Trends Pharmacol. Drug Deliv., 2025, 1, Iss. X, 1-20
DOI: 10.62184/tpdd.jtpdd110020242

SCIENCE PARK PUBLISHER
Trends in Pharmacology and Drug Delivery

Review article

Natural compounds for wound healing: An integrated bioactive prospective

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Received: 29 May 2024
Revised: 8 October 2024
Accepted: 20 November 2024
Published: 17 February 2025

Keywords:
Wound healing; Essential oils; Resins; Phytochemicals; Flavonoids; Polymers; Anti-inflammatory; Antimicrobial

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Abstract: Diverse natural compounds derived from either plant or animal sources have been shown to possess potent antioxidant, anti-inflammatory, antimicrobial and immunomodulatory properties. Such compounds could be beneficial for managing wound healing via developing multipurpose bioactive wound dressings. However, many of these compounds especially essential oils and phytochemicals cannot be used in their free form owing to their sensitivity, bioavailability and contact allergies, which as a result could hamper their implementation in wound healing. In this context, the most important classes of natural compounds implicated in wound healing will be highlighted with special emphasis on their effect in each wound healing phase. Among these compounds are essential oils, phytochemicals, plant resins, and plant-based and animal-based biopolymers. In addition, the most recent trends in developing multi-functional wound dressings based on the integrative actions of these active natural compounds will be highlighted. These wound dressings could be hydrogels, film membranes or nanoparticles-in-nanofibers.

1. Wound healing: an overview

A wound can be simply defined as a disturbance in the integrity of the epithelial lining of the skin, which could occur from either thermal or physical damage. Wound healing is a normal, complex and physiological process with four main phases including coagulation phase immediately after injury, inflammation phase in which swelling might occur, proliferation phase with the formation of new blood vessels and tissue and finally, maturation phase with remodeling of new tissues. These phases are integrative and occur in a well-defined order. Completion of the wound healing phases greatly depends on the wound type [1].

2. Types of cutaneous wounds

Cutaneous wounds can be defined as a damage or injury in the skin. However, wounds are not similar. Each type of wounds is completely different from others as it has different biology and pathophysiology, and hence knowing the wound type is critical before selecting the ideal therapeutic strategy [2]. Cutaneous wounds might occur as a result of some external or internal factors. External factors are mainly environmental factors which can damage skin such as injuries arising from accidents, while internal factors might arise from dysregulation in some metabolic pathways such as diabetes [2]. Cutaneous wounds can be divided into two main types including acute wounds and chronic wounds according to their cause. Acute wounds are caused by environmental factors such as traumatic injury. Acute wounds are characterized by accurate balance of production and degradation of cells and extracellular matrix (ECM), resulting in a faster healing process in comparison to chronic wounds. These wounds can be classified into two major types: traumatic wounds and surgical wounds [3].

Chronic wounds are usually caused by the presence of metabolic imbalances and are characterized by relatively prolonged healing

DOI: 10.62184/tpdd.jtpdd110020242

time due to loss of balance between the production and degradation of cells and ECM. Chronic wounds can be subdivided into four main types including vascular ulcers, diabetic ulcers, pressure ulcers and ischemic wounds [4]. Vascular ulcers are known to occur in the lower extremity (legs), especially in elder or obese persons accounting for more than 70% of chronic wounds [5]. This type of chronic wounds occur due to platelet aggregation, endothelial damage or intracellular edema, which might arise from previous injuries or venous deep thrombosis [6]. Diabetic wounds or ulcers are another important type of chronic wounds which arise because of diabetic conditions [7]. Diabetic patients are characterized by compromised immune system and neuropathic conditions, resulting in failure of the body to prevent infections, and hence conversion of even small wounds to chronic ones [2].

On the other hand, pressure ulcers occur normally in people with paralytic conditions due to restricted body mobility leading to increased pressure on tissues than in capillaries, resulting in decreased blood flow in some tissues mainly muscles [2]. For ischemic wounds, they are caused by restricted blood supply to tissues, leading to reduced glucose and oxygen supplies essential for proper cellular metabolism [8]. All these chronic wounds share some common features such as prolonged inflammation, inability of dermal or epidermal cells to respond properly and permanent bacterial infection, which can end up with the formation of antibiotic-resistant microbial biofilms [9]. Moreover, chronic wounds are also characterized by elevated levels of reactive oxygen species, senescent cells and proteases (**Figure 1**) [10].

