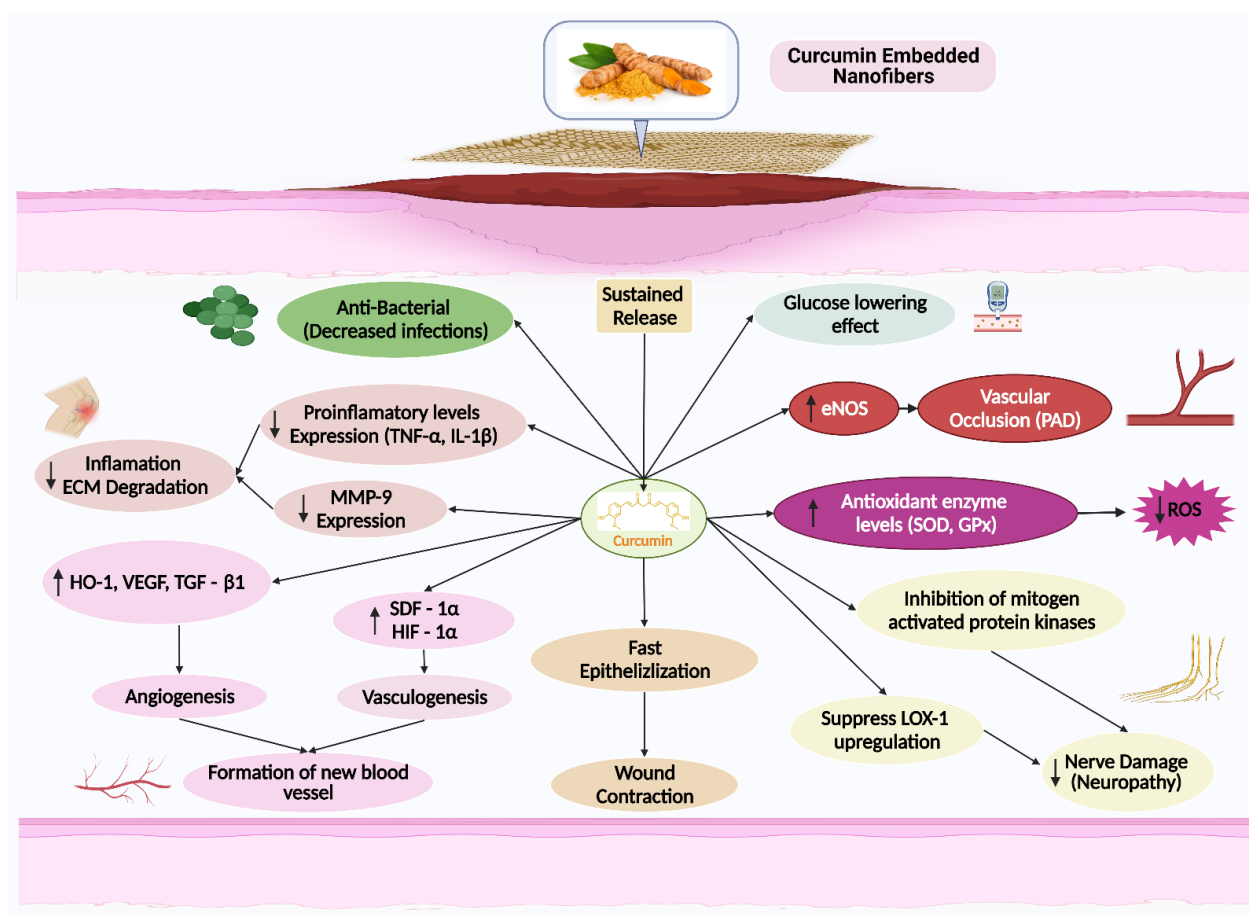
#### 5.8. Wound Contraction

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 [130]. 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 [131,132]. Curcumin-treated wounds had more TGF than the control, which provided a higher number of fibroblasts [133]. Furthermore, the soft

tissue in diabetic mouse wounds showed increased TGF expression in the curcumin-treated group [134].

### 5.9. 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 [135]. 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 [126]. Curcumin exhibits multiple biological activities in treating various aspects of diabetic wound complications (Figure 4).



