

Natural product-based nanomedicines for wound healing purposes: therapeutic targets and drug delivery systems

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Abstract: Wound healing process is an intricate sequence of well-orchestrated biochemical and cellular phenomena to restore the integrity of the skin and subcutaneous tissue. Several plant extracts and their phytoconstituents are known as a promising alternative for wound healing agents due to the presence of diverse active components, ease of access, and their limited side effects. The development of nanotechnological methods can help to improve the efficacy of different therapeutics as well as herbal-based products. Here, we present a review of the efficacy of the plant based-nanomaterials in the management of wounds and discuss the involved therapeutic targets. For this purpose, a profound search has been conducted on in vitro, in vivo, and/or clinical evidences evaluating the efficacy and pharmacological mechanisms of natural product-based nanostructures on different types of wounds. Different pharmacological targets are involved in the wound healing effects of herbal-based nanostructures, including suppressing the production of inflammatory cytokines and inflammatory transduction cascades, reducing oxidative factors and enhancing antioxidative enzymes, and promoting neovascularization and angiogenic pathways through increasing the expression of vascular endothelial growth factor, fibroblast growth factor, and platelet-derived growth factor. Moreover, nanostructure of plant extracts and their phytochemicals can enhance their bioavailability, control their release in the form of sustained delivery systems to the wound site, and enhance the permeability of these therapeutics to the underlying skin layers, which are all necessary for the healing process. Overall, various plant extracts and their natural compounds, used in nanoformulations, have demonstrated high activity in the management of wounds and thus can be assumed as future pharmaceutical drugs.

Keywords: nanomedicine, nanoparticle, nanofiber, natural product, medicinal plants, phytochemicals, herbal products, hydrogels, nanoemulsion, electrospinning, wound healing, wound dressing, nanostructure

Introduction

Wound healing process is an intricate and essential regulated sequence of several well-orchestrated biochemical and cellular phenomena to restore the integrity of the skin. During the wound healing process, wound progresses within three differentiated, though overlapping stages: inflammation, proliferation (neo-angiogenesis, granulation, re-epithelialization), and maturation (extracellular matrix [ECM] remodeling).¹⁻³ Wound management and the efficacy of wound healing in occlusion of the injured tissue can considerably depend on the materials used in the wound dressing.⁴ Traditional wound healing therapies have been investigated experimentally and clinically, and a wealth of information about the role of traditional therapies in alleviating the

underlying causes of nonhealing wounds is found in several studies.⁵⁻⁷ Medicinal plants can be taken into account as the potent and promising therapeutics for improvement of wound healing processes based on the variety of the active and effective components such as flavonoids, essential oils, alkaloids, phenolic compounds, terpenoids, fatty acids, and so on.⁷ These traditional medicines can be preferred over modern therapy due to the low cost, limited adverse effects, bioavailability, and efficacy.^{8,9}

Beside the advantages of medicinal plants for wound management, one of the promising ways to promote their efficacy is to subject them to nanosizing process or incorporate them into nanostructures. Nanomaterials possess unique characteristics due to their nanoscale size and the high surface area to volume ratio, and nanosizing the medicinal plants can occur in association with modification in their physical and chemical characteristics.^{10,11}

Natural product-based compounds can be used directly as medicaments for alleviating the wound or as drug carriers for delivery of other therapeutics.¹² The advantageous efficacy of the nanostructured medicinal plants stimulated the authors to provide a comprehensive review of the plant-based nanomaterials obtained by different methods and their therapeutic targets in regulating the wound healing process.

Search strategy and study design

A comprehensive literature review was carried out by the authors in the electronic databases of Scopus, PubMed, ScienceDirect, and Cochrane Central Register of Controlled Trials. The search was conducted without time restriction and using the following search strings: “Wound” in the title, and “Herb” OR “Plant” OR “Phytochemical” in the title, abstract, and keywords. On PubMed, all these words were searched in “title, abstract”. The reference lists of the former review articles and the retrieved papers were manually reviewed for additional applicable studies. The initial search results, including 6,622 reports, were recorded for investigating whether they used herbal-based nanomaterials. Two individual authors initially assessed the papers based on their title and abstract. In this step, regarding the titles and abstracts, the duplicate articles, review papers, non-English papers, and the papers which were irrelevant to the topic or were not in nanoscale range (totally 6,446 papers) were excluded. The full text of the retrieved articles (176 reports) was carefully examined by the authors to examine the potential of inclusion in the current review, and 96 papers were excluded in this step based on the full text. The exclusion criteria were as follows: the papers that included plant extracts and phytochemicals which have

not undergone nanosizing process; the papers that reported nanoformulations containing biomaterials which were not of plant-based origin; and the papers that included plant-derived nanoformulations which were not directly evaluated for wound healing effect and the involved mechanisms. Finally, 80 original articles, which have reported nanoscale wound healing process based on herbal substances, were extracted from the search results to be used as the main source of study in this paper. The diagram of the search study procedure is illustrated in Figure 1.

Foremost methods used for producing natural product-based nanomedicine for wound healing

Different nanostructured formulations have been successfully produced to help in natural wound healing (Figure 2). Here we discuss the foremost methods in detail.

Electrospinning

The porous structure and excellent pore interconnectivity of nanofibers make them desirable for wound dressing and wound healing due to their oxygen permeability, the ability of keeping the moisture at the desired level, their inhibitory effect on the exogenous microorganism invasions, their conformity to skin at the wound site, and their ability to alleviate scars.¹³⁻¹⁵ Incorporating the herbal extracts and phytochemicals in the nanofibrous membranes has been carried out in several studies, which superposed the advantages of these structures and the benefits of herbal compounds for ameliorating different wounds.¹⁶⁻²² Emodin, 3,8-trihydroxy-6-methyl-anthraquinone, an extract of some medicinal plants (such as *Polygonum* and *Aloe vera*), has been frequently used for treating the wounds. It has several advantages such as anti-inflammatory and antibacterial activity, ability to increase the rate of migration of fibroblasts into the wounded region, and ability to enhance the nucleotide excision repair of DNA damage in human cells.^{23,24} The incorporation of this compound into the polyvinylpyrrolidone nanofibrous nonwoven membrane produced a promising wound healing structure for treating acute full-thickness skin wound, and the drug was well distributed on the porous membrane structure.²³ Electrospinning of polyvinylpyrrolidone/emodin gave the favorable, nontoxic, non-allergenic, and highly biocompatible nanofibrous membrane with a considerably higher dissolution rate of emodin in comparison to the pure drug. The effect of this nanostructure on the full-thickness skin wound in rats promoted fluid retainment and continuity of re-epithelialization with shrinkage of the wound area, in comparison to the free drug. It was also successful in