In acute wounds, the proteases can easily return to their normal physiological levels by the aid of their inhibitors. Conversely in chronic wounds, proteases levels usually exceed those of their corresponding inhibitors, causing excessive degradation of ECM and also degradation of essential growth factors along with their receptors. This destruction of the ECM has two main drawbacks. Firstly, it hampers proceeding of the wound to the proliferative phase, and secondly, it recruits more inflammatory cells causing an extension in the inflammation phase [11].

3. Conventional topical wound therapies

It was strictly thought until the mid-1900's that uncovered and dry wounds will heal more quickly, while covered wounds will heal slower. Afterwards, it was realized that moist or covered wounds will heal better [12]. Topical standard agents for wounds include sterile saline, iodine solutions, hydrogen peroxide, collagenase or honey, which have been utilized for decades in wound healing [13]. Although there are abundant topical therapeutic dressings available for clinical use, very few dressings have prospective information that support their efficiency in wound healing [13]. Sterile cotton gauze dressings have been considered the standard and traditional wound care for a very long time. However, there is extensive work to develop smart and modern multifunctional dressings based on natural components with improved physicochemical properties as the standard topical therapies and dressings never fulfill the required criteria for a potent healing process [14]. Indeed, the material of the wound dressing should be selected based on the wound type. In general, an ideal wound dressing must maintain moist environment, permit migration of epidermal cells, induce angiogenesis, allow gas exchange, and protect against bacterial infections. Furthermore, it must be easily removed without adherence to the wound site, provide debridement to induce leucocytes migration and to be biocompatible without any allergic components (**Figure 2**) [15].

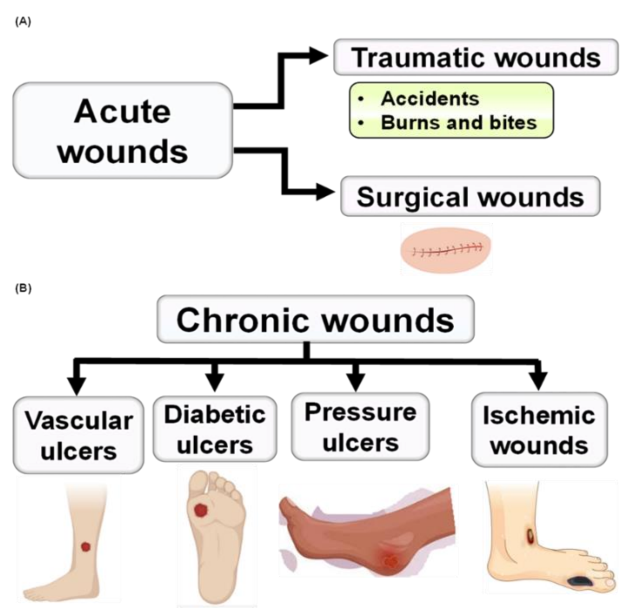

Figure 1. An illustration showing the types and causes of cutaneous wounds. (A) Acute wounds and (B) Chronic wounds.

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Figure 2. An illustration showing conventional topical wound therapies and dressings.

4. Natural compounds for wound healing

Natural compounds have been extensively used thousands of years ago to treat wounds. These compounds can be divided according to their source into plant-derived and animal-derived natural compounds. Both sources are abundant and can be easily extracted or prepared [16]. Natural compounds for wound healing can be also classified according to their bioactivities into anti-inflammatory, antioxidant, antibacterial,collagen promotion and pro-angiogenesis compounds [16].

4.1. Plant-derived natural compounds

Medicinal plant materials and their herbal extracts are now accounting for a large portion of the global medicinal market. These herbal products before consumption should be evaluated for their quality, composition and therapeutic efficiency. Herbal medicines are capable of treating wounds, ulcers, skin inflammation and infection. One important privilege of herbal extracts is that they are usually multi-component materials with many active constituents having the potential to manage wounds via addressing all the phases of the wound healing process [17]. There are various plant components that can be implemented in wound healing including essential oils, phytochemicals, plant resins and plant-derived polymers (**Figure 3**).

4.1.1. Essential oils

Essential oils (EOs) are materials produced by more than 17,000 plants species. These oils are insoluble volatile liquids with characteristic odor and relatively low density except sassafras, vetiver and cinnamon oils. Plant-derived essential oils are stored in several plant parts. Examples include flowers (orange and lavender), roots (vetiver, sassafras), leaves (mint, thyme, and eucalyptus), bark (cinnamon, sandalwood, and rosewood), seeds (carvi and coriander), fruits (fennel and anise) and plant resins (frankincense) (Table 1). They are secondary metabolites with distinguished aroma, containing mainly volatile hydrocarbons and terpenes and possessing antibacterial, antifungal and deterrent activities, which enable plants to defend themselves or adapt to their environments in a proper manner [18-20]. Several studies reported that EOs can enhance wound healing via promoting collagen production, fibroblast differentiation and inducing production of transforming growth factor beta, which can result in wound contraction [21]. Beside their wound healing accelerating effect, some EOs exert antibacterial and antifungal activities with prominent inhibitory effect on the colonization and bacterial growth in the wound bed [22].