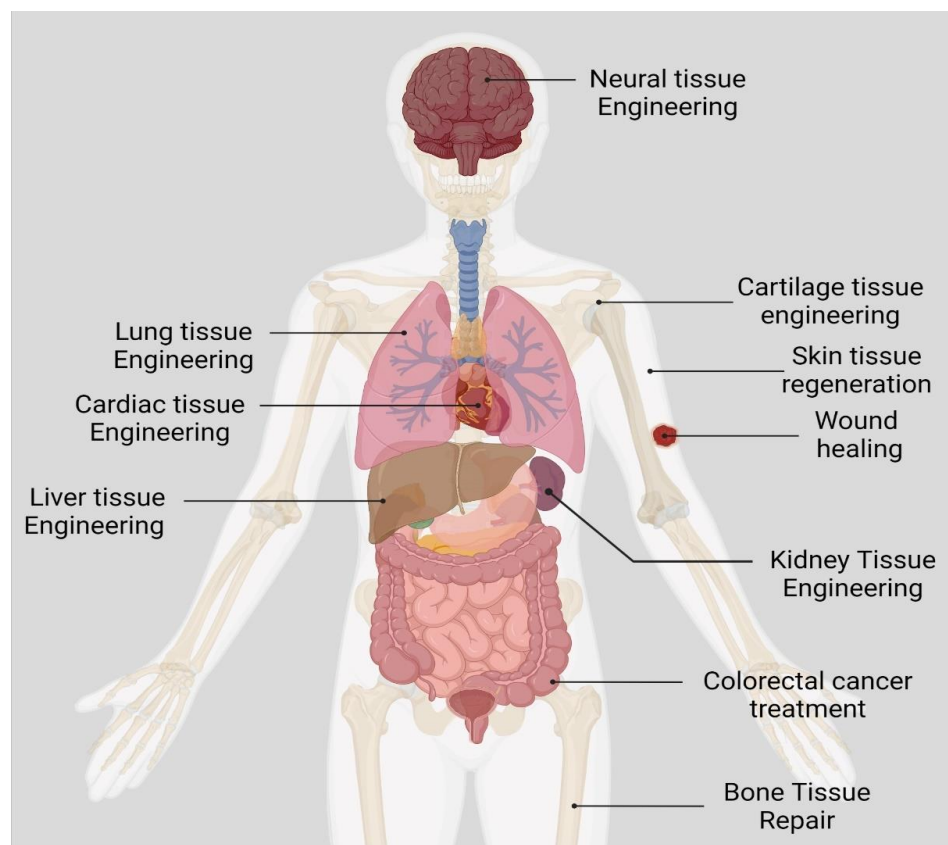
**Figure 4.** Curcumin mechanism of action in treating diabetic wounds (↑: Increases, ↓: decreases). Created with [BioRender.com](https://www.biorender.com) (accessed on 8 September 2022).

## 6. Nanofibers

In combat, various diabetes mellitus-related problems and various delivery strategies based on nanostructures were investigated (Table 4) [136,137]. As a result, nanofibers-based systems have shown incredible potential as delivery mechanisms and synthetic scaffolds for the delivery of medicinal drugs. Nanofibers may provide a sufficient matrix to encapsulate and incorporate therapeutic compounds into a high-efficiency delivery system or reservoir with minimal side effects [138–140]. They can also prevent degradation before therapeutic molecules reach their target areas. Such structures can convey their content, have a high drug-loading capacity, are very efficient at encapsulating, and may produce a variety of morphologies [141–143].

Different techniques are used to incorporate therapeutic agents into the fibers, such as blending the agent with the polymer solution before spinning, coaxial spinning to create core/shell structures, attaching active agents to the fibers' surfaces, post-fabrication surface modification, and surface grafting. Researchers may use these techniques to achieve timely release of therapeutic substances and more exact control over release kinetics, in addition to supporting the essential processes of cells, and artificial scaffolds may be employed to build 3D fibers that closely resemble the natural extracellular matrix [144,145]. An enormous surface area for cell-scaffold interaction/adherence and efficient exchange for oxygen and nutrient delivery may be provided by nanofibers scaffolds with architectural resemblance to native ECM. Nanofibers may be combined with ECM proteins, growth factors, and nanomaterials for tissue-engineered implantation and transplantation to facilitate the development of tissue-like structures [146].