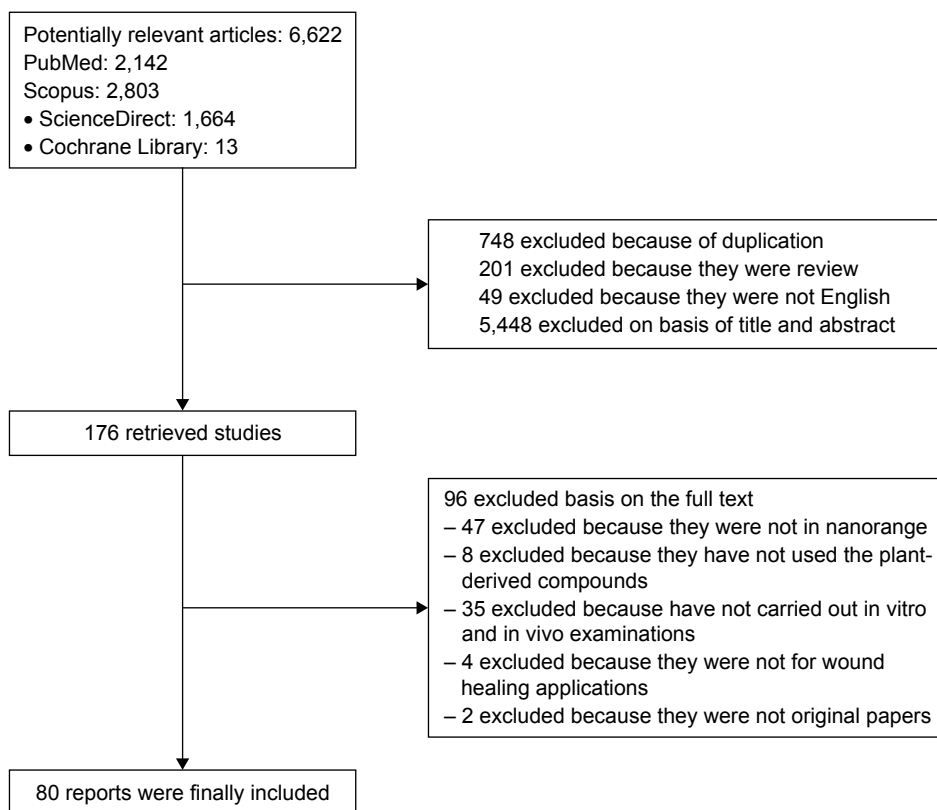


Figure 1 Search diagram of study selection.

accelerating the wound healing process.²⁵ Incorporation of emodin in a nanostructure of cellulose acetate (CA) fiber exhibited the potential to enhance the synthesis of collagen from human dermal fibroblast adults cells >100%.²⁶ CA

is a highly hydrophilic derivative of cellulose with a high potential to absorb water. The electrospun CA nanofibers provided a biocompatible environment for attachment and proliferation of L929 skin fibroblasts.²⁷ In spite of its

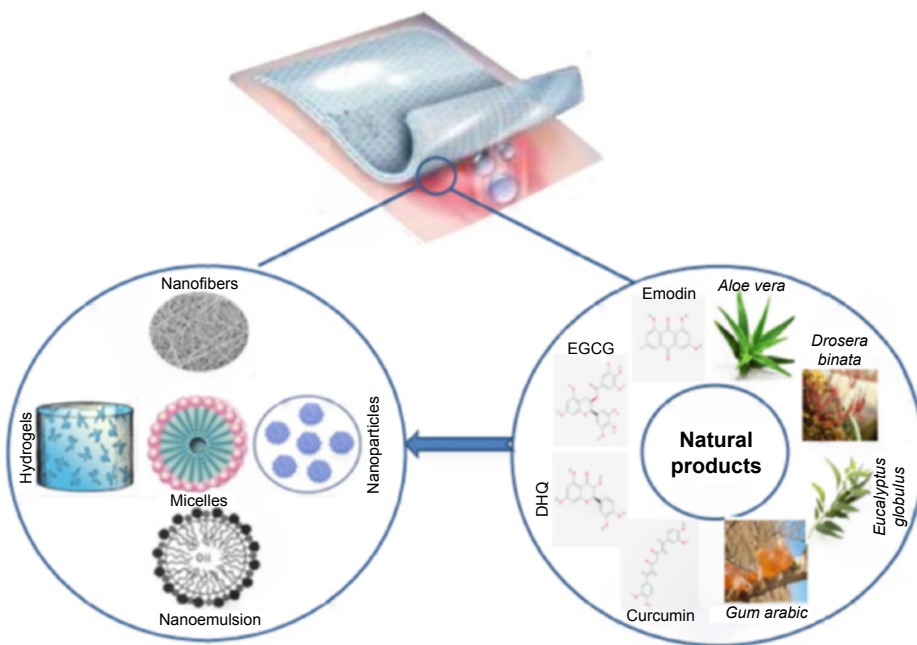


Figure 2 The foremost methods to produce nanoformulations from different natural products. Abbreviations: DHQ, dihydroquercetin; EGCG, epigallocatechin gallate.

advantages, its low breaking stress, strain, and poor resistance are the limitations in clinical use of this biopolymer, and it should be electrospun in combination with other biomedical materials for wound healing applications.^{28–30} Nanostructured wound dressings based on CA have been prepared by co-electrospinning of this biopolymer with polyester urethane,^{31,32} gelatin,^{33,34} poly (ϵ -caprolactone) (PCL)/polyurethane and dextran,^{35–37} polyurethane and zein,²⁸ and polylactic acid (PLA).^{38,39} The polyhexamethylene biguanide-loaded nanofibrous membrane of CA and polyether urethane showed strong antibacterial activity, good moisture retention and air permeability, good physical and mechanical properties, and accelerated the wound healing process. The presence of CA in nanofibrous membrane increased the water uptake of wound dressing and prepared a moist environment for the wound, increased adhesion to the rat skin fibroblast, and supported the rapid regeneration of epidermal layer.³¹ Co-electrospun CA and gelatin membranes can successfully simulate fibrous ECM, which is a complex combination of proteins and polysaccharides. In addition to their ability to mimic the fibrous structure of the native dermis, they can increase the proliferation of human dermal fibroblast, which is necessary for the regeneration stage and healing of any wound; they also possess high fibroblast affinity and collagen secretion, which make them appropriate for healing different types of skin injuries.³³ Higher affinity for the proliferation of fibroblasts and bioactivity was also observed in the presence of CA in PLA nanofibrous membranes.³⁸ This could be due to the high hydrophilicity of CA, which promotes cellular interaction. The CA/PLA nanofibrous membranes were also potent in accelerating the re-epithelialization of wounds in mice and increasing the rate of wound closure in comparison with the control.³⁸ Incorporating the herbal therapeutic agents in CA nanofibers leads to combining the advantages of these biomaterials as an interactive wound dressing material. Asiaticoside (one of the major phytoconstituents of *Centella asiatica*), a trisaccharide triterpene, was loaded on CA nanofibers and provided advantageous antioxidative effect at the initial stage of wound healing.⁴⁰ Asiaticoside showed a significant effect in the proliferation and production of types I and III procollagen mRNAs and also increased the levels of corresponding proteins of skin fibroblasts.^{41,42} The other herbal compound loaded on the CA was curcumin, which enhanced the attachment and proliferation of fibroblasts, increased the amount of collagen synthesis, and protected the normal human dermal fibroblast cells against H₂O₂-induced oxidative stress.⁴³ Curcumin (1,7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione), an active

ingredient of turmeric, is a polyphenolic compound obtained from *Curcuma longa* L. Curcumin is an active ingredient possessing a broad range of innate biological activities such as anti-inflammatory, antibacterial, antioxidant, anticancer, and angiogenic effects,⁴⁴ which make it a valuable agent for treating wounds. Curcumin has long been used in clinical studies and different in vivo animal models for accelerating cutaneous wound healing.⁴⁵ In the in vivo studies on animals treated with curcumin, this phytochemical showed its activity in early re-epithelialization through increasing the rate of collagen synthesis due to upregulating the level of transforming growth factor (TGF)- β 1 growth factors,⁴⁶ increasing the granulation tissue and blood vessels,⁴⁷ enhancing neovascularization, increasing the fibroblast and vascular densities,⁴⁸ and accelerating the migration of cells.⁴⁹ The ethanolic extract of curcumin caused the tissue debris and hemorrhages disappear and formed keratin layer on the epidermal surface of the wound in Black Bengal goats.⁴⁵

