Discover Materials

Review

Electrospun metal–organic framework-based nanofibers with natural therapeutic agents for enhanced diabetic wound healing

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Abstract
Diabetes mellitus (DM) poses a significant global health challenge, with diabetic foot ulcers (DFUs) standing as a serious consequence of this metabolic disorder. The intricate interplay of peripheral neuropathy, compromised blood supply, susceptibility to infections, and delayed healing processes in diabetic patients underscores the urgency for innovative wound management strategies. This review delves into the promising realm of electrospun metal–organic framework (MOF)-based nanofibers loaded with natural therapeutic agents, offering a multifaceted approach to accelerate diabetic wound healing by offering synergistic anti-inflammatory, anti-oxidant, and anti-bacterial properties. The incorporation of MOFs, characterized by their inorganic porous structures, alongside polymeric nanofibers, has the potential to enhance drug loading capacity and prevent burst release effect of nanofibers. This paper aims to provide a comprehensive understanding of the diabetic wound healing process, elucidate the properties of MOFs with exceptional porosity and high surface-to-volume ratios for extended and controlled drug release, and highlight the unique attributes of electrospun nanofibers in creating a conducive wound environment for tissue repair, re-epithelialization and vascularization. Additionally, this review explores seven natural therapeutic agents—borneol, clove essential oil, curcumin, chrysin, honey, aloe vera, quercetin, and rutin, showcasing their potential in diabetic wound care by enhancing the granulation tissue formation, collagen deposition, tissue remodeling and wound contraction. This comprehensive examination serves as a valuable resource for researchers and practitioners seeking advanced solutions for the management of diabetic foot ulcers.

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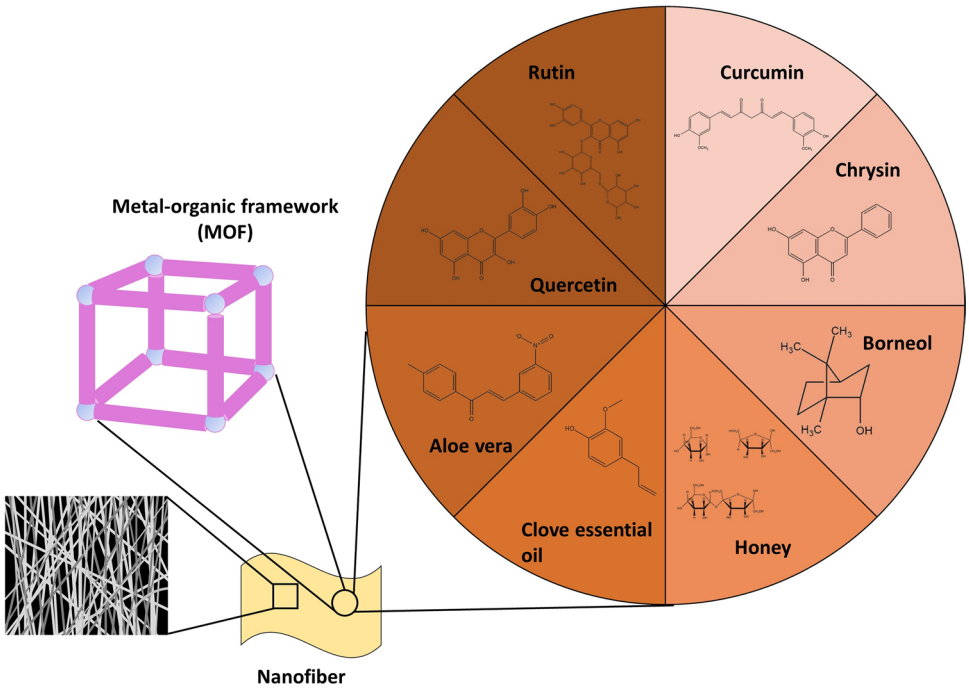
Graphical Abstract



Keywords Metal–organic framework · Diabetic wound healing · Nanofiber · Natural therapeutic agents

Abbreviations

AGE	Advanced glycation end product
AKT	Kinases protein kinase B
Arg	Arginase 1
CHL	Ciprofloxacin hydrochloride
COX	Cyclooxygenase
DFU	Diabetic foot ulcer
DM	Diabetes Mellitus
DPI	Diphenyleneiodonium chloride
ECM	Extracellular matrix
GEL	Gelatin
GSK	Glycogen synthase
HO-1	Heme-oxygenase-1
IKK	Ikappa B kinase
IL-6	Interleukin-6
iNOS	Inducible nitric oxide synthase
LPS	Lipopolysaccharide
MMP	Matrix metalloproteinase
MNP	Metal nanoparticles
MOF	Metal–organic framework
MONP	Metal oxide nanoparticles
NADPH	Nicotinamide adenine dinucleotide phosphate hydrogen
NK-κB	Nuclear factor κ
NRF2	Nuclear factor erythroid 2-related factor 2
PCL	Poly(ε-caprolactone)

PDDA	Poly (diallyldimethylammonium chloride)
PDGF	Platelet-derived growth factor
PI3K	Phosphatidylinositol-3-kinase
PLA	Poly (lactic acid)
PLGA	Poly (lactic-co-glycolic acid)
PLLA-CL	Poly(l-lactide-co-ε-caprolactone)
PPAR-γ	Peroxisome proliferator-activated receptor-gamma
PU	Polyurethane
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
SEM	Scanning electron microscope
TERT	Telomerase reverse transcriptase
TGF T	Transforming growth factor
TIMP	Tissue inhibitors of metalloproteinases
TLR4	Toll-like receptor 4
TNF-α	Tumour necrosis factor alpha
VEGF	Vascular endothelial growth factor

1 Introduction

Diabetes mellitus (DM) remains a persistent and complex metabolic disorder, imposing a considerable burden on global health with manifestations ranging from ocular complications to chronic wounds [1]. The observed 3% escalation in DM mortality rates from 2000 to 2019, as reported by the World Health Organization, underscores the gravity of this health crisis [2]. With a global prevalence of 10.5% (536.6 million) in 2021, projected to reach 783.2 million in 2045, the urgency to address this escalating epidemic is paramount [3].

The ramifications of DM extend to compromised self-repair mechanisms, entwined within the intricate pathophysiological network encompassing vascular, neuropathic, immune, and biochemical components [4]. Hyperglycemia emerges as a chief orchestrator, impeding leukocyte function, curtailing blood circulation, and fostering microvascular dysfunction, thereby augmenting susceptibility to bacterial infections [5]. This cascade culminates in the formidable challenge of diabetic foot ulcers (DFUs), afflicting 19–34% % of individuals with diabetes and exhibiting a disconcerting 65% recurrence rate at 3–5 years [6].

This manuscript embarks on a scholarly exploration of diabetic wound healing, emphasising the imperative for engineered matrices in skin grafts as a therapeutic avenue for DFU management. A focal point of this inquiry is the ideal biomimetic dressing—a construct embodying biocompatibility, non-toxicity, and a spectrum of wound management attributes [7, 8]. Traversing the scientific landscape of the past decade, metal–organic frameworks (MOFs) have garnered attention for their potential in drug delivery systems. These crystalline porous solids, characterized by ultrahigh porosity, offer promise in wound healing by imparting bactericidal efficacy and fostering angiogenesis [9–11]. However, their practical application is hampered by stability concerns, a challenge mitigated through their strategic integration with polymer nanofibers, distinguished by flexibility and sensitivity [12].

Traditional wound dressings such as gauze, and bandages with limitation such as failure to provide moist environment and promote haemostasis, and adherence, has stimulated the interest in advanced wound dressings (film, hydrogel, nanofiber, and sponges) [13]. Recently, several antibacterial wound dressings have been widely suggested as a promising material to manage wound healing [14]. Nanofibers, synthesized in the nanometre range through electrospinning of natural or synthetic polymers, have emerged as versatile agents in diverse fields, including drug delivery and tissue engineering [15]. Compared to other wound dressings, it has the potential to create a three–dimensional microporous structure in order to mimic the human body extracellular matrix (ECM) structure, which is conducive to cell proliferation and adhesion for promoting wound healing [16]. Apart from the role of nanofiber in promoting tissue formation, and vascular regeneration, nanofiber with high porosity enables efficient loading of therapeutic agents, providing continuous drug release to accelerate wound healing [17]. To overcome the burst release effect of nanofiber, MOF has been incorporated into nanofiber to enhance drug loading capacity, slow down the drug release and reduce the toxicity of MOF [18].

This review articulates the narrative of diabetic wound healing, illuminating seven natural therapeutic agents intricately interwoven into nanofibrous scaffolds. As we traverse the terrain of curcumin, chrysin, borneol, honey, clove essential oil, aloe vera, quercetin, and rutin, the narrative converges on MOFs and nanofibers, culminating in the promising prospect of electrospun MOF-based nanofibers loaded with dual-drugs—a beacon of optimism in the quest to enhance diabetic wound healing.

2 Diabetic wound healing

2.1 Normal wound healing

Wound healing is a complex and compelling process which involves the interaction between various cells, signalling molecules, cytokine, and vascular systems. It is divided into four different stages: hemostasis, inflammation, fibroblast proliferation, and wound remodelling [19, 20]. Figure 1 shows the overview of the wound healing process.

In the wound healing process, hemostasis is the earliest reaction to stop the bleeding through vasoconstriction of blood vessels, platelet deposition, and fibrin plug formation at the damaged blood vessel [22]. Fibrin plug permits the recruitment of cells in the wound site by serving as a temporary ECM for migrating cells and releasing growth factors such as platelet-derived growth factor (PDGF) and transforming growth factor (TGF) [23]. In inflammatory phase, it involves the migration of inflammatory cells such as neutrophile, macrophage, and lymphocyte to the injury site as well as their secretion to prevent the risk of infection, induce cellular migration, and angiogenesis [24]. Macrophages and