Nanofiber materials have been extensively used in various medicinal applications, as shown in (Figure 5) [147–149]. Create nanofiber structures for diabetes foot ulcer therapy, several natural materials and synthetic polymers were used. In general, synthetic polymers can be Electrospun considerably more efficiently and have mechanical strength and excellent flexibility, but natural polymers demonstrated improved biocompatibility, good biodegradation, and much-reduced immunogenicity. Utilizing a combination technique is advised in order to get the most benefits out of those materials. Recent years have seen a significant increase in nanofiber-based systems for treating chronic wounds. One of the most notable characteristics of nanofiber-based structures for the treatment of diabetic foot ulcers is the delivery of biomacromolecules, growth factors, and small interfering RNA, as well as anti-diabetic pharmacological agents [25,150–153]. In the case of lower plasma glucose levels, insulin may be mixed into or coated on nanofiber patches and applied dermally, topically, or in other ways, such as sublingually. For example, dressings containing insulin may encourage the development of a wound matrix [154].



**Figure 5.** Biomedical applications of Electrospun nanofibers. Created with [BioRender.com](https://www.biorender.com/) (accessed on 11 September 2022).

**Table 4.** The benefits and drawbacks of the various types of nanocarriers.

S. No	Nanocarrier	Advantages	Disadvantages	Ref
1	Fibers	<ul style="list-style-type: none"> <li>• Nonadherent, nontoxic, nonallergenic,</li> <li>• Allows gaseous exchange</li> <li>• Removes excess exudates</li> <li>• Barrier against microbes</li> <li>• Sustain release</li> <li>• Maintain humidity</li> <li>• Tensile strength</li> <li>• Increased bioavailability</li> <li>• Fibroblast attachment and proliferation</li> <li>• Keratinocyte attachment and proliferation</li> <li>• Tunable porosity</li> <li>• ECM mimicking</li> <li>• Biocompatibility</li> <li>• Electro-catalytic properties</li> <li>• Thermal conductivity</li> <li>• Electrical conductivity</li> <li>• Structural stability</li> <li>• Loading efficiency</li> <li>• High surface area to volume ratio</li> <li>• Mechanical strength</li> </ul>	<ul style="list-style-type: none"> <li>• Unsuitable for third degree, eschar, and dry wounds; if the wound is highly exudative, a secondary dressing is required</li> </ul>	[155]
2	Polymeric nanoparticles	<ul style="list-style-type: none"> <li>• Biocompatible</li> <li>• Low toxicity</li> <li>• Biodegradable</li> <li>• Cost-effective</li> <li>• Possible surface functionalization</li> <li>• Avoids leakage of the drug</li> </ul>	<ul style="list-style-type: none"> <li>• Difficult to scale up</li> </ul>	[156]
3	Liposomes	<ul style="list-style-type: none"> <li>• Ability to carry either hydrophilic or hydrophobic drugs</li> <li>• Biocompatible</li> <li>• Biodegradable</li> <li>• Stable</li> <li>• Possibility of surface functionalization</li> </ul>	<ul style="list-style-type: none"> <li>• Toxic, because the drug can be leaked or displaced into the blood stream</li> <li>• High production cost</li> </ul>	[157]
4	Films	<ul style="list-style-type: none"> <li>• Impermeable to bacteria</li> <li>• Allows the healing process to be monitored</li> <li>• Painless removal</li> </ul>	<ul style="list-style-type: none"> <li>• Hard to handle</li> <li>• Non-absorbent</li> <li>• Adhere to the wound bed and cause exudate accumulation</li> </ul>	[158]
5	Sponges	<ul style="list-style-type: none"> <li>• High porosity</li> <li>• Thermal insulation</li> <li>• Sustain a moist environment</li> <li>• Absorb wound exudates</li> <li>• Enhance tissue regeneration</li> </ul>	<ul style="list-style-type: none"> <li>• Mechanically weak</li> <li>• May provoke skin maceration</li> <li>• Unsuitable for third degree burn treatment or wounds with dry eschar</li> </ul>	[159]
6	Hydrogels	<ul style="list-style-type: none"> <li>• High absorption properties</li> <li>• Provide a moist environment at the wound site</li> <li>• Water retention</li> <li>• Oxygen permeability</li> <li>• Ensure the solubility of growth factor/antimicrobial agents</li> </ul>	<ul style="list-style-type: none"> <li>• Weak mechanical properties</li> <li>• Need a secondary dressing</li> </ul>	[160]



Table 4. Cont.