Essential oils for wound healing are topically applied, which means that they will be in close contact with skin and they can

DOI: 10.62184/tpdd.jtpdd110020242

be absorbed till reaching deeper layers [23]. Although many of these essential oils are generally recognized as safe (GRAS) [24], their inclusion in approved pharmaceutical products is still limited due to their chemical instability, lipophilicity, low aqueous solubility, low absorption, minimal bioavailability, light sensitivity, high volatility, high sensitivity to pH and their tendency to oxidation [25, 26]. As a result, topical application of EOs in their free form is not recommended and their undesirable topical effects can be reduced by entrapment in nanocarriers or nanocomposites fabricated from natural or degradable polymers [27, 28].

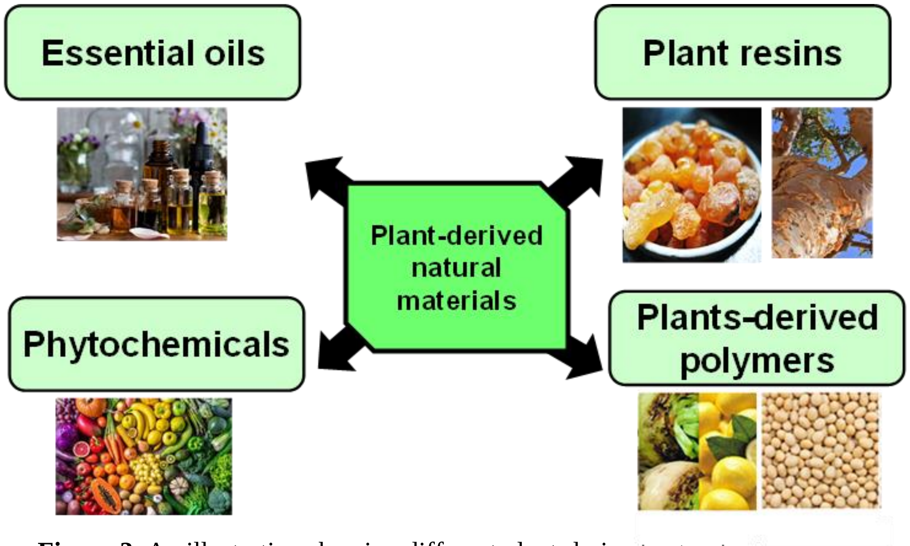

Figure 3. An illustration showing different plant-derived natural materials.

Table 1. Some essential oils with their storage parts in plants [18-20].

Essential oil	Storage part in plants	Density
Orange	Flowers	Less than one
Lavender	Flowers	Less than one
Vetiver	Roots	More than one
sassafras	Roots	More than one
Mint	Leaves	Less than one
Thyme	Leaves	Less than one
Eucalyptus	Leaves	Less than one
Cinnamon	Bark	More than one
Sandalwood	Bark	Less than one
Rosewood	Bark	Less than one
Carvi	Seeds	Less than one
Coriander	Seeds	Less than one
Fennel	Fruits	Less than one
Anise	Fruits	Less than one
Frankincense	Plant resin	Less than one

DOI: 10.62184/tpdd.jtpdd110020242

4.1.2. Phytochemicals

Plant phytochemicals are non-nutritive plant components which have been utilized for centuries in traditional medicine for wounds treatment [29]. They can be classified into primary and secondary metabolites according to their function in plants. Primary metabolites are required for plant survival such as lipids, carbohydrates, proteins, pyrimidines and purines. On the other hand, secondary metabolites are a group of plant chemicals produced via various metabolic pathways that might be derived from primary metabolic cascades [30]. Many studies reported that these secondary phytochemicals have antiviral, antifungal and antibacterial activities which are supposed to protect plants from pathogens. Furthermore, these compounds are strong UV absorbing materials, which can protect plant leaves from excessive light damage [31].