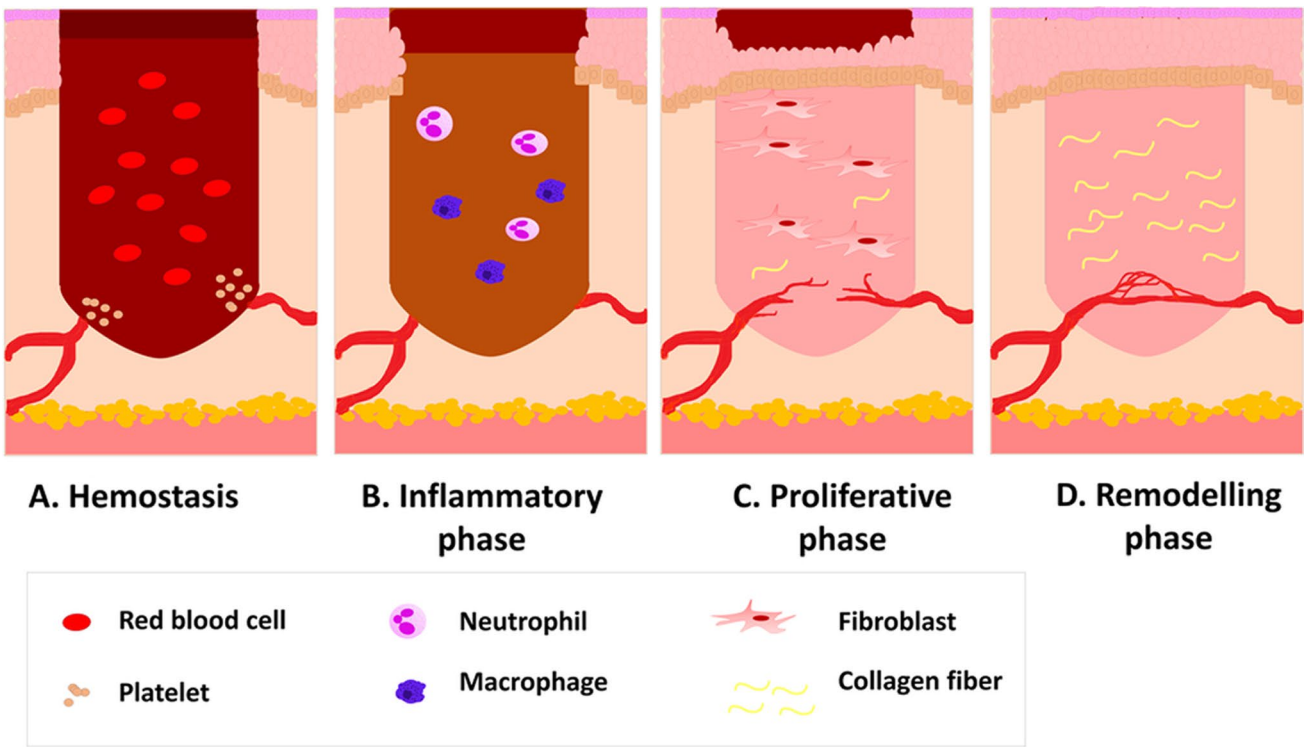


Fig. 1 Overview of wound healing process [21]. **A** Hemostasis. To stop the wound bleeding, vasoconstriction occurs by constricting the blood vessel in the damaged wound area. Aggregation of platelets at the wound site allows the thrombin generation and fibrin formation to prevent blood loss. **B** Inflammation. This stage involves the infiltration of macrophages and neutrophiles to facilitate the phagocytosis of bacteria and debris. **C** Proliferation. Angiogenesis which is genesis of granulation tissues of this phase, occurs to replace the tissues that have been damaged. Production of fibroblast and collagen causes the tissue regeneration of this proliferative phase. This phase involves the construction of new network of blood vessels to provide sufficient oxygen and nutrient for the granulation tissues. **D** Remodelling. Collagen production continues throughout the remodelling phase. Crosslinking of collagen decreases the scar thickness and allows the skin area to become stronger

neutrophiles play a significant role in the regulation of inflammatory response because they are the primary responders to eliminate pathogenic for the prevention of bacterial infection [25]. To prepare the wound bed for the growth of new tissue, the release of reactive oxygen species (ROS) and matrix metalloproteinase (MMP) by inflammatory cells allows the elimination of wound site bacteria and cell debris [26]. Furthermore, the secretion of inflammatory mediators involving prostaglandin and histamine increases the vasodilation and permeability of peripheral blood vessels [19]. Hypoxia, a condition of insufficient amount of oxygen in body tissue, stimulates the keratinocyte migration, angiogenesis, fibroblast proliferation and release of growth factors as well as cytokine [20]. Following, the wound enters the phase 3, proliferative phase which includes: (1) new tissue formation, (2) granulation tissue formation, (3) re-epithelization, and (4) restoration of vascular network [19]. During phase 3, fibroblast is responsible for angiogenesis and formation as well as modification of granulation tissue ECM at the repaired site. ECM which consists of a network of type III collagen, acts as a scaffold to support different cells for angiogenesis and neovascularization [20]. Angiogenesis which is the genesis of granulation tissues of this phase, occurs to replace the tissues that have been damaged. Production of fibroblast and collagen causes tissue regeneration [27]. The proliferation of keratinocytes facilitates the repair of the epidermal barrier through re-epithelization of the wound [23]. Next, the remodelling phase or reconstruction, the last stage of the healing process, causes the reorganization and contraction of the newly formed matrix [28]. In this stage, the granulation tissue disappears while the vascular network reduces. To promote wound closure and scarring, the replacement of type III collagen with stronger type I collagen occurs. Ultimately, the result of tissue repair of a wound is the formation of a scar formation [19, 28].

2.2 Diabetic wound healing

If the wound fails to follow the proper wound healing progress, it results in chronic wound due to delayed healing [26]. Chronic wound such as DFU is accompanied by various pathological changes such as increased of bacterial growth, inflammation, growth impairment of capillaries, reduced of local bioavailability and local concentration of growth factors [1, 29]. Early relative hypoxia stimulates wound healing for regulation of critical processes for wound repair while prolonged hypoxia is a main factor of diabetic wounds leading to delayed healing [1, 30]. Figure 2 shows the overview of the diabetic wound healing process.

For diabetes patients, high blood glucose level contributes to delayed diabetic wound healing process by preventing the proper blood flow. Accordingly, poor blood circulation results in deficiency of oxygen and nutrient supply followed by inhibition of angiogenesis [1, 32]. Besides, high blood sugar level attenuates the wound healing rate by inhibiting the nutrient and oxygen uptake from energizing cells. Apart from that, DM reduces the capability of red blood cells passing through vessels leading to augumented of blood glucose level, and increased of blood thickness [1]. Owing to the high

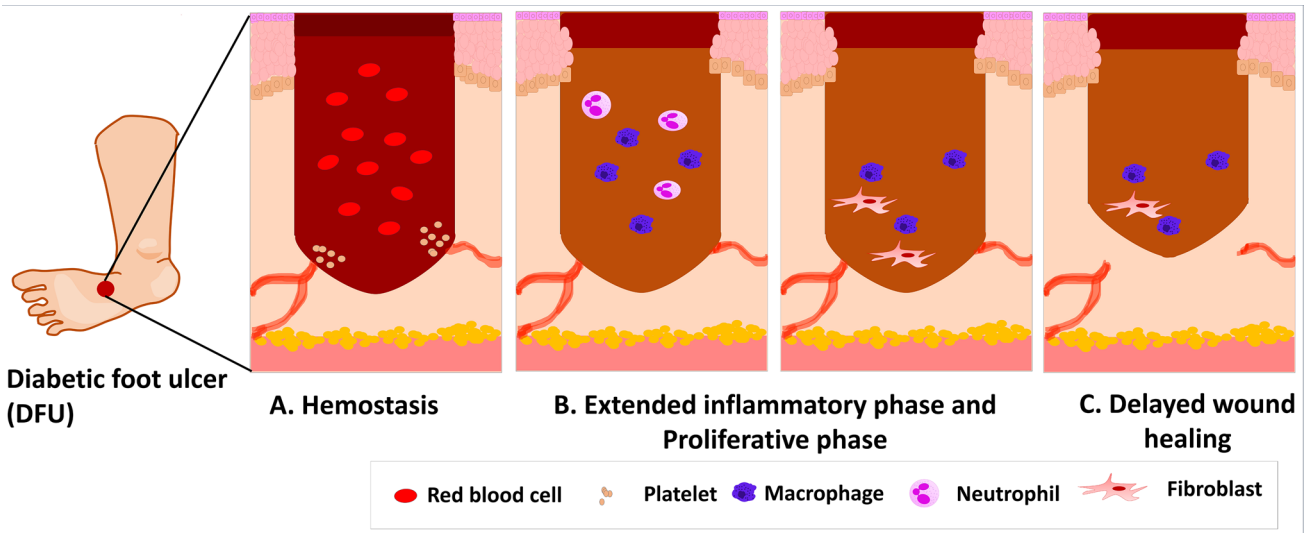


Fig. 2 Overview of the diabetic wound healing process. In the inflammatory and proliferative phases, diabetic wound causes sustained production of pro-inflammatory cytokines, impaired macrophage and neutrophils function, and impaired angiogenesis. Extended inflammatory and proliferative phases leads to delayed wound healing, thereby scar formation [31]

blood glucose level in diabetes patients, advanced glycation end product (AGE) inhibits the wound healing process by delaying the inflammatory and proliferative phases. Also, AGE increases the free radical generation contributing to oxidative stress, tissue damage, and ultimately delayed of wound healing [33, 34]. Inflammation induced by oxidative stress in diabetic wound impairs collagen depositions and ECM remodelling [20]. ROS overexpression and persistent inflammatory responses are important factors for chronic diabetic wound [34].

Additionally, hyperglycaemia in diabetes contributes to the dysfunction of the immune response by preventing the immune cells from fighting against invading bacteria [35]. By weakening the immune system in diabetes patients, the number and ability of immune fighter cells are decreased leading to an increased risk of infection and a reduced wound healing rate. The inability of the wound to heal is associated with a high blood sugar environment that upregulates the risk of infection by providing favourable conditions for bacterial growth, thereby further delaying wound healing. When the blood sugar level is high, bacteria grow faster than in a normal wound. Once infection occurs, the proliferation of bacteria affects haematosis leading to prolonged inflammation [36].

3 Metal–organic framework (MOF)

Transitioning from the complexities of wound healing to potential solutions, metal–organic frameworks (MOFs) present a novel avenue for wound care. It is a novel type of crystalline porous coordination containing two major components: coordinating metal or inorganic metal ion, and organic ligand to form various topological isomeric structure [10, 37]. Similar to the antibacterial action of metal (MNP) or metal oxide nanoparticles (MONP) [38], MOF provides the condition for the gradual release of metal ions for continuous and long-term antibacterial effect [39]. Nevertheless, MOF has an advantage over MNP and MONP by preventing the metal oxidation and agglomeration [9].

MOF can improve the therapeutic outcome due to its unique crystal structure properties, non-toxic, and low cost [10]. Apart from that, important properties of MOF involve ease of engineering, high specific surface area, ultrahigh porosity, good biocompatibility and biodegradability, low skeleton density, adjustable uniform pore size, high thermal stability, and facile functionalization [9–11]. Therefore, MOF is widely used in the field of gas adsorption and separation [40], biosensing [41], bioimaging [42], energy storage [43], luminescence [44], catalysis [45], proton conduction [46], diagnostic and therapeutic biomedicine [9]. Importantly, this effective wound-healing device is critical in the biomedical field due to its targeted delivery stability, controlled release of loaded content, and biological properties [9, 10].

There are several types of MOF synthesis methodology with different yield synthesis, and physicochemical characteristics involving: solvothermal or hydrothermal synthesis, sonochemical synthesis, conventional solution method, diffusion synthesis, ionothermal synthesis, microwave-assisted synthesis, and electrochemical synthesis. Geometric morphologies, biological function and application of MOF are correlated with the methodology of MOF synthesis selected [47, 48].

The synthesis and morphologies of MOF are based on the types of metal sources and ligands utilised in the reaction process [47, 49]. Metal ion, the central metal element of MOF, includes copper [50], zinc [51], cobalt [52], and silver [53]. Different metal ion has different antibacterial mechanisms [53]. Metal ion changes the cell membrane permeability allowing leakage of internal nutrients to cause cell death [39]. To damage bacteria, the production of ROS by metal ions induces an oxidative stress response. It also reduces the content of reduced coenzyme II (NADPH) oxidase inhibitor (DPI) in bacterial cells. When the cell's electron transport is destroyed by metal ions, it results in the inactivation of bacteria [39, 54].

MOF functions not only as a reservoir and also reasonable wound healing device. As an effective and controlled drug delivery system for wound healing, MOF provides a long term antibacterial effect because MOF materials act as biocatalysts or drug carriers for improving wound healing. The antibacterial effect of MOF prevents bacterial growth in the wound site facilitating angiogenesis in the degradation process of MOF [10, 39].

4 Nanofiber

Expanding our exploration of wound care materials, nanofibers, characterized by diameters in the tens of nanometers, emerge as versatile wound dressings [15]. It has advantages over other nanocarriers (polymer nanoparticles, micelles, liposome, nanotubes, dendrimers, hydrogels, mesoporous silica nanoparticles, and thin film) because of its high surface-area-to-volume ratio, good wettability, ease of scalability, improved mechanical strength, ultrafine diameter, high porosity, morphological organization similar to native ECM, high drug-encapsulating efficiency, enhanced cell adhesion,

proliferation, migration, and differentiation [55]. Interestingly, this biocompatible matrice has the potential to act as a substrate for the attachment and growth of cells [15].