However, the low insolubility of curcumin, poor absorption, and instability cause inherent limitations impeding the use of curcumin alone.⁵⁰ Incorporating curcumin into hydrophilic nanoformulations is a useful way to circumvent unwanted properties of this herbal compound.^{51,52} The incorporation of curcumin into gelatin biomimetic nanofibrous mats was studied in acute wound in rats.⁵³

Green-synthesized metal nanoparticles using plants

Metal-based nanoparticles are extensively used in diverse fields such as engineering, chemistry, biology, and medicine.^{54–56} There is growing interest on the biological applications of metal nanoparticles in medicine and pharmacy. Tremendous growth in these expanding applications has opened applied frontiers and novel methods for synthesis of these nanoparticles, including physical and chemical methods. Most of these methods are expensive and environmentally hazardous due to the application of toxic and perilous chemicals with high biological risks.^{57–59} The biologically inspired experimental processes have been evolved to overcome these drawbacks and are more acceptable in medical applications due to high biocompatibility, biodegradability, nontoxicity, and the green nature of the agents, and also their cost-effectiveness. The most common metallic nanoparticles in biomedical and medicinal applications are silver- and gold-based nanostructures (nanoparticles, nanocomposites, and nanocoating), which have drawn the attention of researchers. Silver nanoparticles (AgNPs) and different silver salts have recently intrigued

medical scientists in the fields of clinical and fundamental researches due to their excellent antibacterial and antimicrobial activities,⁶⁰ which could be attributed to their large surface area to volume ratio, and could be remarkably interesting due to growing microbial resistance against metal ions, antibiotics, and the development of resistant strains.⁶¹ In addition to these characteristics, these nanoparticles possess the advantages of high chemical stability, antiviral, antifungal, and anti-inflammatory activities, and possibility to be incorporated into different composite structures, cosmetic products, food industry, and so on.^{57,62,63} These plant-mediated biosynthesized nanoparticles exhibit potential in wound healing and in efficiently retarding and preventing bacterial infections.^{64,65} The biological methods for preparation of AgNPs are based on the administration of reducing agents such as bacteria, fungi, and plant extracts to interact with the Ag ions and reduce them into AgNPs. A large variety of herbal extracts have been used to develop the green-synthesized AgNPs and prepare proper medications for wound. Some of the prominent examples of these plants are *Cassia roxburghii*,⁶⁶ *Drosera binata* Labill.,⁶⁷ *Indigofera aspalathoides* DC.,⁶⁸ *Azadirachta indica* A. Juss.,⁶⁹ *Arnebia nobilis* Rech.f.,⁷⁰ *Melia dubia* Cav.,⁷¹ *Terminalia chebula* Retz.,⁷² *Lansium domesticum* Corrêa,⁷³ *Orchidantha chinensis* T.L.Wu,⁷⁴ *A. vera* (L.) Burm.f.,⁷⁵ glucuronoxylan,⁷⁶ *Momordica charantia* L.,^{77,78} *Carica papaya* L.,⁷⁹ *Cymbopogon citratus* (DC.) Stapf,⁸⁰ *Nyctanthes arbor-tristis* L.,⁸¹ *Naringi crenulata* (Roxb.) Nicolson,⁸² *Phytophthora infestans*,⁸³ *Biophytum sensitivum*,⁸⁴ *Propolis*,⁸⁵ and *Bryonia laciniosa* L.⁸⁶

Most of these extracts possess inherent antibacterial and antimicrobial activity, which makes them appropriate for wound care. The importance of the presence of antimicrobial agents in wound dressing is their substantial role in controlling the microorganism colonization and subsequent proliferation, which helps accelerating wound healing process.^{67,87–89} In vivo treatment of mice with AgNPs, synthesized with *Catharanthus roseus* leaf extract, could successfully control bacterial and fungal growth, prompt the closing of wound, and considerably reduce the wound site.⁹⁰ In addition to the extracts applied for green synthesis of AgNPs, the antibacterial endophytic fungus of *O. chinensis* was also advantageous in biosynthesis of AgNPs and treated the infected wounds developed on the Sprague Dawley rats.⁷⁴ It produced well-stabilized AgNPs and inhibited different bacterial strains by metabolizing special proteins as well. Additionally, it successfully accelerated wound healing process, enhanced the wound contraction rate, completely re-epithelialized the epidermis,

minimized the scars after treatment period, minimized the bacterial count in the infected wound site, and downregulated the level of proinflammatory cytokines tumor necrosis factor alpha (TNF- α), interleukin (IL)-1 β , and IL-6.

The other parameter which can be controlled to accelerate the wound healing process is the rate of synthesis of collagen.⁷³ The first step in synthesis of collagen is hydroxylation of proline to form hydroxyproline.⁹¹ Thus, the hydroxyproline content is a good marker for collagen deposition, which has been determined in several studies on the application of green-synthesized AgNPs. Phytosynthesized AgNPs by *L. domesticum* fruit peel extract were potent in the enhancement of hydroxyproline content, a marker of collagen deposition, as well as the wound closure time. Complete epithelialization with keratinization as well as fibrous connective tissue proliferation were also the results of administration of nanoparticles.⁷³ The level of hydroxyproline and total proteins at the initial phase of wound healing was also increased in the presence of biosynthesized AgNPs, which confirmed the effect of these biosynthesized nanoparticles on cellular hyperplasia and deposition of matrix proteins in granulation tissues.⁷⁴ The linseed hydrogel was another choice for the green synthesis of AgNPs, possessing the advantages of increasing the wound closure percentage and also the collagen content at the wound site.⁶⁰

Cassia auriculata L.-mediated AgNPs were effective on both incision and excision wound models in Wistar albino rats. Although the wound healing activity of *Cas. auriculata* extract alone has been established in the literature, the *Cas. auriculata* AgNPs exhibited better performance in wound healing process rather than the extract and also Povidone Iodine ointment. Nanoparticles were also more effective on enhancement of excision wound contraction.⁹²

Wound tensile strength is a key parameter governing neocollagen production, and the quality and speed of tissue regeneration is directly related to the collagen content of wounds.⁹³ Biosynthesized AgNPs can promisingly be applied to enhance the collagen content and tensile strength of wounds. The administration of *L. domesticum*-mediated and linseed-mediated AgNPs to the animals increased the tensile strength of wound due to organization of collagen fibers.^{60,73} Guar gum/AgNPs were other phytosynthesized medications possessing significant effect on the tensile strength and modulation of collagen deposition, in addition to regulation of keratinocytes and accelerating the essential re-epithelialization process.⁹⁴

In addition to the abovementioned nanostructures, green-synthesized AgNPs can be included into/or coated

on the common dressings, electrospun nanofibers, and nanofibrous membranes. This integrates the advantages of electrospun nanostructures, AgNPs, and the medicinal plants. *M. charantia* fruit extract was used to prepare AgNPs by biological reduction, and then, addition of PLA to AgNPs caused stabilization of the Ag particles and made them electrospinnable. The electrospun nanofibers were found to be capable of wound healing and were highly efficient against bacteria and highly cytocompatible. Although AgNPs alone possessed antibacterial activity, the presence of *M. charantia* extract caused potentiation of antimicrobial activity as well as reduction of cytotoxic activity against fibroblasts.⁷⁷ AgNPs prepared using *Piper nigrum* leaf extracts were included in PCL membrane and this nanostructure was found highly promising in inhibiting bacterial colonization in wounds.⁹⁵