S. No	Nanocarrier	Advantages	Disadvantages	Ref
7	Hydrocolloids	<ul style="list-style-type: none"> <li>• Non-adherent</li> <li>• High density</li> <li>• Painless removal</li> <li>• High absorption properties</li> </ul>	<ul style="list-style-type: none"> <li>• Can be cytotoxic</li> <li>• Have an unpleasant odor</li> <li>• Low mechanical stability</li> <li>• Maintain acidic pH at the wound site</li> </ul>	[161]

### 7. Curcumin Embedded Electrospun Nanofibers for Wound Healing

Merrell et al. developed Polycaprolactone (PCL) nanofibrous scaffolds incorporated with curcumin to treat diabetic wounds. Advantages of FDA-approved polymers in skin tissue engineering are shown in Table 5. 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 [27]. (Table 6) shows the effect of curcumin-loaded nanofiber diameters and release profiles on electrospinning parameters and polymer/solvent combinations.

Table 5. List of FDA approved polymers used in the formation of Electrospun nanofibers.

S. No	Polymers	Advantages
1	PCL	<ul style="list-style-type: none"> <li>• FDA approved</li> <li>• Biocompatible, Biodegradable</li> <li>• Mechanical stability</li> <li>• Soluble in most of the organic solvents</li> <li>• Good electrospinning properties</li> </ul>
2	PLA	<ul style="list-style-type: none"> <li>• FDA approved</li> <li>• Good biocompatibility</li> <li>• Biodegradability, Bioresorbability</li> <li>• Good processability</li> <li>• Good ductility</li> </ul>
3	Cellulose Acetate	<ul style="list-style-type: none"> <li>• FDA approved</li> <li>• Biocompatible, Biodegradable</li> <li>• Mechanical stability</li> <li>• Cost-effectiveness</li> <li>• Hydrophilic nature</li> <li>• Purity</li> </ul>
4	PEG	<ul style="list-style-type: none"> <li>• FDA approved</li> <li>• Reasonable control over structural and compositional properties</li> </ul>

Table 5. Cont.

S. No	Polymers	Advantages
5	PHBV	<ul style="list-style-type: none"> <li>• FDA approved</li> <li>• Biocompatible, Biodegradable</li> <li>• Oxygen permeable</li> </ul>
6	Polyurethane	<ul style="list-style-type: none"> <li>• FDA approved</li> <li>• Good mechanical strength</li> <li>• Creates a moist environment</li> <li>• Suitable coverage for burns</li> </ul>
7	PVP	<ul style="list-style-type: none"> <li>• FDA approved</li> <li>• Hydrophilic nature</li> <li>• Soluble in water/most organic solvents</li> <li>• Low toxicity</li> <li>• Excellent biocompatibility</li> </ul>
8	PVA	<ul style="list-style-type: none"> <li>• FDA approved</li> <li>• High solubility</li> <li>• Biodegradability</li> <li>• Relatively low-cost</li> <li>• Long-lasting durability</li> <li>• High-temperature stability</li> </ul>
9	SF	<ul style="list-style-type: none"> <li>• FDA approved</li> <li>• Biocompatibility</li> <li>• Water vapor transmission rate</li> <li>• Water retention capacity</li> <li>• Elasticity</li> </ul>

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* [162].

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 [163].

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 [164].

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% [165].

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 [166].

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  $\mu\text{m}$ , making them appropriate for skin tissue regeneration. The nanofibrous scaffolds were cytocompatible with L929 cells and enhanced cell adhesion [167].

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 [168].

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 [169].

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% [170].

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 [171].

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 [172].

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 [173].

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  $80.1 \pm 0.5\%$  and  $91.6 \pm 0.4\%$ . 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 an-

tibacterial 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 [174].

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 [175].

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  $461 \pm 215$  nm, subsequently shrank to  $293 \pm 110$  nm with an average elongation at a break of  $117.4 \pm 4.135\%$  and tensile strength of  $5.27 \pm 0.34$  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 in vitro 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  $99.7 \pm 0.85\%$  [176].

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  $121.8 \pm 3.4$  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 [177].

Celebioglu et al. created nanofibrous scaffolds based on hydroxypropyl- $\gamma$ -cyclodextrin and hydroxypropyl- $\beta$ -cyclodextrin embedded with curcumin. The nanofibrous scaffolds had a homogeneous fibrous structure without beads. The nanofibrous scaffolds were  $165 \pm 65$  nm in diameter on average. In the nanofibrous scaffolds, the curcumin encapsulation effectiveness (%) was  $98.8 \pm 1.6\%$  and  $99.3 \pm 1.0\%$ , 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- $\beta$ -cyclodextrin. The hydroxypropyl- $\gamma$ -cyclodextrin nanofibrous webs coated with curcumin have promise as wound dressings [178].