Nanofiber fabrication is conducted by several physical and chemical methods including electrospinning [56], physical vapour deposition [57], laser ablation [58], chemical vapor deposition [59], electrochemical deposition [60], and template-assisted synthesis [61]. However, electrospinning, a simple, inexpensive and versatile nanofabrication technique, is widely used for processing a wide variety of polymers biomaterials into nanofiber because it provides commercialization ease, enhanced production rate, high material choice and low cost [15]. In addition, this attractive technique in which centrifugal force continuously draws the fiber from viscoelastic fluid instead of the electric field is able to control over the thickness, composition of nanofiber, and porosity of nanofiber meshes [55].

Natural and synthetic polymers are widely used in nanofiber preparation via electrospinning. Synthetic polymers used for nanofiber generation involve poly (lactic acid) (PLA) [62], polyurethane (PU) [63], poly(ε-caprolactone) (PCL) [64], poly (lactic-co-glycolic acid) (PLGA) [65], poly(ethylene-co-vinylacetate) (PEVA) [66], and poly(l-lactide-co-ε-caprolactone) (PLLA-CL) [65]. In contrast to synthetic polymers with high toxicity, and poor biocompatibility [67], natural polymers have been widely utilised for nanofiber production due to their cost-effectiveness, biocompatibility, biodegradability, bioactivity, and low toxicity [68]. Natural polymers are classified into two classes: polysaccharides and proteins of either plant or animal origins [68]. Other than polysaccharides of plant origin such as pectin [69], cellulose [70], and alginate [71], the animal polysaccharides-based biopolymers involve chitosan [72], chitin [73], hyaluronic acid [74], and silk [75]. Whereases, animal protein-based biopolymers include collagen [76], gelatin [77], and keratin [78].

Generally, electrospinning originated from electrospraying, is divided into 4 consecutive steps [79]. Firstly, the formation of Taylor cone or cone-shaped jet is initiated by applying an electric field on the liquid droplet. A charged jet is extended along a straight line when the stable jet is accelerated and stretched. To form nanofiber, the electrical bending instability, known as whipping instability, is required for stretching the jet into finer ones instead of spitting the jet into particles [80]. The rapid growth of whipping instability by bending or stretching the jet is critical to obtain ultra-thin nanofiber. After the thinning of the jet, the final step is the deposition of fiber. It involves the solidification of the jet due to the evaporation of solvent or cooling of melt followed by the collection of jet as a nonwoven web in the collector [79, 80]. Figure 3 shows the overview of electrospinning.

The electrospinning process is affected by system and process parameters [79]. For system parameter, the diameter of the nanofiber is determined by the polymer solution properties such as viscosity, surface tension, and conductivity to prevent bead formation. In addition to system parameters, optimization of process parameters is critical for the electrospinning process. For instance, diameter of nanofiber is based on the orifice diameter, fluid flow rate, and applied voltage. Furthermore, the tip-to-collector distance affects the extent of evaporation of solvent from nanofiber. Also, optimization of the motion collector is needed for the determination of the pattern formation during the deposition of fiber [15, 79].

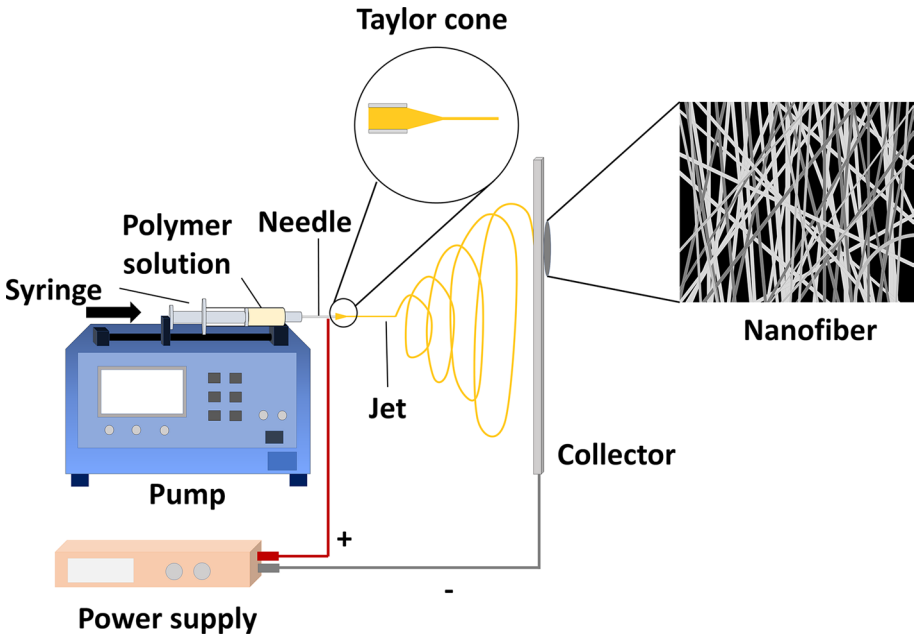


Fig. 3 Overview of uniaxial electrospinning [81]

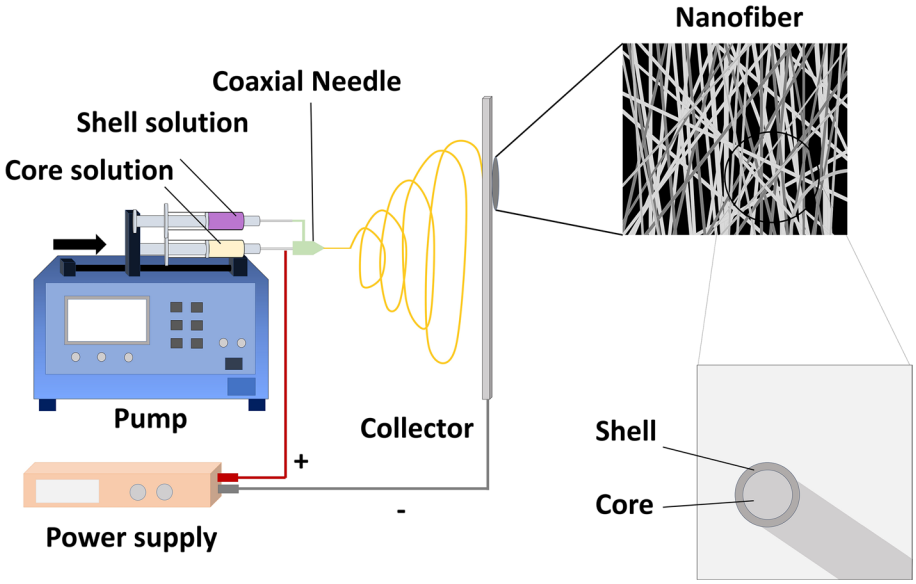


Fig. 4 Overview of coaxial electrospinning [91]

In addition to uniaxial or simple electrospinning, several types of electrospinning have been used to fabricate nanofiber for diabetic wound healing applications such as coaxial electrospinning and melt electrospinning [82]. To obtain core–shell nanofibers, coaxial electrospinning utilises a coaxial spinneret made up of outer and inner needles [83]. By placing the two needles coaxially, the internal needle is used to pump the inner liquid while the external needle is used to deliver the shell material (Fig. 4) [84]. Compared to uniaxial electrospinning, the advantages of coaxial electrospinning include the high loading capacity of drug molecules, allows encapsulation of multiple drugs with different hydrophilicity in the core and shell, and more sustained release of drug [85]. Previous studies reported that the core–shell nanofiber by coaxial electrospinning accelerated diabetic wound healing by improving the antibacterial and antioxidant effect due to the superior efficacy of core–shell morphology in controlling the drug release [86–88]. Kazemi et al. reported that the core–shell nanofiber with a core composed of polyacrylamide and a shell comprising L-Arginine in aloe vera and keratin not only resulted in smaller fiber diameter but also increased the surface area to volume ratio leading to higher water holding capacity and L-Arginine release [89]. Furthermore, core–shell nanofibers exhibited superior re-epithelization, angiogenesis effect and enhanced collagen deposition [89]. In rat model, Tavakoli et al. demonstrated that the core–shell nanofiber containing polyvinyl alcohol, gelatin shell and advanced platelet-rich fibrin accelerated the wound healing process by showing 97.83 ± 2.03% of wound closure within 11 days [90]. Other than the low output of core–shell nanofiber by coaxial electrospinning, the optimization of the compatibility of core and shell fluids is important for core–shell nanofiber formation [83].

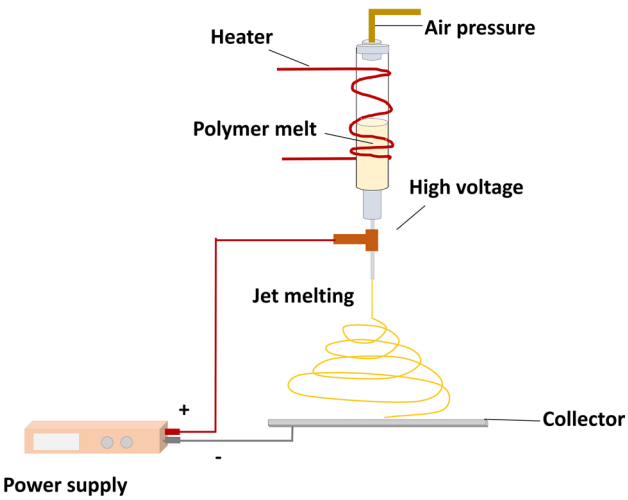


Fig. 5 Overview of melt electrospinning [92]

To fabricate scaffold with 3D structure, melt electrospinning forms the micro-, and nanofibers by melting the polymers under high temperature conditions (Fig. 5) [92]. Contrary to solution electrospinning, melt electrospinning is more environmentally friendly because this method is a solvent-free process [92, 93]. Mirzaei et al. demonstrated that the melt electro written polycaprolactone modified with yeast derived peptides exhibited superior anti-inflammatory effect and increased fibroblast macrophage penetration, as well as the cell proliferation [94]. Nonetheless, drawbacks of melt electrospinning include the formation of fiber with larger diameter, and higher degradation rate due to high melting point [92].

Other than the pre-electrospinning modification by incorporating the biologically agents before the electrospinning process, post-electrospinning modification is a treatment of the membrane surface after the electrospinning process [95]. Post-electrospinning modification is divided into two types: physical and chemical modifications [95, 96]. Post-electrospinning physical treatment includes physical adsorption and layer-by-layer assembly while the chemical approach involves the wet chemical functionalization and covalent grafting [96]. In contrast to pre-electrospinning methods, the post-electrospinning modification only alter the surface of fiber [96, 97]. For wound healing application, chemical modification on the surface of fiber allows better cell infiltration and favourable cell attachment by providing steady bioactive sites for biomolecules immobilization [15, 95, 98]. Despite many advantages, there were several disadvantages of post-electrospinning modification such as mechanical weakening due to molecular degradation of polymer chain, surface crystallinity, and temporary cell adhesion for physical adsorption method [96, 99].

One of the main characteristics of nanofiber is the drug release by occurring in two phases: (1) burst release, and (2) sustained release [100, 101]. Burst release is caused by the release of unbound surface drug on nanofiber while sustained release is due to slow digestion of polymer and release of drug encapsulated. Generally, drug release relies on several factors such as drug concentration, degree of hydrophilicity of polymer, linkage or non-linkage between drug and polymer, and degree of drug encapsulation in polymer [85, 101].