Green-synthesized titanium dioxide, gold, and copper oxide nanoparticles are other wound healing enhancers, which cause rapid wound healing and prevent/decrease infections and posttreatment side effects. Gold nanoparticles synthesized by *Coleus forskohlii* root extract remarkably accelerated re-epithelialization of excision wound created on rats, increased connective tissue formation, and promoted the rate of proliferation and migration of epidermal cells.⁹⁶ The synthesis of titanium dioxide nanoparticles (TiNPs) in the presence of *Moringa oleifera* leaf extract enhanced wound contraction and reduced the excision wound site in Albino rats.⁹⁷ Similar results were observed in Albino rats after treating the excision wound with biosynthesized copper oxide nanoparticles using *Ficus religiosa* leaf extract. These nanostructures also possessed persistent inhibitory activity against human pathogenic bacteria, and effectively increased the formation of macrophages, fibroblast, and collagen fibers.⁹⁸

Incorporation of natural products in different forms of nanoparticles to achieve a controlled delivery system to the wound site

Another common technique for utilizing the medicinal plants for wound healing involves their incorporation into different forms of nanoparticles. In drug delivery systems, control over the release of drug at the target organ is critically important. Several forms of biocompatible drug carriers are used in controlled drug delivery systems, including nanoparticles, nanoemulsion, nanohydrogels, nanofilms, and nanoliposomes. These systems are capable of diminishing the side effects and increasing the efficacy

of different therapeutic agents by providing a sustained and controlled delivery system, and they increase the dissolution rate of the drugs based on their surface characteristics.^{99–105} Besides the advantages of the herbal-based compounds in wound healing process, nanosizing these therapeutics or incorporation of these materials in nanoparticles provides a chance of controlling their delivery to the injured side and can increase their chemical activity.¹⁰⁶ For instance, nanosizing the curcumin particles provided a well-regulated and sustained delivery system and enhanced their wound healing activity by increasing the antimicrobial effect and accelerating the formation of granular tissues and collagen synthesis.^{99,107}

Nanoemulsions are nanostructures that provide the possibility to nanosize different essential oils. Upon application of nanoemulsions on the injured sites, the droplets form a film on the injured sites after evaporation of their water content. The plant essential oils have attracted considerable attention because of their high content of bioactive components.¹⁰⁸ The essential oil of *Eucalyptus globulus* was nanosized by nanoemulsification method, which promoted its antibacterial activity. The high activity and accelerated wound healing could be attributed to the existence of 45.4% 1,8-cineole (eucalyptol), which is known to be an active compound facilitating the penetration in transdermal and topical drug delivery systems.¹⁰⁹ Similar results were obtained in the in vitro and in vivo studies on application of tragacanth gum nanoemulsions impregnated with *A. vera* extract, which was attributed to the potential of *A. vera* in modulation of proteases.¹¹⁰ The encapsulation of active components of medicinal plants into nanoemulsions has provided a new approach for controlled drug delivery. A vital issue in the topical administration of lipophilic drugs for wounds is the localization of these ingredients in the superficial skin layers. Encapsulation of these drugs into nanoemulsions facilitates their penetration into the skin layers and provides a dispersed oil droplet phase to improve their solubility.^{111–113}

Nanohydrogels are a group of nanostructures for wound dressing that offer discrete advantages of high flexibility, high hydrophilicity, high mechanical strength, tunable structure, and the ability to absorb wound exudates as well as permeate oxygen and prevent wound dehydration.^{114,115} Due to their porous structure, they can be considered as another promising nanostructure for providing a sustained and controlled delivery system to the wound.¹¹⁶ Li et al prepared a sticky micro/nanohydrogel from alginate-gum arabic. Adhesive nanohydrogels possess the ability to bind to the injured tissues, and can successfully act as

hemostat and provide a microenvironment to facilitate the proliferation, differentiation, and migration of cells.¹¹⁷ As mentioned, curcumin as an active herbal compound suffers from the drawback of low water solubility and low bioavailability, which restrict its therapeutic applications. One promising method to overcome this drawback of curcumin and other hydrophobic compounds is to incorporate them in the aqueous nanostructures such as nanohydrogels. Incorporation of curcumin in polyethylene glycol (PEG)-PCL and PEG-PCL-PEG hydrogels improved the solubility and bioavailability of the drug, accelerated the re-epithelialization of wound, and regulated the granulation tissues.¹¹⁸

In addition to the mentioned formulations, nanoliposomes can be considered as the nanostructures which could be utilized to improve the solubility and efficacy of poorly soluble herbal-based therapeutics. Nanoliposomes (liposomes in nanometric scales) are colloidal structures composed of lipids and/or phospholipid bilayers encapsulating aqueous compartment(s), and they possess the ability to improve bioavailability, cause sustained transdermal delivery of different medicinal compounds, and overcome the possible drug overdose and the toxicity.^{119,120} Modification of nanoliposomes with polymers for dermal delivery of therapeutics causes the promotion of skin permeability and prolongs the retention time. PEG is one of the polymers successfully used in association with liposomes to enhance the dermal delivery of natural compounds. Entrapment of curcumin in PEG-nanoliposomes promisingly prolonged its anti-inflammatory activity, promoted the permeation rate into the dermal layers, and accelerated the wound closure.^{120,121}

Cellular and molecular mechanisms involved in the wound healing potential of herbal-based nanostructures

Antioxidative stress

Oxygen is an important local factor which is critical for the wound healing process due to its vital role in different stages of wound healing by mediating angiogenesis, enhancing re-epithelialization, and increasing collagen synthesis and fibroblast proliferation.^{122,123} Reactive oxygen species, such as hydrogen peroxide (H_2O_2) and superoxide (O_2^-), by-products of oxygen metabolism in the human body, are important regulators of wound healing.^{124,125} For maintaining the levels of free radicals at the desired level, medicinal plants are promising choices due to their inherent antioxidant

potential, which are potent in regulating enzymes SOD, glutathione peroxidase, and catalase. The herbal-based compounds, plant extracts and essential oils, such as curcumin, genistein, cellulose (extracted from *Citrus reticulata*), Asiaticoside, *Chromola enaodorata* extract, *Co. forskohlii* root extract, black seed oil, and wheat germ oil, in wound dressings inhibit the oxidative stress and exert antioxidant activity.^{40,89,96,120,121} Curcumin is known as a potent antioxidant compound, and nanosizing this herbal-based compound can be achieved without any significant alteration in its intrinsic antioxidant activity. This has been recognized by Li et al who observed <1% reduction in the antioxidant activity of nanocurcumin incorporated into chitosan/alginate hydrogels, in comparison to the unmodified curcumin (native form).¹¹⁹ The inclusion of curcumin in wound dressings significantly decreased the wound oxidative stress by diminishing the SOD level.¹¹⁸ In another study, bioconjugation of AgNPs by *Cat. roseus* leaf extract caused strong antioxidant activity, rather than the conventional AgNPs, due to adherence of the functional groups of *Cat. roseus* extract to the nanoparticles.⁹⁰ *Fraxinus angustifolia* bark and leaf extracts showed antioxidant activity against H_2O_2 -induced oxidative stress in both in vitro and in vivo studies, which was due to the presence of a high content of quercetin and tannic acid, two of the most potent antioxidants. Apart from these results, the ability of these extracts was proved in chelating ferrous ions and this inhibited their activity to convert peroxides to free radicals. Their high chelating activity could be another reason for their antioxidative ability in the wound tissue. The higher cellular uptake of nanoformulated samples led to higher antioxidant activity and better wound healing function of these structures.¹²⁶