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 [179].

Esmaili 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 [180].

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  $386 \pm 121$  nm to a diameter that ranged between  $333 \pm 124$  and  $380 \pm 113$  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 [181].

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 [182].

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 [183].

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 [184].

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  $3.78 \pm 0.17$  MPa dropped to  $1.84 \pm 0.12$  MPa. Curcumin-loaded nanofibrous scaffold's water contact angle investigations revealed that they were hydrophilic, with a contact angle of  $48.9 \pm 5.4$ . 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 [185].

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 [27].

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 [186].

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  $58 \pm 7\%$  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 [187].

Curcumin-loaded PCL and gelatin membranes increased collagen content in diabetic wounds and were effective promoters of wound healing in the early stages, as well as accelerating the healing process. The observed effect could be attributed to the scaffolds' nanofibrous structure, which mimics natural ECM, the high biological properties of gelatin, the sustained release of curcumin for 20 days, and the high physical-mechanical properties of PCL, which cause scaffold stability in the presence of blood and fibrin. Histo-chemical results showed much better healing performance for scaffold stem cells followed by acellular scaffolds compared with control samples because of stem cells' ability to regenerate collagen and provide the signals needed for tissue building. Nanofibers decreased blood glucose levels compared with control samples. In conclusion, the application of scaffolds was effective in the healing of wounds in the diabetic rat models [165].

**Table 6.** The effect of curcumin-loaded nanofiber diameters and drug release profiles on electrospinning parameters and polymer/solvent combinations.

S. No	Curcumin & Additives	Solvents	Dosage	Electrospinning Setting			Diameter (nm)	Drug Release Profile	Ref
				kV	cm	mL/h			
1	PCL	CHCl <sub>3</sub> : Methanol	3 & 17% w/w	25	10	2	300–400	3%—20 µg at 3 d 17%—35 µg at 3 d	[27] December 2009
2	p(HEMA)	Ethanol: H <sub>2</sub> O	3 & 5 wt%	25	17	0.5	20–110	63% at 120 h 72% at 240 h	[162] January 2015
3	PLA	CHCl <sub>3</sub> : DMAc	0.125, 1.250, 6.250 wt%	11	12	1	300–1200	–	[163] June 2013
4	CA	IPA: EA	5, 10, 15, 17.5, 20 wt%	12	15	1.5	300	309.02 µg/cm <sup>2</sup> at 24 h	[164] September 2017
5	PCL/GT	Acetic acid	1, 3, 8, 24%	15	15	1	667 ± 33	42.6% at 10 d 65% at 20 d	[166] March 2016
6	PCL	Acetic acid: Formic acid	0.5 wt%	11	10	0.4	499	80% at 2 h	[167] November 2019
7	PLA	CHCl <sub>3</sub> : Acetone	10 wt%	20	15	0.5	430–750	9 µg/cm <sup>2</sup> at 24 h	[168] April 2020
8	PHBV	CHCl <sub>3</sub> : DMF	0.1, 0.3 0.5% w/v	17	20	0.01	207–519	45%, 63%, 78% at 200 min	[169] February 2018
9	PCL	DCM: DMF	0.5 wt%	8.5	16	0.8	300–1200	5, 4.1 µg at 24 h	[170] November 2014
10	PCL-PEG -PCL	Acetone: CHCl <sub>3</sub> CH <sub>3</sub> OH	5%, 10% w/w	28–30	10	2	50–300	59, 68, 81.5%, respectively	[171] December 2019
11	PLA	CHCl <sub>3</sub>	10, 15 wt/wt%	13–15	12	0.5	516	32 µg/mL at 72 h	[172] March 2017
12	PCL-PEG	CHCl <sub>3</sub> : Acetone	8.7%	18	15	2	400 ± 20	95.11% at 24 h	[173] April 2018
13	PCL	HFIP	5, 10 wt%	20	21	0.5	427–651	burst release at 24 h	[174] February 2020
14	PCEC	DCM	20 wt%	18	12	6	535	burst release within the first 24 h	[175] April 2014
15	PLLA-PCL	HFIP	2.0%, 4.0% 6.0% w/w	10	15	1.2	293 ± 110	sustain released over 72 h	[176] Nov. 2014
16	CA-PVP	Acetone: H <sub>2</sub> O	10%	25	15	3	1560 ± 145	22% (1.2 µg/mL) at 120 min	[177] April 2017
17	PU-CA	DMF: THF DMF: Acetone	4.0 wt%	17	15	0.4	222 ± 44	–	[180] February 2020
18	PLLA	DCM: DMF	0.2, 0.5, 1.0% w/w	24	15	-	380 ± 113	22, 34, 58% at 50 h	[181] October 2019
19	CA	Acetone: DMAc	5, 10, 15, 20 wt%	17	15	1	340 ± 98	90 to 95% at 50 h	[183] December 2007
20	PCL	HFIP	2.5 mg/mL	18	20	0.3	1548 µm	23% at 6 h Until 106 h	[185] June 2020