Importantly, nanofiber is able to limit and remove the adverse effect of drug incorporated by reducing the initial burst of release drug [100]. Application of nanofiber for wound healing provides moist environment for wound healing stimulation such as haemostatic phase to allow full regeneration of injured tissue. Besides, it helps to leave no scar and reduce the risk of bacterial infection by protecting the wound from bacterial penetration [102–104]. Importantly, the incorporation of therapeutic agents such as curcumin, chrysin, borneol, honey, clove essential oil, aloe vera, quercetin, and rutin into nanofibers acts as functionable wound dressing for improvement of therapeutic outcome of diabetic wound healing.

5 Metal–organic frameworks (MOFs) based nanofiber

Previously, direct application of MOF for wound healing management has attracted extensive attention due to its role of drug carrier of antibacterial agents [105]. MOF regulates the cellular behavior and inhibits bacterial growth, accelerating the wound healing process [105–107]. However, the topical application of MOF at wound site still remains in the laboratory level compared to other drug carrier nanomaterials such as nanofiber [108]. The disadvantages of direct application of MOF for wound healing include high toxicity, higher concentrations of metal ions and organic ligands, and low degradation rate in cells [107]. When the MOF is modified with the drugs by using one-step synthesis, the drug molecules degrade under high temperature and pressure [107].

Despite there were extensive researches on the nanofibers loaded with natural therapeutic agents for wound healing application, burst release of drug molecules from nanofibers was one of the main limitations [109]. To overcome this problem, the presence of MOF within the nanofiber is expected to slow down the drug release [110]. Based on previous finding conducted by Wang et al., the polyacrylonitrile composite nanofiber loaded with Portulaca oleracea L. extract and a zinc-MOF slowed down the cumulative drug release from 90.54% for nanofiber without MOF to 65.92% for nanofiber with MOF within 72 h [110]. Furthermore, MOF which acts a drug carrier, has better drug loading capacity than polymer blend for nanofiber formation [110, 111]. Therefore, it is expected to load the natural therapeutic agents into MOF followed by the loading of the drug-loaded MOF into nanofibers to lower the toxicity of MOF and enhance the wound healing effect.

Nonetheless, the research on the integration of MOF-based nanofibers carrying dual drugs for wound healing application still remains in the early stages. In addition to the optimisation of MOF modification with drugs, the selection of the solvent used for the MOF synthesis and nanofiber formation must be consider to decrease the toxicity and prevent drug degradation [108].

Now, let's delve into the synergy between MOFs and nanofibers. Combining the unique properties of MOFs with nanofiber design creates structures with hierarchical porosity via electrospinning, offering advantages such as lightweight,

Table 1 The MOF-based nanofibers for wound healing application

MOF-based nanofibers	References
Glucose oxidase/carbon dots@copper-MOF-based nanofiber	[115]
Curcumin and silver-MOF loaded three-dimensional (3D) layered nanofiber	[116]
Copper-MOF-based nanofiber	[117]
Zirconium-based MOF armed polyvinyl alcohol nanofiber	[118]
Tannic acid and zinc-based MOF loaded chitosan-based nanofiber	[119]
Silver-MOF loaded PLA nanofiber	[120]

high porosity, large surface area, numerous active sites, high flexibility, and loading capacity [69, 112]. The presence of organic–inorganic nature and low density of MOF-based nanofiber allows the high compatibility between MOF and polymeric fiber rather than MOF-based composite (metal, metal oxide, and clays) [69, 112]. MOF-based nanofiber has been widely utilised in several applications: biomedical delivery [69], air filtration [113], water treatment [112], and sensor application [114]. Recently, several MOF-based nanofibers have been studied in the wound healing application (Table 1).

MOF-based nanofiber is synthesized by two different synthesis strategies including synthetic composites from pre-synthesized MOF and in situ MOF on nanofiber surface [69, 112, 121]. Synthetic composite from pre-synthesized MOF using direct electrospinning method is conducted by direct electrospinning the mixture slurry containing MOF particles and polymer solution into composite nanofiber to allow the embedment of MOF into polymeric nanofiber matrix. Nonetheless, accessibility of MOF activity is limited because the polymer matrix covers the surface and inner pores of MOF particles [122]. To overcome this limitation, in situ MOF on nanofiber surface using surface decoration permits the growth of MOF particles on the surface of nanofiber without affecting the physical and chemical properties of MOF. Two-step preparation is necessary for this growing method by involving electrospinning of polymeric nanofiber layer followed by the growth of MOF with crystalline size and controlled thickness on the surface of the nanofiber [121]. Optimization of experiment conditions (concentration of MOF, viscosity of slurry and voltage) and chemical compatibility of polymers, solvent, and MOF component is critical for this strategy [123]. By comparison, immobilization of MOF with drug on fiber surface using the growing method has higher drug release capacity and better antibacterial effect than the electrospinning method. Also, the growing method allows higher drug loading, regulation of drug release rate as well as fast recovery effect [69, 124].

In addition to the single-drug delivery system, MOF has the potential to act as a single carrier for the co-delivery of two distinct drugs [125]. Dual-drug-loaded MOF not only offers a synergistic effect of two drugs leading to enhanced therapeutic effect, but also provides stabilization of unstable components through intermolecular interactions [126]. It has advantages over single-drug delivery systems such as low doses of individual drugs, low potential of individual drug-related side effects, and reduced drug resistance [126, 127]. Dual-drug delivery system is able to slow down the drug release of the individual drug due to the loading of two drugs into different porous cavities of MOF [125]. By delivering two drugs simultaneously, the two drug molecules act synergistically to promote wound healing by reducing inflammation, killing pathogenic bacteria, decreasing oxidative stress and increasing cell proliferation [107, 126]. Previous studies have reported that dual drug delivery system with synergistic antibacterial effects accelerated the wound healing process by decreasing the rates of antibacterial resistance and inhibiting the formation of multidrug-resistant pathogens in wound site [107, 128]. Thus, dual-drug-loaded MOF has the pivotal potential for delivering a suitable amount of individual drugs required to exert the desired therapeutic effect compared to the single-drug delivery system.

Compared to other drug delivery systems, the advantages of MOF-based nanofiber include high surface area to volume, enhanced drug loading capacity, extended drug release, long-term durability, stability and protection from physical degradation [129]. Loading of drug-loaded MOF into nanofiber is classified into encapsulation, entrapment, and absorption. MOF is encapsulated in the core of the nanofiber by allowing the polymer to wrap the MOF. Entrapment of MOF into nanofiber involves the adherence of MOF to the pore of the nanofiber by depending on the pore size of the nanofiber. On the other hand, adsorption of MOF into nanofiber is the most simple technique by only adhering MOF to the surface nanofiber through cationic-anionic interactions [129–131]. After the preparation of drug-loaded MOF, the polymeric solution which completely wraps the drug-loaded MOF, is electrospun to form nanofiber encapsulated with drug-loaded MOF. Therefore, MOF-based nanofiber has the potential to overcome the burst effect of nanofiber alone because it results in extended and controlled release of drugs. If there is a risk of drug leaking out from the MOF, MOF-based nanofiber is able to prevent premature drug release. This is because the nanofiber of MOF-based nanofiber protects the drug seeped out from MOF to cause the drug to remain in the delivery system. Accordingly, the drug in MOF needs

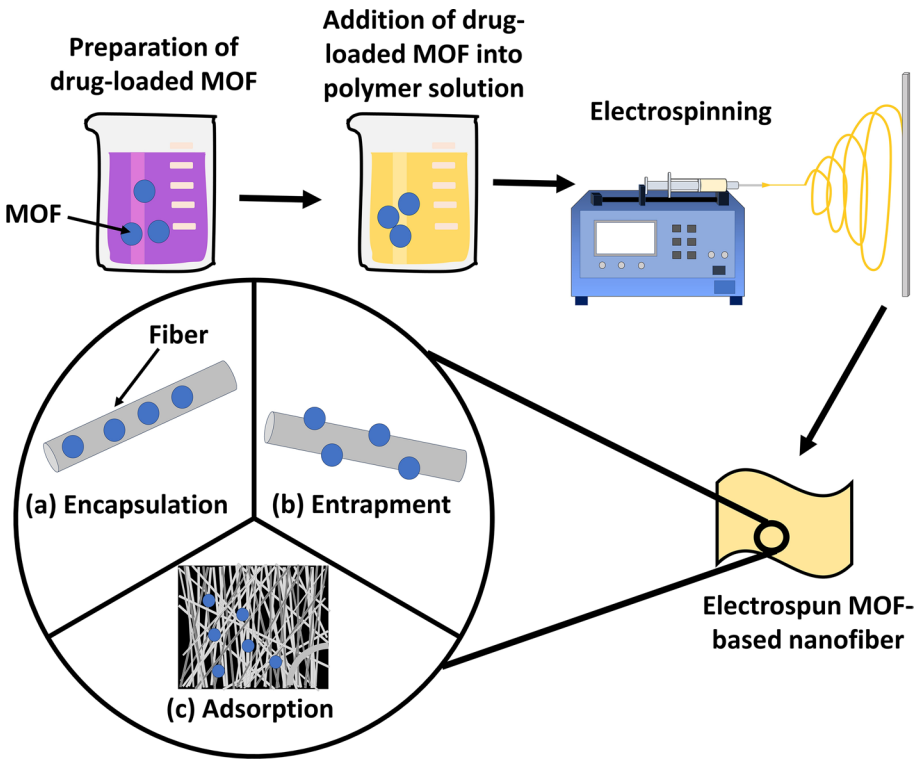


Fig. 6 The steps for the formation of MOF-based nanofiber involves drug-loaded MOF preparation, addition of drug-loaded MOF into polymer solution, and electrospinning process. Incorporation of drug-loaded MOF into nanofibers leads to three impacts: encapsulating entrapping, and adsorbing [129]

to cross the barrier between MOF and nanofiber during the release, leading to prolonged slow drug release [129, 131]. Figure 6 shows the formation of MOF-based nanofiber.

6 Natural therapeutic agents

Recent studies have proved the wound healing properties of different natural therapeutic agents including borneol [132], clove essential oil [133], curcumin [134], chrysin [135], honey [136], aloe vera [137], quercetin [138], and rutin [139]. Based on their biosynthetic origins, natural products are classified into terpenoids, flavonoids, and alkaloids. In addition to terpenoid-based natural therapeutic agents such as borneol and clove essential oil [140, 141], flavonoid-based natural therapeutic agents include curcumin [142], chrysin [143], quercetin [144], rutin [145], honey [146], and aloe vera [147]. Terpenoid, a modified class of terpenes with different functional groups at different positions, is a naturally occurring organic chemical derived from five-carbon isoprene units [148]. Flavonoid, a class of polyphenolic secondary metabolites derived from plants, consists of a 15-carbon skeleton or C6-C3-C6 structure containing two phenyl rings and a heterocyclic ring [149]. In contrast to flavonoids which are found mainly in plants, terpenoids are derived from all classes of organisms [150]. Figure 7 shows the molecular, origin and therapeutic application of natural therapeutic agents.

Topical application of these natural therapeutic agents for wound healing has been limited by several drawbacks such as poor solubility, bioavailability, and rapid degradation [134, 157]. Furthermore, the efficacy of topical application of the use of honey on the wound is decreased by bacterial contamination, poor penetration into the wound site, and short-term antimicrobial action [158]. The topical application of quercetin is hindered by its chemical instability, hydrophobic nature, and loss of protein function [159]. Apart from that, a low dose of clove essential oil at the wound site causes allergic reactions and dermatitis [160]. To cater for these drawbacks, these natural therapeutic agents have been incorporated into suitable nanocarriers such as hydrogel and nanofiber [161–167]. Nonetheless, most studies on the nanofibers were carried out due to the poor mechanical properties, rapid degradation, and diffusion limitation of hydrogel [168].