Anti-inflammatory activity

Inflammation is involved in the first stage of wound healing process, which is characterized by the migration of leukocytes into the wound, and mainly starts by the aggregation of platelets followed by infiltration of leukocytes. Leukocytes are indispensable cellular components involved in the inflammatory response, which affect the pathogens, tissue degradation, and tissue formation, as well.¹²⁷ The inflammatory response is crucial for the healing process, which orchestrates the cellular cascades associated with wound healing by supplying the growth factor as well as cytokine signals.³ On the other hand, in the physiological inflammatory response, inflammatory cells can cause preventive and inhibitory effects against bacterial invasion and debris degradation, as well.¹²⁸

The infiltration of cells at the wound site occurs after the invasion of monocytes into the wound tissue and their differentiation into macrophages. Macrophages can provide several growth factors and proinflammatory cytokines such as IL-1 α and IL-1 β , TNF- α , platelet derived growth factor (PDGF), TGF- α , keratinocyte growth factor, and vascular endothelial growth factor (VEGF).¹²⁹ It is worth noting that inflammation can cause either advantageous (attraction of the immune system elements to the injury site, facilitating the repair of damage) or destructive (tissue dysfunction within prolonged inflammatory phase) effects during treatment of different disorders,¹³⁰ and thus, control over inflammation is highly crucial. Based on the various growth factors and cytokines involved in normal and acute wound healing, the mechanism of modulation of inflammatory processes in wound repair should be cleared for different types of medications. Polyphenolic compounds are the promising candidates for regulating and modifying inflammatory responses. They have been found to be potent in regulating the levels of TNF- α , interferon- γ , and different types of ILs.^{131,132} Curcumin, one of the most important polyphenols, has long been used due to its high radical scavenging activity and its ability to reduce the inflammatory response, inhibit NF- κ B, and downregulate TNF- α , COX2, LOX, NOS, and MMP-9, all of which play a significant role in the inflammatory phase.^{46,133,134} In a study, curcumin showed efficient pro-healing activity against excision wounds in rats, which was due to decreasing the level of TNF- α , increasing the level of IL-10, and up-regulating the production of TGF- β 1.⁴⁶ The anti-inflammatory activity of other polyphenol-rich plants, such as *Fraxinus angustifolia*,¹²⁶ confirmed the effectiveness of this group of herbal-based products on early stages of wound healing.

Biosynthesized AgNPs and plant-loaded AgNPs are the other nanostructures possessing intrinsic anti-inflammatory activity. Bamboo cellulose nanocrystals impregnated with AgNPs were administered to mice, where they caused decreased inflammation through downregulating the levels of proinflammatory cytokines IL-6 (which is responsible for stimulating fibroblast proliferation) and TNF. The high levels of these two cytokines cause hyperinflammation and delay the wound healing process.¹³⁵ The AgNPs formulated using *Co. forskohlii* root extract caused decrease in the number of neutrophils, macrophages, and other inflammatory cells.⁹⁶ Application of *B. laciniosa* leaf extract in preparing AgNPs resulted in a significant decrease in the levels of proinflammatory cytokines IL-6 and IL-10 and consequently diminished the inflammation and provided scarless wound healing.⁸⁶

Neovascularization and angiogenesis

After controlling inflammation, re-epithelialization, and collagen synthesis, capillary tissues, called granulation tissues, are formed due to growth of capillaries and lymphatic vessels from the pre-existing vessels at the wound site.² Two of the most important stimuli for angiogenesis are fibroblast growth factor (FGF) and VEGF.¹²⁷ VEGF induces healing by aiding in vascular permeability and prevents inflammatory cells to reach the injured site, and accelerates the proliferation and migration of endothelial cells.¹³⁶

The tragacanth gum scaffold incorporated with curcumin showed high efficacy in enhancing angiogenesis and forming new blood vessels. Curcumin could be responsible for the well-increased angiogenesis.¹³⁷ The angiogenesis can be triggered by green-synthesized metal nanoparticles.¹³⁸ Apart from other effects of curcumin on wound healing stages, nanosizing curcumin causes enhancement in neovascularization and angiogenesis, which could be due to its effects on nitric oxide synthase.¹⁰⁷ Gold nanoparticles are an important group that successfully triggered angiogenesis by differential regulation of growth factors such as VEGF and related protein expression.^{36,139,140} The green-synthesized AuNP-deposited hydrocolloid membranes showed accelerating effect on angiogenesis-related proteins by upregulating the expressions of VEGF, Ang-1, and Ang-2.¹²¹ Biosynthesized CuO nanoparticles (synthesized with *F. religiosa* leaf extract) and AgNPs (synthesized with guar gum and *L. domesticum* fruit peel extract) were also found potent in enhancing the capillary blood formation and facilitating angiogenesis and regulating proteins.^{73,94,98}

PDGF is another growth factor possessing inhibitory effect in the wound microenvironment and regulating wound vascularization.¹⁴¹ Impregnation of bamboo cellulose nanocrystals by AgNPs vascular network formation induced angiogenesis by intensifying the production of VEGF and FGF ($P < 0.05$) and also increased the PDGF level.¹³⁵ The production and accumulation of these growth factors could be due to the high capability of the prepared nanostructure to absorb water and regulate the moisture content of the wound microenvironment well, which enhances the proteolytic activity and induces wound repair.¹⁴²

Re-epithelialization and wound regeneration

The synthesis of collagen, from fibroblast cells, is a key factor in homeostasis, re-epithelialization, and regeneration of wound healing process. Based on this fact, the probable effective role of different plant-based nanostructures on promoting collagen synthesis has been investigated. Emodin

acts as a promoter of collagen synthesis and fibroblast proliferation, after encapsulating in fibrous mats.^{25,26} Fenugreek, *Trigonella foenum-graecum*, is an herb capable of modifying the physicochemical characteristics of collagen and has been used for preparation of collagen-based materials.⁸⁹ Incorporation of fenugreek in silk fibroin nanofibrous mats was another way to improve the collagen synthesis and deposition, due to the high amounts of saponins and flavonoids present in it.¹⁴³

Nanosized curcumin could successfully increase collagen deposition in the granulation tissue, increase myofibroblasts and blood vessels in the granulation tissue and capillary formation, and enhance the contraction of wounds in a mouse model. This could be due to the fact that the nanostructure enhanced the bioavailability of curcumin at the wound site and was potent in absorption of growth factors and cytokines.¹¹⁹

Tragacanth gum causes quicker regeneration due to the faster signaling pathway, which simulates the natural ECM and causes absorption of fibroblast cells to the dermal layer.¹³⁷ This biopolymer comprises mineral constituents, namely, calcium (a key factor for epidermal cell migration and regeneration), acts as promoter in normal homeostasis of the dermal cells, and successfully modulates the proliferation of keratinocytes.¹⁴⁴ On the other hand, magnesium is effective in the motility of fibroblast cells as well as keratinocytes.¹⁴⁵