## 8. Concluding Remarks and Future Perspectives

Diabetic wound healing is still a complex clinical issue, and wound treatment must be done correctly and efficiently. Wound care has received much attention, focusing on innovative treatment techniques and technological development for acute and chronic wound management. One hundred pharmaceutical companies produce numerous curcumin formulations for treating numerous illnesses, including cancer, diabetes, inflammatory bowel disease, cardiovascular disease, and neurological disorders. Many of these formulations are also undergoing clinical trials. However, curcumin has been found to have various pharmacological effects, and its anti-inflammatory and antioxidant qualities notably support its future use as a treatment for wounds. There are several curcumin-based dietary supplements on the market right now, including CurcuMIND, Longvida RD CAVACURMIN, CurcuVIVA™, Theracurmin™, Biocurcumax™, and BCM-95, and many more. Numerous topical formulations of curcumin, including nano-architectures, have been created and tested to improve the drug's capacity to promote wound healing. The main benefits of the topical nanoformulation of curcumin include its solubility, enhanced bioavailability, and sustained release of curcumin in an active form, all of which are unquestionably very advantageous for maintaining a steady dose of the medication over an extended period to enhance wound healing. Before future clinical development, it is crucial to comprehend the ideal dosage of curcumin for several targets, most notably its complicated involvement in the inflammatory response during wound healing.

Over the last two decades, electrospinning technology has garnered a growing interest as a very adaptable method for producing micro-nanofibers of different sizes. Electrospun fibre material has an exceptionally high specific surface area, porosity, surface functionality, and fiber morphological adjustability. These features provide the Electrospun fiber material with an array of perfect properties that may satisfy the application needs of various sectors, including biomedicine and tissue engineering. Moreover, Electrospun nanofibers may transport a range of bioactive compounds and continually release medications which are particularly advantageous for enhancing the diabetic wound's overall effectiveness. The literature reviewed here demonstrates that incorporating curcumin into Electrospun nanofibers and topical application at the wound site has been investigated to prevent or treat skin infections and to facilitate more effective skin regeneration by mediating the distinct phases of wound healing.

However, this innovative dressing must be examined in many clinical studies before its ultimate clinical use. The execution of clinical trials is essential for commercializing Electrospun membrane-based drug delivery systems intended to promote skin regeneration and improve patients' quality of life. In addition, additional research is required to determine the shelf life and optimal storage conditions of Electrospun mats. Before that, Electrospun-based wound dressings must be improved in production and reproducibility, wound healing research must be accelerated, and more clinical trials of Electrospun-based wound dressings must be accelerated. Bioactive ingredients of antimicrobials, antibiotics, anti-inflammatory agents, and traditional medicines might be incorporated into the Electrospun solution to develop new bioactive Electrospun nanomaterials that can be released into the wound site to accelerate the healing of diabetic wounds.

This review's summary states that several topical Electrospun nanofiber formulations of curcumin have been created to improve therapeutic benefits by steadily delivering curcumin to the injury site. However, the research should take a systematic approach to explore the molecular processes underlying its capacity to control cellular wound environment and chronic inflammation. Although current research on several topical formulations of curcumin seems encouraging, clinical studies are still required, since most published data are generated from *in vitro* and *in vivo* tests. Therefore, shortly, experimental human clinical studies should clarify the therapeutic wound-healing effectiveness of different nanofiber topical formulations and answer concerns about their safety in biological systems.

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