Having laid the foundation with the symbiosis of MOFs and nanofibers, let's now bridge our exploration towards natural therapeutic agents. While MOFs and nanofibers offer structural support and controlled drug release, natural therapeutic agents add a layer of bioactivity to the wound healing process. These agents, including curcumin, chrysin, borneol, honey, clove essential oil, aloe vera, quercetin, and rutin, are incorporated into nanofibrous scaffolds to capitalize on their inherent healing properties. Their integration into wound dressings aims to create a biomimetic environment,

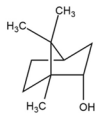
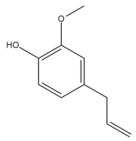
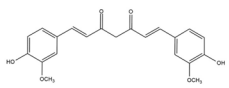
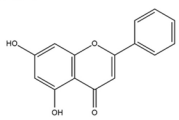
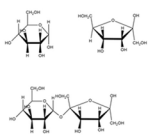
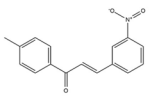
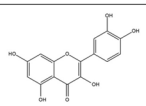
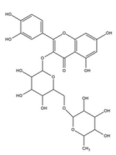
Natural therapeutic agents	Molecular and structural formula	Origin	Therapeutic applications
Terpenoid-based			
Borneol	$C_{10}H_{18}O$ 	Rosemary 	Inflammation, digestive issues, stress, and anxiety, heart disease, bronchitis and asthma
Clove essential oil	$C_{10}H_{12}O_2$ 	Clove 	Oral infections, cancer, boosting immunity, stress relief and inflammation
Flavonoid-based			
Curcumin	$C_{21}H_{20}O_6$ 	Rhizomes of Curcuma longa 	Cancer, diabetes-related complications, including heart, kidney, and liver disease
Chrysin	$C_{15}H_{10}O_4$ 	Passiflora caerulea Plant 	Cancer, degenerative disorders, diabetes, and neurodegenerative diseases
Honey	$C_6H_{12}O_6$ 	Flower nectar 	Cancer, respiratory, cardiovascular, gastrointestinal, and nervous systems
Aloe vera	$C_{16}H_{13}NO_3$ 	Aloe vera plant 	Burn healing, herpes simplex, lichen planus, and psoriasis
Quercetin	$C_{15}H_{10}O_7$ 	Citrus fruit 	Cardiovascular diseases, cancer, arthritis, bladder infections, and diabetes
Rutin	$C_{27}H_{30}O_{16}$ 	Japanese pagoda tree 	Cancer, central nervous, gastrointestinal system, endocrine, and cardiovascular systems

Fig. 7 The molecular formula, structural formula, origin and therapeutic application of natural therapeutic agents [140, 141, 151–156]

Table 2 Recent research studies on borneol for the treatment of DFU

Components Incorporated	Formulation developed	References
Borneol, curcumin, and gelatin	Nanofiber	[177]
Borneol, and PVP	Nanofiber	[178]

Table 3 Recent research studies on clove essential oil for the treatment of DFU

Components Incorporated	Formulation developed	References
Clove Extract, and zinc oxide	Nanofiber	[185]
Clove, and cellulosic textile	Nanocomposite	[186]
Clove Oil, and chitosan oleate salt	Nanoemulsions	[187]
Clove oil, and levofloxacin	Nanoscale emulgel	[188]

fostering an ideal milieu for cell proliferation, reducing inflammation, and promoting the reconstruction of damaged tissue. Now, let's delve into the synergistic potential of these natural therapeutic agents within the MOF-based nanofibers, envisioning a comprehensive approach to diabetic wound healing that amalgamates the strengths of materials science and nature-inspired remedies.

6.1 Terpenoid-based natural therapeutic agents

6.1.1 Borneol

Borneol (1,7,7-trimethylbiciyclo [2.2.1] heptan-2-ol) is a bicyclic monoterpenoid alcohol derived from Dryobalanops aromatica Gaertn f. and Blumea balsamifera DC. This natural product exists as white coloured lump-solid with a sharp camphor-like odour. Borneol exists in essential oils of plants such as species of genus Lavandula and Valerian as flavouring in cosmetic [169]. Apart from that, it is widely applied in the treatment of cardiovascular and cerebrovascular diseases [170]. It has been employed for a wide range of various medical treatments (analgesic, antibacterial, antifungal, anti-inflammatory, and antioxidant), mainly in traditional Chinese medicine [170, 171].

Besides, borneol suppresses the proinflammatory cytokine (IL-1β and IL-6) mRNA expression and serves as a bioactive material in the cellular signal transduction system [172]. To promote anti-fibrosis activity, it decreases the fibroblast growth, collagen production, MMP-2 activity as well as TIMP-1 production [173]. Other than anti-inflammatory and antibacterial activity, borneol possesses an antioxidant effect by decreasing the increase of NO and iNOS enzymatic activity, increasing intracellular ROS generation, and reducing intracellular ROS generation. It was found the antioxidant properties of borneol were due to the stimulation of DNA repair mechanisms including the metabolic enzymes instead of the direct antioxidant effects of borneol [173, 174].

To prevent external infection without harming the skin flora, previous research has obtained outstanding antimicrobial performance of the new type of antimicrobial chitosan by introducing borneol into chitosan film. By killing the skin flora, it will attenuate the host's resistance to pathogenic flora. The results of the guinea pig skin experiment have reported that this borneol-modified chitosan did not damage skin flora but enhanced the antibacterial effects of chitosan in the presence of borneol. Borneol helps to promote the healing of ulcer wound by reducing the wound infection and increasing the granulation tissues to allow a faster wound healing process [175]. Nevertheless, borneol is ineffective for DFU with sinus tracts or deep [175, 176].

So far there is limited report of borneol in nanofiber production for wound healing applications (Table 2). Importantly, borneol helps to improve the bioavailability of other drugs because it is able to facilitate the transport of multiple drugs to specific sites and harmonise the effect of drugs [177].

6.1.2 Clove essential oil

Clove (*Syzygium aromaticum L. Myrtaceae*) essential oil is derived from the clove trees, *Syzygium aromaticum*. Eugenol, a major component of clove essential oil, has several biological properties such as antibacterial, antioxidant, antifungal, insecticidal, anti-cancer and anti-inflammatory effects [141, 179–181]. Based on the previous findings, clove essential

oil helps with skin problems, neurological disorders, pain reliever, asthma, and inflammatory disorders [141, 182–184]. Furthermore, clove essential oil has been widely used for diabetic wound healing (Table 3).

The effect of clove essential oil on wound healing has been studied by using Type 1 diabetic albino rats (Rattus norvegicus). It was found that the clove essential oil reduced the wound size by improving the mRNA expression of wound healing markers, growth factor signalling pathways, and inflammatory cytokines [189]. Apart from that, wound healing effect of clove essential oil has been widely studied due to its antibacterial, antioxidant, and anti-inflammatory activity [187–190]. The antibacterial effect of clove essential oil was more effective against Gram-negative bacteria than Gram-positive bacteria [190]. The eugenol of clove essential oil reduces the bacterial count by destroying the cell wall and inhibiting DNA and protein synthesis, leading to an accelerated wound healing process [191, 192]. In previous studies, the antimicrobial effect has been shown by the synergistic effect of eugenol with β-lactam antibiotics [189, 193]. Due to the presence of eugenol, clove essential oil inhibits lipid peroxidation, indicating its significant antioxidant effect and free radical scavenging activity [189, 194]. Furthermore, clove essential oil exerts its anti-inflammatory by inhibiting the LPS, the expressions of cyclooxygenase II enzyme, and the NK-κB pathway [195, 196].

As an alternative to antibiotics for DFU therapy, clove essential oil has been widely loaded into nanofibers for effective diabetic wound healing [192, 197, 198]. Hameed et al. reported that the good wound healing potential of chitosan and poly-ethylene oxide (PEO) nanofiber loaded with clove essential oil by showing its superior antibacterial properties against *Staphylococcus aureus* and *Escherichia coli* [192]. By using 100 male Wistar rats in the study, clove essential oil-loaded nanofiber resulted in better granulation tissue through the formation of collagen compared to Zinc Oxide Nanofibers [185]. Other than the antibacterial effect of clove essential oil, Qin et al. demonstrated that the zein/clove essential oil fibrous membranes fabricated by in situ electrospinning process showed superhydrophilicity for wound exudate absorption and superior wound healing effect in mice wound model study [197]. For wound healing studies, Jawad et al. demonstrated that the antibacterial effect of a honey/chitosan nanofiber loaded with clove essential oil and aluminium oxide nanoparticles was compared with the Meropenem and Imipenem antibiotics [198]. In contrast to work conducted by Hameed et al. [198], Jawab et al. obtained higher antibacterial against gram-positive than gram-negative bacteria [192].

6.2 Flavonoid-based natural therapeutic agents

6.2.1 Curcumin

Curcumin or diferuloylmethane (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione), is known as a main natural polyphenol found primarily in turmeric or rhizome of Curcuma longa (Indian spice) used for treatment of diabetic

Table 4 Recent research studies on curcumin for the treatment of DFU

Components Incorporated	Formulation developed	References
Curcumin, *Gymnema sylvestre* extract, graphene oxide, polyhydroxybutyrate, and sodium alginate	Nanocomposite	[209]
Curcumin, chitosan, polyvinyl alcohol, Carbopol, and polycaprolactone	Nanofibrous composite	[210]
Curcumin, PVA, and collagen	Film	[211]
Curcumin, and silica	Nanoparticles	[212]
Curcumin, and chitosan	Polymeric bandages	[213]
Curcumin, chitosan, gelatin and PCL	Sandwich-like nanofibrous membrane	[214]
Curcumin, graphene oxide, titanium dioxide, and cellulose acetate	Nanofibrous membrane	[163]
Curcumin, and silver	Hydrogel	[215]
Curcumin, pectin, and chitosan	Films	[216]
Curcumin, silk fibroin, PVA, and PCL	Nanofibrous mat	[217]
Curcumin, and α-tocopherol	Nanoemulsion	[218]
Curcumin, chitosan, and carboxymethyl cellulose	Hydrogels	[219]
Curcumin, and iron Oxide	Nanoparticles	[220]
Curcumin, and zinc-MOF	MOF	[221]
Curcumin, and chitosan	Nanoparticles	[221]

ulcer, rheumatism, anorexia, cough, metabolic syndrome, hyperlipidaemia, and sinusitis [199, 200]. This primary bioactive substance used to target multiple signalling molecules possesses properties of anti-inflammatory [201], anti-oxidant [202], anti-carcinogenic [203], anti-infective [204], and anti-aging [205]. Nonetheless, the development of a suitable delivery carrier for curcumin is indispensable due to its poor bioavailability and in-vivo stability [206]. Due to the wound healing effect of curcumin, extensive research on curcumin for diabetic wound healing applications has been conducted (Table 4). Importantly, the therapeutic benefits of curcumin for wound healing mainly are due to its anti-inflammatory and anti-oxidant through its direct or indirect interaction with molecular targets involving transcription factors, enzymes, cell cycle proteins, receptors, cell surface adhesion molecules, growth factors, and protein kinases [207]. Curcumin, a wound healing agent, plays a significant role in regulating the physiological and molecular events involved in inflammatory, proliferation, and remodelling phases of wound healing [208].

In the inflammatory phase, curcumin interferes with the inflammatory pathway by inhibiting the pro-inflammatory cytokines production (tumour necrosis factor alpha (TNF-α) and interleukin 1 (IL-1) released by monocyte and macrophage for modulation of inflammatory response [201, 223]. Recruitment of M2-like macrophage caused by curcumin into white adipose tissue leads to reduced of inflammatory response by increasing the anti-inflammatory cytokines generation. Besides, the anti-inflammatory effect of curcumin affects the activity of kinases protein kinase B (AKT), phosphatidylinositol-3-kinase (PI3K), and Ikappa B kinase (IKK) to inactivate and inhibit nuclear factor κ (NK-κB) transcription factor that mediates the initiation of inflammatory response. Furthermore, curcumin offers its anti-inflammatory effect on the peroxisome proliferator-activated receptor-gamma (PPAR-ɣ) by increasing the PPAR-ɣ activity and reducing the oxidative stress to reduce the angiotensin II induced inflammatory response and proliferation of vascular smooth muscle cells. To inhibit inflammation, curcumin also prevents the interaction of lipopolysaccharide (LPS) with MD2 to suppress Toll-like receptor 4 (TLR4) pro-inflammatory signalling [166, 201, 208].