Concluding remarks

Wounds are severe disorders affecting the quality of life of people all over the world. An efficient and fast healing process can reduce the costs and hospitalization, but achieving an ideal medicament is still an issue due to the complexity of skin tissue structure. In spite of the recent advances in the field of wound management and novel medications for wound healing and skin regeneration, traditional methods based on herbal and natural therapeutics are still known as promising alternative medications due to the diversity of active components, ease of access, and their limited side effects and low costs. There are several review studies in the literature about the role of natural products as wound dressing. Some of them have analyzed the role of biomaterials from animal origin^{146–148} and some others have dedicated their focus of interest on plant-based biomaterials, but not in nanosize scales.^{2,149,150} The potential of these natural occurring products has been well presented in these studies. In a recent review, Andreu et al¹⁰⁰ elucidated the efficacy of natural origin compounds in combination with the common wound dressings. They have examined the current methods for preparation

of nanostructured wound dressing from both natural and synthetic product polymers. Furthermore, the role of herbal medicine in management of different wounds has been reviewed in their study, while the studied compounds were not in the nanoscale. This study, for the first time, addressed the nanosizing method considerations for herbal-based natural compounds, as well as the mechanistic evaluation of the present herbal-based nanoformulations for wound dressing. In fact, this review presented a comprehensive study on the nanoformulations of herbal origin for wound management from both engineering and mechanistic points of view, while there is currently no similar review article available in the literature. Tables S1 and S2 give a summary of the plants and plant-derived phytochemicals that help in alleviation and healing process successfully. At this time, in spite of the advantages of the natural products in wound dressing and wound healing, development of these medicaments is continuously required to be improved. The appearance and development of nanoscience and technology could help to improve the efficacy of different therapeutics as well as herbal-based products. In recent years, nanostructures and nanoformulations have promisingly overcome the drawbacks of common medicaments, provide a smart healing process, regulate the release of therapeutics, reduce the doses required for healing, and provide a unique opportunity to facilitate healing even for chronic wounds. Different nanoformulation methods have long been used for producing plant-based nanostructures in the presence or absence of synthetic materials. Electrospinning method successfully provides wound dressings which includes herbal compounds as the base material. The well-regulated porosity and the similarity of electrospun nanofibers to the skin tissue, in association with several other benefits such as the possibility of incorporation of various types of materials, make them the ideal dressing for wound management. According to the literature review, it can be concluded that, at this time, the plant-based electrospun nanofibers mainly facilitate the adhesion, proliferation, and differentiation of fibroblasts and keratinocytes. This could be attributed to their ability to provide ideal microenvironments due to the porous structure and promising permeability and moisture retention of these herbal-based nanostructures. Another advantage of these nanostructures is the ability for co-electrospinning of the herbal-based compounds with other biomaterials, combining the advantages of all the constituents. Application of medicinal plants and their extracts in forming metal-based biocompatible nanoparticles in a green and cost-effective method has produced a group of nanostructures with excellent antibacterial and antimicrobial activities. Different plant-mediated metal nanoparticles

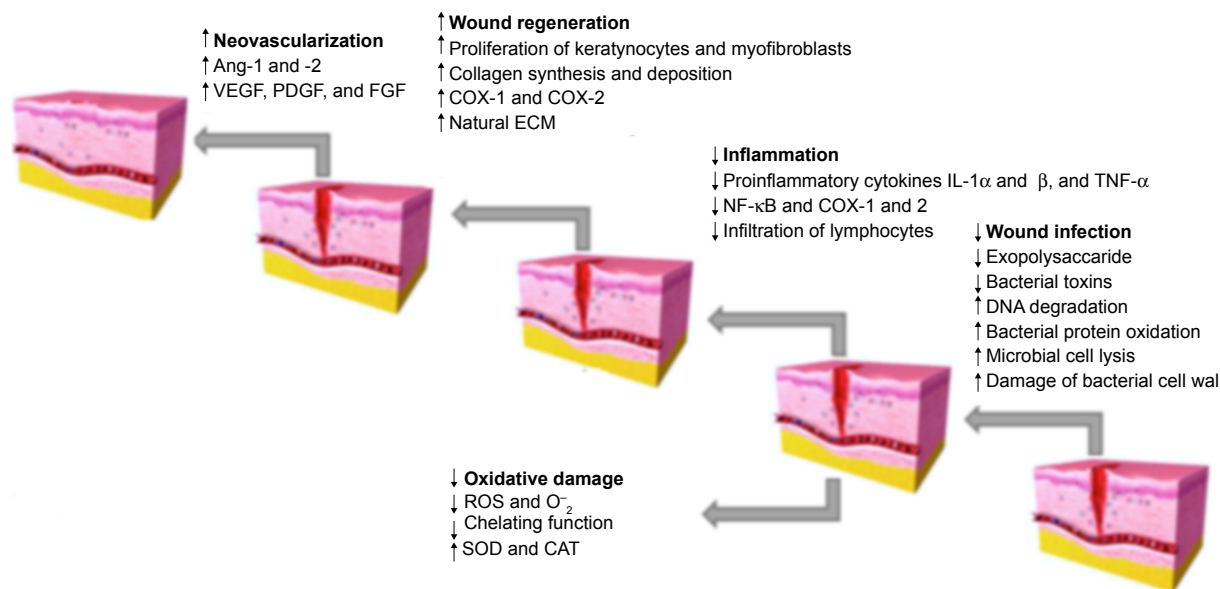


Figure 3 The role of natural nanoformulations in different stages of wound healing.

Abbreviations: ECM, extracellular matrix; FGF, fibroblast growth factor; IL, interleukin; PDGF, platelet-derived growth factor; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor; ROS, reactive oxygen species; SOD, superoxide dismutase; CAT, catalase.

possess the ability of preventing the bacterial colonization as well as prolonging the anti-inflammatory effects. According to the literature, impregnation of herbal-based compounds in nanoparticles, nanoemulsion, nanoliposomes, hydrogels, and so on is one of the most effective methods for enhancing their availability, controlling their release in the form of sustained delivery system to the wound site, and enhancing the permeability of these therapeutics even to the underlying skin layers, which all are necessary to the healing process. The water-insoluble herbal-based compounds are commonly used in this method to improve their solubility and wound healing efficacy.

The most important cellular and molecular mechanisms corresponding to the herbal-based nanostructures are anti-oxidative stress, anti-inflammatory activity, angiogenesis, neovascularization, and re-epithelialization (Figure 3). Medicinal plants are the richest sources of antioxidants such as polyphenols and flavonoids. Nanostructures including herbal products such as curcumin, Asiaticoside, and *Cat. roseus* possessed radical scavenging activity and regulated the oxygen level in the wound site. Controlling the inflammatory phase could be achieved by reducing the inflammatory responses, inhibiting NF- κ B, targeting inflammation pathways (intracellular transcription and transduction), and downregulating the proinflammatory cytokines. Curcumin-based nanostructures were found to be the most potent herbal-based nanostructures in inflammatory phase, regulating the levels of TNF- α , IL-10, and TGF- β 1. Biosynthesized AgNPs were another group of

plant-based nanostructures playing a vital role in controlling the wound inflammation. Different herbal-based compounds and extracts (such as *Co. forskohlii*, *B. laciniosa*, *O. chinensis*) used in the preparation of AgNPs caused a considerable anti-inflammatory activity attributed to the downregulated levels of TNF- α , IL-6, IL-1 β , and IL-10. Improving angiogenesis and vascularization during the wound healing process depends on the stimulation of FGF, VEGF, and PDGF. Curcumin and plant-mediated metal nanoparticles were found to be potent in triggering angiogenesis via regulating these growth factors. Another key factor in wound healing process is the rate of re-epithelialization. Nanostructures including natural products such as emodin, fenugreek, curcumin, and tragacanth gum are some of the examples with the ability of prompting collagen synthesis and proliferation of fibroblasts, resulting in accelerated re-epithelialization. It is worth noting that although all of the prepared herbal-based nanostructures were successful in ameliorating wounds, curcumin-based nanostructures were found to be the most potent nanostructures, which play a significant role in controlling most of the wound healing stages. Among different methods used for preparing nanoformulations of phytochemicals, metal-based nanoparticles (especially AgNPs) involve the most pharmacological targets in the wound healing process, indicating their best therapeutic properties. The results of the current review article mainly confirmed the significance of natural compounds as alternative choices for healing different wounds and corroborated the success of nanotechnology in

enhancing the efficacy of different medicaments. The impact of nanostructure approaches for natural wound healing agents has gained wider attention because of improvement in targeted therapy and bioavailability, as well as development of stability. Further pharmacological experiments are mandatory to evaluate the intracellular targets involved in wound healing effects of natural nanomedicine. Also, conducting well-designed clinical trials is necessary to confirm the safety and efficacy of natural product-based nanoformulations in treating wounds.

Disclosure

The authors report no conflicts of interest in this work.

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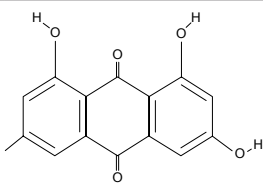
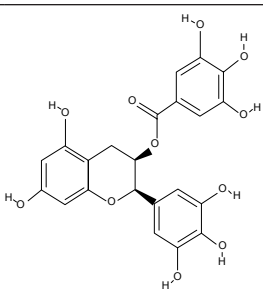
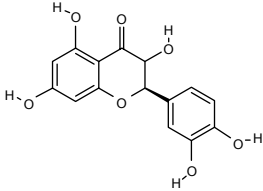
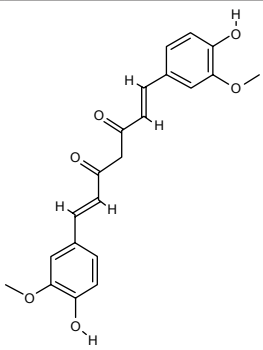
Supplementary materials

Table S1 Herbal-based nanoformulations used for wound management

Plant name	Fraction/extraction	Wound healing model	Reference
Electrospinning			
<i>Astragali Radix</i>	Hydroethanolic extract	In vivo on Sprague Dawley rats	1
Tragacanth gum	–	In vivo on Sprague Dawley rats	2
<i>Calendula officinalis</i>	NM	In vivo on Sprague Dawley rats	3
Henna	Leaves ethanolic extract	In vivo on Wistar rats	4
Fenugreek	Seed extract	In vivo on Wistar rats	5
Soybean	Protein isolates	In vitro against primary HDFs	6
<i>Spartium junceum</i> L.	Vegetable branch extracts	In vitro against human keratinocytes (HaCaT)	7
<i>Tecomella undulata</i>	Bark methanolic extract	In vitro	8
<i>Centella asiatica</i>	Crude extracts	In vitro on NHDF	9
Green-synthesized metal nanoparticles			
<i>Cassia roxburghii</i>	Aqueous extract	In vivo (male Wistar albino rats)	10
<i>Arnebia nobilis</i>	Root aqueous extract	In vivo on Wistar albino rats	11
<i>Biophytum sensitivum</i>	Aqueous extract	In vitro on L929 fibroblast	12
Cellulose gum	–	In vivo Sprague Dawley rats	13
<i>Coleus forskohlii</i>	Aqueous root extract	In vivo on albino Wistar rats	14
<i>Drosera binata</i>	Leaf chloroform extract	In vitro on human keratinocytes	15
<i>Ficus religiosa</i>	Leaf aqueous extract	In vivo on Wistar albino rats	16
<i>Naringi crenulata</i>	Aqueous extracellular leaf extract	In vivo on Wistar albino rats	17
<i>Citrus reticulata</i>	Toluene:ethanol extract	In vitro	18
<i>Moringa oleifera</i>	Aqueous leaf extract	In vivo on male albino rats	19
Potato starch	–	In vivo on Swiss albino rats	20
Guar gum	–	In vivo on Wistar rats	21
<i>Nyctanthes arbor-tristis</i> L.	Ethanol leaf extract	In vitro	22
Turmeric	Acetone extract	In vivo albino rats	23
<i>Bryonia laciniosa</i>	Aqueous leaf extract	In vivo on Wistar rats	24
<i>Cassia auriculata</i>	Aqueous leaf extract	In vivo on Wistar albino rats	25
<i>Lansium domesticum</i>	Fruit peel aqueous extract	In vivo Sprague Dawley rats	26
<i>Phytophthora infestans</i>	Aqueous leaf extract	In vivo on albino rats	20
<i>Azadirachta indica</i>	Aqueous leaf extract	In vivo on rabbits	27
<i>Piper nigrum</i>	Aqueous leaf extract	In vitro	28
<i>Catharanthus roseus</i>	Methanolic leaf extract	In vivo on albino rats	29
Propolis	Propolis:gelucire aqueous extract	In vivo on Wistar rats	30
<i>Orchidantha chinensis</i>	Endophytic fungus OC-11 isolate	In vivo Sprague Dawley rats	31
Linseed	Linseed hydrogels obtained from aqueous extract	In vitro	32
<i>Momordica charantia</i>	Fruit ethanolic extract	In vitro on L929 fibroblast	33
Loading on different nanoparticles			
<i>Eucalyptus</i>	Eucalyptus essential oil	In vivo on Sprague Dawley rats	34
<i>Aloe vera</i>	Aqueous extract	In vitro against human fibroblast cells	35
<i>Cal. officinalis</i>	Aqueous extract	In vitro against conjunctival epithelial cells	36
<i>Dendrocalamus hamiltonii</i>	NM	In vivo on Swiss albino mice	37, 38
<i>Bambusa bambos</i>	Leave extract	In vivo on Swiss albino mice	37, 38
Danggui Buxue	Aqueous extract	In vivo on Sprague Dawley rats	39
Black seed	Essential oil	In vitro against HaCaT cells	40
Wheat germ	Essential oil	In vitro against HaCaT cells	40
<i>Pluchea indica</i>	Leaf ethanolic extract	In vitro against HO-I-N-I buccal mucosa carcinoma-derived cells	41
Tragacanth gum	–	In vitro against human fibroblast cells	35
<i>Silybum marianum</i> L.	Isolated silymarin content	In vivo on male BALB/c mice	42
<i>Fraxinus angustifolia</i>	Leaf ethanolic extract	In vivo on CD-1 mice	43
Gum arabic	–	In vivo on C57BL6 mice	44

Abbreviations: HDF, human dermal fibroblast; NHDF, normal human dermal fibroblast; NM, not mentioned.