Oxidative stress is correlated with inflammation by showing the release of ROS by inflammatory cells at the site of inflammation causing oxidative stress [34]. Moreover, this relationship between inflammation and oxidation is also shown by the oxidant responsive NK-κB containing several anti-oxidant targets [224]. In addition to its anti-inflammatory effect, curcumin has antioxidant properties by improving systemic markers of oxidative stress and enhancing the activities of antioxidant enzymes such as superoxide dismutase, glutathione peroxidase, and catalase to protect cells from toxic ROS levels [225]. Other than the prevention of ROS-generating enzymes (lipoxygenase/cyclooxygenase, and xanthine hydrogenase/oxidase), curcumin which is a lipophilic compound, has scavenging action against different forms of free radicals ROS and reactive nitrogen species (RNS) by involving its electron-donating group (phenolic hydroxyl group). Therefore, curcumin is able to accelerate the healing cycle into a proliferative phase with a minimal inflammatory phase [201, 208, 225].

Furthermore, curcumin has the potential to discard unwanted cells such as inflammatory cells by inducing apoptosis allowing the wound to mature and advance into the proliferative phase. During the proliferative phase, it regulates the infiltration of fibroblast into the wound site in proliferative phase to facilitate the differentiation of fibroblast into myofibroblast during the granulation tissue formation [208]. Chronic wound causes loss of TGF-β because this mediator for tissue repair involves inflammation, stimulating angiogenesis, fibroblast proliferation, collagen synthesis, deposition and remodelling of new ECM [226]. Therefore, increasing TGF-β production and fibroblast proliferation induced by curcumin in the remodelling phase are able to increase the rate of the healing process [166, 208].

To overcome the low solubility and rapid metabolism of curcumin, curcumin has been utilized extensively in wound healing applications by loading curcumin in nanofiber [166]. Previously, several studies of curcumin-loaded nanofiber have been performed to allow the curcumin release from nanofiber due to its antibacterial, anti-inflammatory activity on wound healing application [210, 227–230].

In the study by Rathinavel et al., mesoporous silica incorporated PCL/Curcumin nanofiber for wound healing application has been synthesized by showing the role of curcumin in re-epithelization of tissue, collagen deposition and formation of granulation tissue. The antibacterial effect of curcumin against gram-positive (*Bacillus subtilis*) and gram-negative (*Escherichia coli*) strains was shown [231]. Other than providing high moisture content, the controlled release of curcumin from nanofiber promotes rapid fibroblast proliferation and epithelial cells in tissue regeneration by preventing bacterial growth in the wound site [230]. Furthermore, it was found that burst release of curcumin at the starting stage with 45% of curcumin released to cell proliferation and adhesion, making this curcumin-loaded nanofiber a promising candidate for diabetic wound healing application [232, 233]. Downregulation of pro-inflammatory markers, interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α) were shown indicating the anti-inflammatory and wound-healing effects of curcumin-loaded curcumin [234]. Apart from that, research on the hybrid chitosan-silk fibroin nanofiber containing silver (Ag) nanoparticles was performed for the investigation of curcumin sustained release for efficient wound healing. Other

than the improvement of curcumin's low solubility, this wound dressing was able to facilitate the pH-response release of curcumin and enhance curcumin loading and encapsulation efficiency. Importantly, lower chitosan concentration in the nanofiber resulted in a higher inhibitory effect in bacterial growth [235]. Silk fibroin-protein-based polymer has the potential to support binding and spreading, and fibroblast proliferation [236]. The involvement of metal compounds such as Ag in nanofiber enables the prevention of infection when it reaches the nanoscale because nanosized Ag alters the metabolism, respiration, and reproduction of microorganisms. Nevertheless, a lower concentration of Ag in nanofiber was more useful than a higher Ag concentration [166, 235].

To discover the new curcumin derivative for efficient and powerful wound healing, synthesis of in-silico curcumin-loaded nanofiber for wound healing was performed to obtain biological activities of new curcumin designed toward GSK-3β and TbetaR-I proteins involved in wound recovery. It involved the prediction of the ligand-receptor binding site and the addition of different chemical groups on the curcumin scaffold via molecular docking. By containing phenolic and methoxy group o phenyl ring and 1,3 diketone operating system in curcumin, it has at least 10 times more antioxidant activity compared to vitamin E [237].

6.2.2 Chrysin

Chrysin (5,7-dihydroxy-2-phenyl-4H-chromene-4-one or 5,7-dihydroxyflavone), is a naturally occurring 15-carbon backbone-based flavonoid available in bee pollen, propolis, plant species (Indian trumpet flower, and European propolis) [167]. The beneficial pharmacological activities of chrysin involve anti-oxidant [238], anti-inflammatory [167], anti-cancer [239], and anti-genotoxic [240]. The anti-microbial effect of chrysin strains such as *Escherichia coli*, *Salmonella typhimurium*, *Staphylococcus aureus*, and *Listeria monocytogenes* is higher than apigenin and lutein [241]. However, there are several limitations of chrysin such as poor solubility in water, rapid intestinal and hepatic metabolism, and low physiochemical characteristic [167]. Hence, several studies on the incorporation of chrysin into nanomaterial (Table 5) to allow the slow release of chrysin for the wound healing process and to improve the physiochemical properties.

Chrysin is able to increase the functionality of nanofiber by providing an excellent nanoplatform for wound healing. It blocks the interaction of nuclear factor for IL-6 to COX-2 promoter leading to a decrease in LPS-induced COX-2 expression in macrophage [243]. In previous research, the role of chrysin-loaded nanofiber in regulating the expression of tumor protein p53 and nitric oxide synthase (iNOS) involved in the wound healing process was observed. Rapid proliferation required for tissue repair reduces the tumor protein p53 expression [244, 245]. In the study, Mohammadi et al. reported that 20% w/w of chrysin-loaded PCL-Gelatin (GEL) nanofiber caused p53 inhibition to accelerate the healing compared to 5%, 10%, and control groups for all stages of wound healing [245]. Sadeghi-Soureh et al. demonstrated that the increased of chrysin concentration increased the average diameter of chrysin-loaded PCL-GEL nanofiber [246]. Although a higher chrysin concentration of 15% w/w increases the interconnection of nanofiber, it alters the viscosity of the spinning solution resulting in a decreased of evaporation rate and an increased of nanofiber diameter [246]. Other than that, the unique anti-oxidant and anti-inflammatory effects of electrospun nanofibrous scaffold loaded with chrysin also have important role in the last stage of wound healing which is called efferocytosis by involving anti-inflammatory cytokines to drive polarization of M1 macrophage toward pro-regeneration or anti-inflammatory M2 state. It is followed by the liberation of anti-inflammatory mediators (IL-4, IL-10, and TGF-β), wound healing mediators (arginase, and ECM), and growth factors (vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and insulin-like growth factor (IGF) to allow efficient regeneration of tissue function [246, 247].

Additionally, the potential ability of chrysin to shorten the inflammatory stage in which the M2 phenotype becomes dominant [246]. The conversion of the M1 macrophage to the M2 state permits the transition of the inflammatory phase to the proliferation stage [248]. The aggregation of M2 macrophage in the repair stage secretes anti-inflammatory factors (IL-4, IL-10, and IL-12), growth factors (IGF-1, VEGF, and TGF), and MMP for breakdown of provisional ECM. M2 macrophage also works on the elimination of pathogens and debris as well as coordination of the reparative processes for wound resolution. Therefore, impaired wound healing is related to the delayed of M1 to M2 macrophage polarization due to the continued

Table 5 Recent research studies on chrysin for the treatment of DFU

Components Incorporated	Formulation developed	References
Chrysin, curcumin PCL, PEG, and PCL	Nanofibers	[178]
Chrysin	Nanoemulsion	[242]
Chrysin, PCL, and chitosan	Nanofibers	[164]

dominance of M1 macrophage that aggregates at the inflammatory phase to secrete pro-inflammatory factors. In response to inflammatory stimulus, NK-κB is triggered to increase iNOS expression contributing to the nitric oxide (NO) overproduction [248]. Accordingly, it was found that both iNOS and Arg-1 were able to act as a marker for the presence of M2 macrophage for wound healing by showing increased iNOS and reduced Arg-1 expression in cells cultured in chrysin-PCL-GEL nanofiber [246].

6.2.3 Honey

Honey is known as a carbohydrate-rich syrup with several monosaccharides, including glucose, sucrose, and fructose [249]. Due to the broad therapeutic effects of honey, this nutritious thick syrup is widely used in traditional medicine. Honey exhibits various therapeutic effects such as antibacterial, antiparasitic, and pain-reliever properties [250]. The antibacterial effect of honey depends on various factors such as several compounds, low pH, hydrogen peroxide, methylglyoxal, and several compounds. Honey contains phytochemical components including flavonoids and phenolic acids. Both of these components have a major role in anti-oxidant effects. Also, it creates a moist environment and stimulates human monocytes to cause cytokine production. The application of honey saves the integrity of the wound area because it is non-adherent [136, 251] (Table 6).

Several studies reported that the antibacterial properties of honey against a wide variety of microbes increase the rate of wound healing because of its osmolarity, low pH, and hydrogen peroxide production [136, 252, 253]. Honey provides bacterial barriers to prevent cross-infection and recover the development of new tissue by healing the wound via epithelization. Bacterial invasion is inhibited by creating an osmotic stress due to the high sugar concentration of honey with low moisture content [136, 252, 253]. As an effective wound dressing, honey accelerates the wound healing process by creating an acidic environment in order to promote the growth of fibroblast cells. The free radical scavenging activity of honey helps to avoid the cell from damage by free radicals and reduce the inflammatory response for effective wound healing [249, 254]. Furthermore, honey is able to stimulate wound debridement, scarring inhibition, and tissue regeneration to reduce inflammation [252]. However, liquefaction and leakage caused by the direct application of honey to wound areas are some of the limitations of honey, which limit their application. This is because honey liquefy at high temperature. Hence, it is challenging to maintain the required therapeutic concentration of honey in the wound area for a long period. Encapsulation of honey into hydrogel is able to overcome these limitations of honey for wound dressing application [255, 256]. Accordingly, more research has been done on the preparation of honey-loaded nanofibers for potential clinical use (Table 6). The advantages of honey-loaded nanofiber include enhancement of water absorption and swellability, support epithelization, increased cell proliferation, and antibacterial effect to improve wound healing [257, 258].

Based on Tang et al. incorporation of honey into an alginate/PVA electrospun nanofiber has been carried out to act as a potential bioactive wound dressing [259]. It was found the increase of honey content controlled the overproduction of ROS indicating the improvement of antioxidant activity. The addition of honey in PVA electrospun nanofiber conferred the film with better antibacterial effect against gram-positive bacterium and gram-negative bacteria. Additionally, the incorporation of various amounts of honey (5%, 10%, and 20%) within nanofiber was performed resulting in bead-free and smooth nanofiber with diameter of 335.30 ± 96.652, 342.80 ± 91.001, and 375.86 ± 120.907 nm, respectively. This is due to the increased of honey concentration within the nanofiber elevates the viscosity of the polymer solution to improve the mechanical properties of nanofiber and cell proliferation for the wound healing process [252, 258, 259].