Table S2 Nanoformulations of different phytochemical compounds used as wound healing agents

Phytochemical name	Structure	Nanostructure method	Wound healing model	Therapeutic outcomes	Reference
Emodin		Electrospinning (encapsulated in cellulose acetate fiber mats)	In vitro (HDFa)	The nontoxic nature of CA fibers containing emodin between 0.005% and 0.1% wt against HDFa cells (96.8%–87.2% viability) Toxic nature of CA fiber mats containing 1.0% wt (31.6% viability) ↑Collagen synthesis of HDFa (twofold) for emodin-loaded fiber mats in comparison to the neat emodin	45
		Electrospinning with PVP	In vivo on mice	promoting fluid retainment and accelerating re-epithelialization of wound in mice Decreasing the wound area	46
EGCG		EGCG-loaded nanoliposomes	In vivo on male BALB/c mice	Potent antibacterial activity against <i>Staphylococcus aureus</i> bacterial strain Protective effect on infections induced by methicillin-resistant <i>S. aureus</i>	47
Dihydroquercetin		Nanocomplex with lecithin nanoparticles	In vivo on rats	↓Wound area ↑Epidermis regeneration rate High antioxidant activity	48
Curcumin		Electrospinning (loaded on CA nanofibers)	In vitro on NHDF	↑Cell viability ↓H ₂ O ₂ -induced cellular death ↑Collagen synthesis ↑Proliferation rate	49
		Electrospinning (curcumin/gelatin-blended nanofibrous mats)	In vitro on HS-27 cells/in vivo on rats	↑Cell metabolism and proliferation ↑Cell adhesion and spreading ↑Mobilization and migration of fibroblasts ↓Wound closure time ↑Re-epithelialization and granulation rate ↑Collagen deposition	50

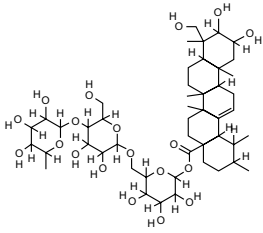
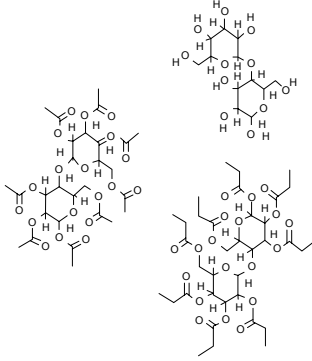
(Continued)

Table S2 (Continued)

Phytochemical name	Structure	Nanostructure method	Wound healing model	Therapeutic outcomes	Reference
		Electrospinning (curcumin-loaded gum tragacanth/poly(ϵ -caprolactone) electrospun nanofibers)	In vivo on rats	↑Healing rate ↓Wound area ↑Collagen content ↑Rate of granulation tissue formation ↑The rate of transition from inflammation to tissue granulation phases	51
		Loading on the collagen functionalized nano-graphene oxide	In vitro against NIH 3T3 embryonic fibroblast/ in vivo on the Wistar rats	↑Cell adhesion due to the high hydrophilicity of scaffold Faster cell migration (90% coverage of the scratch area within 24 hours) Potent antibacterial activity ↑Wound closure rate	52
		Nanocomposite hydrogel (composed of curcumin, <i>N,O</i> -carboxymethyl chitosan, and oxidized alginate)	In vivo on rats	↓Wound area ↑Re-epithelialization and granulation rate ↑DNA and protein content on seventh day post-wounding ↑Collagen deposition	53
		Loading the curcumin/Ag nanoparticles on the nanocellulose-dispersed chitosan film	In vivo albino rats	↓Scars at the closure of wounds ↑Collagen fibers and angiogenesis ↑Wound contraction rate ↑Epithelialization rate ↓Wound area (up to 97% within 27 days)	23
		Chitosan/poly-g-glutamic acid/pluronic/curcumin nanoparticles	In vitro (HSF) In vivo	↓Inflammation and infection ↑Neocollagen regeneration ↓Nitric oxide production	54
		Curcumin-loaded polycaprolactone-polyethylene glycol nanofibers	In vitro (on mouse myoblast cell line C2C12) and mouse macrophage cell line RAW264.7/ in vivo on female BACB/c	High biocompatibility of scaffold ↑Proliferation rate of C2C12 cells ↑Attachment and growth of C2C12 cells due to porous structure of scaffold Inhibition of NO production in RAW264.7 cells Antibacterial activity against <i>S. aureus</i> ↑Wound closure rate	55
		Encapsulation in propylene glycol nanoliposomes	In vitro (on HDF)	Considerable recovery rate Complete wound contraction after 18 days	56
		Loading on chitosan-based nanoemulsion gel	In vivo on excisional wounds in Wistar rats	Full wound closure after 12 days Enhancing granulation tissue formation	57

(Continued)

Table S2 (Continued)

Phytochemical name	Structure	Nanostructure method	Wound healing model	Therapeutic outcomes	Reference
		Loading on gel-core hyalurosomes	In vivo on Sprague Dawley rats	↑Wound contraction rate High permeation of curcumin to the underlying skin layers complete healing on day 7 ↑Density of collagen fibers ↑Deposition of collagen fibers ↑Re-epithelization rate ↑Skin penetration and dermal localization	58
		Entrapment in hyperbranched polyglycerol electrospun nanofibers	In vivo on rats/ in vitro on 3T3 Swiss mouse fibroblast cells	High fibroblast cell adhesion and spreading Efficient cell to cell interaction Complete cell migration	59
		Hydrogel encapsulated in micelles	In vivo on rats	↑Wound breaking strength ↑Collagen content ↑Wound maturity ↑Catalase activity at the wound site ↑Wound closure ↑Wound contraction and re-epithelialization	60
Asiaticoside		Electrospinning (loaded on the CA nanofibers)	In vitro on NHDF	↑Cell viability and proliferation rate ↓H ₂ O ₂ -induced cellular death ↑Collagen synthesis	61, 62
Cellulose acetate		Electrospinning (with polyester urethane composite)	In vivo on Wistar rats	Inhibition of the growth of bacteria such as <i>Escherichia coli</i> Good adhesion of cells to the nanofibers High viability percentage of fibroblast cells ↑Regeneration rate and recovery performances	63
		Electrospinning (with gelatin)	In vitro on NHDF	↑Proliferation rate of cells Good adhesion of cells to the nanofibers ↑Expression of collagen	64
		Electrospinning (with PCL)	In vitro against NIH 3T3 embryonic mouse fibroblast	↑Growth rate of cells ↑Cell attachment High antibacterial activity against <i>S. aureus</i> and <i>E. coli</i> bacteria	65

(Continued)

Table S2 (Continued)

Phytochemical name	Structure	Nanostructure method	Wound healing model	Therapeutic outcomes	Reference
		Electrospinning (with PLA)	In vivo on BALB-c male mice	↑Rate of wound closure ↑Re-epithelialization rate and granulation tissue ↑Collagen deposition	66
		Electrospinning (with zein and polyurethane)	In vitro against 3T3-L1 fibroblasts	↑Growth rate of cells ↑Cell attachment High antibacterial activity against <i>S. aureus</i> and <i>E. coli</i> bacteria	67
		Wet electrospinning	In vitro against L929 fibroblasts	↑Growth rate of cells ↑Cell attachment	68
		Electrospinning (with gelatin/hydroxyapatite nanocomposite)	In vivo on Wistar rats	↑Wound closure ↑Re-epithelialization rate ↑Angiogenesis index and neovascularization	69

Abbreviations: EGCG, epigallocatechin gallate; HDF, human dermal fibroblast; HDFa, human dermal fibroblast adult; HSF, human skin fibroblast; NHDF, normal human dermal fibroblast; PCL, poly (ϵ -caprolactone); PLA, polylactic acid; PVP, polyvinylpyrrolidone; CA, cellulose acetate.

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