Table 6 Recent research studies on honey for the treatment of DFU

Components Incorporated	Formulation developed	References
Honey, alginate, and PVA	Nanofibrous membrane	[259]
Honey, pomegranate, and PVA	Nanofibers	[258]
Honey, and silk fibroin	3D porous scaffold	[260]
Honey, chitosan, capsaicin and gold nanoparticles	Nanofibers	[261]
Honey, and chitosan	Nanosheets	[262]
Honey, aloe, polysaccharide, and PVA	Hydrogel	[263]
Manuka honey, PVP, chitosan, and titanate	Nanofiber	[264]
Honey, and Poly (diallyldimethylammonium chloride) (PDDA)	Nanofiber	[265]
Honey, and sericin	Hydrogel	[266]

In 2023, Gashti et al. has prepared a poly (diallyldimethylammonium chloride) (PDDA)/honey nanofiber wound dressing for diabetic wound-healing [265]. The results obtained showed the antibacterial effect of honey-loaded nanofiber by preventing 99.9% of *Staphylococcus aureus* and *Escherichia coli* bacteria due to hydrogen peroxide (H_2O_2) and antioxidant polyphenol within the composition of honey. Polyphenol is considered a strong pro-oxidant in the presence of transition of metal ions resulting in hydroxyl radicals from H_2O_2 through the Fenton process. Furthermore, this nanofiber was able to influence fast autolytic debridement and inhibit inflammation by indicating a decreased of number of inflammatory cells [265]. Honey with high sugar content draws the fluid from the wound via osmosis leading to bacteria death. There is an association between the antibacterial effect of honey with high sugar content, acidity and capability for hydrogen peroxide production [253, 265].

6.2.4 Aloe vera

Aloe vera is considered a traditional medicine from the Liliaceae family, Aloe Barbadensis Miller for treating various dermatologic disorders, for example: infections, burns, and other skin conditions. It is a shrubby plant with fleshy green leaves, conical and filled with a clear and viscous gel [137, 267]. Aloe vera containing 99% high-water content acts as a modulator for wound healing and inflammation because it contains several therapeutic effects such as anti-inflammatory, anti-oxidant, antimicrobial activity, tissue regeneration and antiseptic properties [137, 268–270]. Based on previous studies, an association of Aloe vera with the treatment of skin injuries including cuts, burns, frostbite, radiation, and electrical injuries was shown [267, 271–273].

Additionally, Aloe vera consists of two potential bioactive substances: Acemannan and Glucomannan. Acemannan, a substance in aloe polysaccharide gel, accelerates the wound healing process by increasing the angiogenesis, collagen synthesis in the wound bed, oxygen consumption, cellular proliferation, migration, cytokine production [274, 275]. Furthermore, it helps to attenuate the inflammation via the synthesis of prostaglandin and inhibition of leukocyte infiltration. In contrast to Acemannan, Glucomannan has the ability to affect fibroblast growth and increase cell and collagen proliferation [267, 275, 276].

Due to the biocompatibility and unique wound healing of Aloe vera (Table 7), Aloe vera-loaded hydrogel serves as a natural matrix for hydrogel [277, 278]. As an alternative to synthetic drugs administrated for infected wound treatment, Aloe vera is able to stimulate fibroblast proliferation and collagen synthesis [273]. Incorporation of Aloe vera extract into the wound bed allows the film dissolution to accelerate wound healing process. Inflammation is reduced by the Aloe vera gel penetration into the tissue network to inhibit potent vasoconstrictor thromboxane synthesis increasing the blood supply. Aloe vera accelerates the wound healing rate by controlling the inflammatory phase and serving as a source of nutrients [101, 273, 278]. Other than that, the advantages of Aloe vera include balancing the blood glucose and reducing the pain of the wound [101, 270, 279].

Ranjbar Mohammadi Bonab [287] prepared 5% aloe vera loaded poly(ε-caprolactone)/gum tragacanth nanofibers as dressings for wound care [287]. The SEM results showed that the nanofiber diameter with bead-free morphology and smooth surface decreased from 1118 ± 53 to 501 ± 69 nm for poly(ε-caprolactone), and 184 ± 34 to 123 ± 22 nm for poly(ε-caprolactone)/gum tragacanth mats after the aloe vera loading. This indicated that the higher the aloe vera loading, the smaller the diameter size of the nanofibers [287]. Accordingly, the addition of aloe vera increased the solution conductivity and decreased the viscosity blend [288]. Furthermore, the finer nanofiber due to the presence of aloe vera enhanced the fibroblast cell proliferation and caused favourable cell attachment for wound healing process [289, 290].

Furthermore, Rafieian., 291 incorporated the electrospun PVA nanofibers with aloe vera-containing chitosan film with the electrospinning parameters of 9% PVA solution concentration, 28 kV, 0.8 ml/hr, and 25 cm from the pump to collector

Table 7 Recent research studies on aloe vera for the treatment of DFU

Components Incorporated	Formulation developed	References
Aloe vera	Hydrogel	[280]
Aloe vera, alginate, and zinc chloride	Film	[281]
Aloe vera, and insulin	Nanoemulsion	[282]
Aloe vera, hypericum perforatum, PCL, and gelatine	Nanofiber	[283]
Aloe vera, and chitosan	Hydrogel	[284]
Aloe vera, bovine serum albumin, and amyloid	Hydrogel	[285]
Aloe vera, and cellulose	Biocellulose Sheet	[286]

[291]. These PVA nanofibers with aloe vera were non-toxic to fibroblast because the aloe vera was able to improve the cell activity. The results showed the accumulation of fibroblast with spindle-shaped on the surface of the film indicating good cell proliferation. However, it was found that more than 50% of aloe vera within the film suppressed the antibacterial effect of the chitosan [291]. The negative charge of Gram-negative bacteria and OH^- group in aloe vera act competitively toward absorbing the NH_3^+ chitosan chain [291, 292]. Hence, the increased of the aloe vera inhibited the chitosan from moving toward the bacterial membrane.

Based on Baghersad, tetracycline hydrochloride (TCH) loaded poly(caprolactone)/gelatin/aloe vera nanofibers with hybrid and blend structures were developed to improve the wound healing process [293]. The addition of aloe vera provided a superior wound healing rate by enhancing the cell attachment and expansion. Aloe vera has a protective effect against keratinocyte mortality and a proliferative effect on keratinocytes as well as fibroblast [270, 273]. Other than that, aloe vera helps the host cells to maintain their phenotype and stimulate the proliferation of migrating cells by providing a moist microenvironment for naïve and migrating cells [271, 273]. However, there is limited research on the.

6.2.5 Quercetin

Quercetin is considered a polyhydroxy flavonoid present in diverse sources: red wine, onion, green tea, apple, berries, citrus, leafy vegetables, herbs spices [294]. This plant pigment is widely found in Oxytropis falcata bunge for promising healthy compound for angiogenic and anti-inflammation activity [295]. Other than that, it has pharmacological activities such as anti-oxidant, and immune regulation [296]. It has therapeutic potential for prevention and treatment of arthritis [297], diabetes [298], cardiovascular [299], cancer [300], and neurodegenerative disease [301].

The anti-inflammatory effect of quercetin is shown by regulating the inflammatory response to decrease the inflammatory factors TNF-α, IL-1β, and IL-6. However, a high dose of quercetin increases the IL-1β level. By reducing the IL-6 and TNF-α, heme-oxygenase-1 (HO-1) suppresses the activation of inflammatory signalling [302]. As a scavenger of ROS, and RNS, quercetin is an excellent candidate for decreasing oxidative stress because of its high propensity for electron [302, 303]. Besides that, quercetin has an important role in increasing the protein level of Wnt-β-catenin [304]. Expression of growth factor is increased by the Wnt-β-catenin signalling pathway and TERT (Telomerase reverse transcriptase). Furthermore, mesenchymal and epithelial cell secretes fibroblast growth factors (FGF) via the Wnt-β-catenin signalling pathway for skin injury and scar-free repair [304, 305]. Therefore, the presence of FGF is able to reduce the ROS-caused keratinocyte apoptosis at the wound site [305]. Similar to chrysin, quercetin increases the level of VEGF and TGF-β. As a key factors for wound healing promoters, VEGF stimulates angiogenesis by acting on the vascular endothelial cells to upregulate vascular permeability leading to higher proliferation. Besides, VEGF also helps to promote collagen deposition, epithelial formation, and fibroblast migration for tissue remodelling through collagenase production [303]. Additionally, quercetin also plays a critical role in regulating macrophage polarization from M1 to M2 macrophage [306]. Other than anti-oxidant and anti-inflammatory effect, quercetin also exhibits a broad spectrum of antibacterial activity by destroying the cell wall and cell membrane of bacteria to facilitate fibroblast proliferation for wound contraction [294, 307].

In contrast to conventional wound dressing, quercetin has advantages including small pores for gaseous exchange, cell–cell communication, nutrient and metabolic waste transport, prevent dehydration, and bacterial infection. Recently, quercetin has been widely utilised in several nanomaterials for DFU treatment due to its superior therapeutic effect (Table 8). According to previous studies, quercetin-loaded nanofiber has been synthesized from a wide range of materials such as Eudragit L-100 with the addition of polyethylene glycol 4000 (PEG) [308], gold nanorods (GNP) [309], fibrous

Table 8 Recent research studies on quercetin for the treatment of DFU

Components Incorporated	Formulation developed	References
Quercetin and oleic acid	Nano-hydrogel	[312]
Quercetin, chitosan, and sodium tripolyphosphate (STPP)	Nanoparticles	[313]
Quercetin, and silver nanoparticle	Hydrogel	[314]
Quercetin, alginate, and chitosan	Nanoparticles	[315]
Quercetin	NanoVelcro dressing	[316]
Quercetin, copper sulfide	Nanogel	[317]
Quercetin, polylactic acid, and poly(vinylpyrrolidone)	Nanofibrous membrane	[318]
Quercetin, phenylboronic acid functionalized-quercetin	Nanoparticles	[319]
Quercetin, and gelatin methacryloyl	Hydrogel microneedle	[320]

polycaprolactone with graphene oxide [161], and polylactide (PLA) [310]. The Eudragit, a biodegradable polymer, is able to act as drug carrier delivery material and desired dressing material due to its excellent spinnability, good tissue affinity, and slow degradation [311]. It was found that the addition of PEG-4000 into nanofiber has enhanced the ductility of nanofiber and increased the drug release rate to avoid the wound from microorganism penetration [308]. Furthermore, Mahmoud et al. have revealed that the slow pattern of quercetin release was obtained from quercetin-gold nanorods (GNP) nanofiber. GNP has advantages over fiber-free GNP by showing smooth, more uniform and decreased number of beads in SEM images. This indicated that GNP has high porosity and hydration potential to prevent infection and inflammation to enhance wound healing [309].

To enhance the stability of quercetin, a new formulation of anti-bacterial properties has been produced by using modified star-shaped PLA with β-CD core for its different supramolecular interaction [310]. Furthermore, Ajmal et al. have synthesized PCL-based nanofiber loaded with ciprofloxacin hydrochloride (CHL) and quercetin [321]. The advantage of fluoroquinolone antibiotics such as CHL in nanofiber includes the low minimal inhibitory concentration value against both Gram-negative and positive microorganisms and lower risk of microbial resistance. Therefore, the antimicrobial effect of CHL is effective for wound infection [322]. Ajmal et al. have revealed that this quercetin nanofiber was able to inhibit bacterial infection and excess free radical activity. Moreover, the ability of this nanofiber to preserve the functionality of the red blood cell through the protection of red blood cells against lipid oxidation was shown [321].

6.2.6 Rutin

Rutin or quercetin-3-O-rhamnosylglucoside, is a low molecular weight polyphenolic compound distributed in citrus fruit, berries (Ruta graveolens, and Morus alba), vegetable, and medicial herbs (asparagus, and buckwheat) [151, 323]. Buckwheat (Fagopyrum esculentum) is considered as the best dietary source of rutin [324]. Rutin is also a flavonoid glycoside containing medical usage including antibacterial [325], anti-inflammatory [139], anti-oxidant [326], anti-tumor [327], anti-allergic [151], cytoprotective [328], vasoactive [329], anti-platelet [330], antispasmodic [151], anti-hypertensive [331], and anti-viral [332].

Rutin is available as an orally administrated supplement for wound healing. However, rutin has low bioavailability after oral administration due to its low water solubility [151]. To increase the water solubility of rutin, enzymatic polymerization of rutin into polyrutin was conducted [333]. Rutin acts as an anti-oxidant by scavenging and preventing free radicals [139]. Polyrutin has higher anti-oxidant activity than rutin because polymerization enhances the anti-oxidant capacity of rutin. This indicates that high-molecular-weight polyphenol has stronger anti-oxidant activity compared to low-molecular-weight polyphenol [333, 334].

Apart from that, the therapeutic beneficial of rutin is able to reduce the inflammatory cell, inflammation mediator production, NK-κB mediated-MMP expression, and VEGF expression [151]. Thus, oxidative stress and inflammatory response are attenuated accelerating the wound healing rate. Rutin plays significant roles in upregulating the NF-E2-related factor 2 (NRF2) activity and antioxidant enzyme expression, decreasing inflammatory response, as well as promoting nerve growth for wound healing. Rutin exerts its antioxidant effect by protecting cells from oxidative stress via the removal of excess ROS [139].

After ingestion of rutin, it is metabolized by gut microflora causing little to be absorbed for its therapeutic beneficial [151]. To overcome the constrained bioavailability of rutin, Ilbasmis-Tamer et al. have synthesized starch-copper nanoparticles/rutin nanofiber hybrid scaffold [335]. Poor solubility of rutin limits its activity for wound healing. Therefore, Ilbasmis-Tamer et al. have showed that the ability of polyvinylpyrrolidone (PVP) electrospun nanofiber to act as a drug carrier for rutin. Other than that, it was found that the addition of coated copper nanoparticle before electrospinning potentially enhanced the rutin activity [335]. By comparison with curcumin, chrysin and quercetin, there is limited research on the rutin-loaded nanofiber for wound healing applications (Table 9).

Table 9 Recent research studies on rutin for the treatment of DFU

Components Incorporated	Formulation developed	References
Rutin, Zeolitic imidazolate framework-8	Nanocomposite	[336]
Rutin, PVA, gallic acid, catechin, rutin, kaempferol-3-O-rutinoside, quercetin-3-O-rhamnoside, kaempferol-3-O-rhamnoside, quercetin, and kaempferol	Nanofiber	[337]
Rutin, 4-carboxyphenylboronic acid-modified chitosan	Hydrogel	[338]

7 Dual-drug-loaded nanofiber

In addition to single-drug delivery, dual-drug-loaded nanofiber has been investigated. Mohammadi et al. have synthesized curcumin-chrysin loaded in PCL-PEG nanofiber as a novel compound for increasing the rate of wound healing [245]. Compared to curcumin nanofiber and chrysin nanofiber, the results of curcumin-chrysin nanofiber showed that more significantly increased IL-6 expression, MMP-2, TIMP-1, TIMP-2 and reduced iNOS expression leading to shortening of wound healing [245].

To replace conventional wound dressing, the incorporation of curcumin and borneol into nanofiber for wound healing application was conducted [177]. Previous studies reported that curcumin has antioxidant properties by scavenging ROS [339]. As mentioned in previous session, borneol is widely used in combination with multiple drugs to improve their bioavailability [340]. Based on Lv et al., the results of the concentration-dependent system showed the maximum antioxidant rates of curcumin-loaded nanofiber without borneol (80%) and curcumin-loaded nanofiber with borneol (85%). The addition of borneol with curcumin in nanofiber enhanced the antioxidant capacity of the film compared to nanofiber loaded with a single drug. Other than that, the synergistic effect of both curcumin and borneol resulted in an inhibition zone of 5.4 ± 0.2 mm in diameter showing their improved antibacterial effects to prevent bacterial infection and sepsis [177].

In comparison to the combination of curcumin with chrysin and borneol, electrospun nanofiber loaded with honey and curcumin was widely conducted for wound healing application [341–343]. Gaydhane et al. prepared curcumin–honey-loaded multilayered polyvinyl alcohol/cellulose acetate electrospun nanofibrous mats by reporting that the synergistic effect of curcumin and honey has enhanced the 93% antioxidant activity against diphenyl-picrylhydrazyl (DPPH)-free radical compared to pure ingredient [341]. This indicates the combined effect of both curcumin and honey. Furthermore, Shahid et al. successfully prepared a nanofibrous membrane using stingless bee honey and curcumin with 159.08 ± 53.88 nm diameter [342]. By comparison with single-drug nanofiber, dual-drug loaded nanofiber containing honey and curcumin exhibited better wound contraction of $89.05 \pm 0.47\%$. To study the antibacterial efficiency by shake flask method, the study results showed that the antibacterial activity of nanofiber loaded with curcumin alone was lesser than nanofiber loaded with honey alone exhibiting moderate antibacterial activity. The paper highlighted that the honey and curcumin-loaded nanofiber showed 90% antibacterial activity [342]. For wound healing studies, Samraj et al. reported that curcumin-honey-loaded nanofiber has better wound contraction of $89.05 \pm 0.47\%$ than single drug-loaded nanofiber [343].

Honey with high osmolarity and low pH has the ability to produce peroxide hydrogen for therapeutic use while the pharmaceutical properties of aloe vera are due to the presence of a large variety of chemical compounds within aloe vera such as amino acids, anthraquinones, chromone, enzymes, hormone, steroids, minerals, and vitamins [136]. Aloe vera provides a moist microenvironment to allow cell migration. Furthermore, polysaccharides of aloe vera cause hyaluronic acid and hydroxyl proline production leading to the acceleration of wound healing by rebuilding the external matrix structure of cells [267]. According to Samadieh et al., the addition of (5, 10, and 20%) honey into chitosan and gelatin film improved the tensile strength and flexibility of the film [344]. The concentration of honey up to 20% has an antibacterial effect but 5 and 10% of honey loaded into chitosan and gelatin film showed no antibacterial effect. Other than the combination of honey with curcumin, loading of aloe vera into chitosan–gelatin film was able to improve the stability of the film due to the higher amount of honey. Based on the results, the honey and aloe vera-loaded chitosan–gelatin film resulted in growth inhibition with 30 mm and 28 mm diameters against *S.aureus* and *P. aeruginosa*. Apart from that, SEM images showed that the honey and aloe vera-loaded nanofiber allowed the growth of fibroblast cells [344].

On top of that, quercetin-rutin-loaded PCL/chitosan oligosaccharide nanofiber has been introduced to act as an antibacterial dressing with high biocompatibility. This dressing with dual drug exhibited superior antibacterial and antioxidant effects compared to single-drug nanofiber. [162] Apart from that, the effect of the quercetin-curcumin mixture on in-vitro wound healing has been investigated by showing their stimulation of fibroblast migration and, the effect of antibacterial and anti-oxidant. However, this combination has not been established as a nanofiber for wound healing applications [345].

8 Future outlooks

By combining current advanced technologies, dual-drug-loaded MOF, and nanofiber, it could overcome the limitations that when the MOF and nanofiber are used alone as a single drug delivery system. When the dual-drug-loaded MOF with synergistic effects is loaded into a nanofiber, it will slow down the drug release because it will take a longer period

for the dual-drug-loaded MOF to release the drugs into nanofibers. Also, this newly developed hybrid system has the potential to promote angiogenesis and fibroblast proliferation for shortening the diabetic wound healing process. In future, the synergy of dual-drug-loaded MOF and nanofiber may result in a new form of superfunctional composite to act as a biomimetic skin, reservoir, and sustained drug delivery system for fast diabetic wound healing.

Currently, the dual-drug loaded MOF-based nanofibers are still in the early stage of research. Since the synergistic effects of natural therapeutic agents within nanofibers are still uncertain, further studies are needed to explore the molecular mechanism regarding the interaction of natural therapeutic agents with polymers. A major challenge for MOF-based nanofiber is the compatibility of MOF with polymer solution before combining them. Therefore, the selection of the proper MOF, polymer and additives for MOF-based nanofibers formation plays a significant role in the therapeutic effect of the nanofibers by affecting their drug-release behaviour. Additionally, the determination of the mean particle size of MOF is critical because it will affect the incorporation of MOF into nanofiber. If the mean particle size of the MOF is too large, it will cause the MOF to be stuck on the surface of the nanofiber, leading to burst release. Therefore, further studies are needed to explore the drug release mechanism of the MFO-based nanofiber and the compatibility of MOF with nanofiber for wound healing applications. The experimental successes of this MOF-based nanofiber will play a crucial role in bringing it into the clinical domain. In future, it will result in more effective therapeutic efficacy from this novel drug delivery system in the wound healing application by encouraging clinical evidence.

9 Conclusion

Understanding the mechanism of action for normal wound healing and diabetic wound healing would allow us to explore new approaches in diabetic wound healing. In addition, an overview of MOF and nanofiber for wound healing purposes has been discussed. The natural therapeutic agents highlighted in this paper were curcumin, chrysin, borneol, honey, clove essential oil, aloe vera, quercetin, and rutin. Application of these therapeutic agents incorporated into nanofiber for wound healing has been reviewed followed by the hybridization of dual-drugs encapsulated into nanofiber.

Despite impressive advances in MOF designed as a drug carrier, direct contact of MOF powder with wound site increases the inflammation and minimizes tissue regeneration [10]. Thus, attachment of MOF onto a flexible and sensitive supporting substrate such as polymeric-nanofiber could be designed as a novel hybrid drug-delivery system [12]. As an alternative to conventional wound dressing, this hybrid system is expected to be loaded with dual drugs containing superior anti-inflammatory and anti-oxidant properties to improve the quality of diabetic wound management material. Therefore, the application of electrospun MOF-based nanofiber associated with dual therapeutic agents for effective and sustained drug release to wounds may be an alternative for DFU management in future. To enable extensive use of this advanced dressing, some challenges need to be addressed such as scalability, health, safety, and high cost due to the use of specialized equipment and high energy consumption [346]. To meet industrial demands, scaling up nanofiber production is considered one of the major challenges by involving issues such as equipment design, and consistent quality for fiber mass production [346]. The examination of this advanced dressing for its safety and efficacy through randomized and controlled clinical trials would remain a challenge for speeding up its use in routine clinical practice.

To introduce desired functionalities and complexities into nanofiber for effective wound care, the selection of suitable materials and therapeutic agents is important for novel MOF-based nanofiber production. Recently, ceramic-based nanofibers composed of bioactive glass and glass ceramics have depicted their great potential in wound healing applications due to their chemical stability, good mechanical properties, and the ability to mimic the hierarchical architecture of the ECM [347]. As an alternative to polymeric nanofiber, it has advantages over polymeric nanofiber such as a higher number of surface-active sites, and excellent surface nano-topographical features for cell adhesion and deposition of new tissue [347, 348]. As a new horizon of research, there is still limited research on ceramic nanofiber for wound healing. Therefore, there is still room for improvement in this area. Further studies on this advanced wound dressing could be carried out to enhance the performance of nanofibers and to thoroughly understand its cytocompatibility in terms of cellular adhesion, proliferation, and differentiation. In addition, more in vivo studies, particularly on animal models, and human and clinical trials need to be carried out to evaluate the real impacts and support the utilization of this novel drug delivery system in wound care, facilitating the transition from lab to market.

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Declarations

Competing interests The authors declare no competing interests.

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