Secondary plant phytochemicals can be classified into three main groups according to their chemical structure into: (1) phenolic compounds such as flavonoids and phenylpropanoids, (2) nitrogen-containing compounds such as alkaloids and glucosinolates and (3) terpenes [32]. Phenolic compounds are derived from pentose phosphate and phenylpropanoid pathways in plants. They have an aromatic ring in their structure with one or more hydroxyl groups [33]. Alkaloids are a class of nitrogen-containing compounds, which are produced by plants as a response to biotic or abiotic environmental conditions and they are characterized by the diversity in their structures and functions [34]. Glucosinolates are characterized by the presence of both sulfur and nitrogen atoms in their structure, besides being stable under normal conditions [35]. Terpenoids are one of the most abundant groups of plant phytochemicals with a wide range of biological activities. They are produced by various plant parts including roots, flowers and vegetative tissues [36]. The majority of the beneficial effects of these compounds in wound healing could be related to their potent antioxidant and anti-inflammatory effects [37], in addition to their potential to accelerate tissue epithelization and promote angiogenesis [38]. Despite the diverse pharmacological applications of these phytochemicals, their utilization in wound healing is hampered due to their hydrophobic nature, light sensitivity, limited skin penetration and low bioavailability [39], which can be overcome by suitable formulations **(Figure 4)** [40].

4.1.3. Resins

Plant resins or oleo-gum-resins are usually produced by plants that grow in dry areas in African or Middle Eastern countries. Resins are metabolic products which are produced in the form of natural exudates as a result of a wound or an injury in the bark of some plants. Among oleo-resins are *Boswellia serrata* and *Commiphora myrrha*. They usually contain traces of the essential oil of the plant. In the pharmaceutical sector, resins are commonly used as stabilizers, emulsifiers, thickeners and binding material. In most studies, resins were topically applied in the form of either an ointment or a cream with certain concentration to manage wound healing. Results revealed that resin-based formulations were able to enhance early collagen tissue formation, wound contraction and tissue strengthening in the wounded site [41].

One of the most famous plant resins is frankincense resin derived from the tree's bark of the genus Boswellia [42]. It is mainly comprised of alcohol soluble components such as di- and tri-terpenes (30–60%), essential oils (5–10%), and the remaining component is gum composed of water-soluble saccharides (pentose and hexose) [43]. Frankincense resin was involved in many cosmetic formulations including soaps, creams and lotions for skin softening and treatment of some skin disorders [44]. This resin was shown to have an anti-inflammatory effect due to presence of boswellic acids (BA) among its components, which can inhibit 5-lipoxygenase, responsible for leukotrienes synthesis [44]. In addition, frankincense resin can reduce skin irritation and induce uniform skin pigmentation, which suggests that this resin can be a sophisticated material for wound healing [45]. In a recent study, this resin was utilized to fabricate a biocompatible film for wound healing, in which frankincense essential oil was first encapsulated into whey nanoparticles (NPs), which were incorporated in a dressing film fabricated from the resin [28]. Results showed that this film was an efficient wound dressing material with improved anti-inflammatory and tissue regeneration properties [28].

Another example of plant resins is gum arabic or acacia gum which is the exudate of Acacia senegal or Acacia seyal trees [46]. It is a mixture of polysaccharides (galactose, rhamnose and glucuronic acid) and proteins (2-3%) [47]. Gum arabic, one of the oldest and most utilized gums [48], has a wide range of applications in pharmaceutical, cosmetic and food sectors owing to its low viscosity, availability, hydrophilicity and

DOI: 10.62184/tpdd.jtpdd110020242

biocompatibility [49]. In addition, gum arabic has good film formation and emulsification properties due to presence of some hydrophobic protein fractions within its structure [50].

Arabic gum can be utilized to fabricate hydrogels depending on the presence of glucuronic acid (COO^-) at its surface which could be crosslinked with other anionic polymers via divalent cations such as Ca^{2+} or Mg^{2+} leading to the formation of hydrogels with enhanced water retention ability, which can further serve as a platform to incorporate different active components or phytochemicals to be used in topical wound healing applications [51].

4.1.4. Biopolymers

Plant-based biopolymers have been investigated many years ago for biomedical applications as most of them are multifunctional, tunable and can be prepared in versatile forms with sustained drug release according to the assigned application [52]. In general, plant-derived biopolymers can be sub-divided into polysaccharides such as pectin, starch, alginate and cellulose [53] and proteins such as soya, gluten and zein [54]. These biopolymers share some beneficial features which make them an attractive target for researchers. They are biocompatible, abundant, non-immunogenic and non- carcinogenic [54]. Several studies reported that these biopolymers can be used in wound healing via their formulation into different architectures such as hydrogels, membranes, nanofibers, composites so as to afford smart and multifunctional wound dressing materials [55].

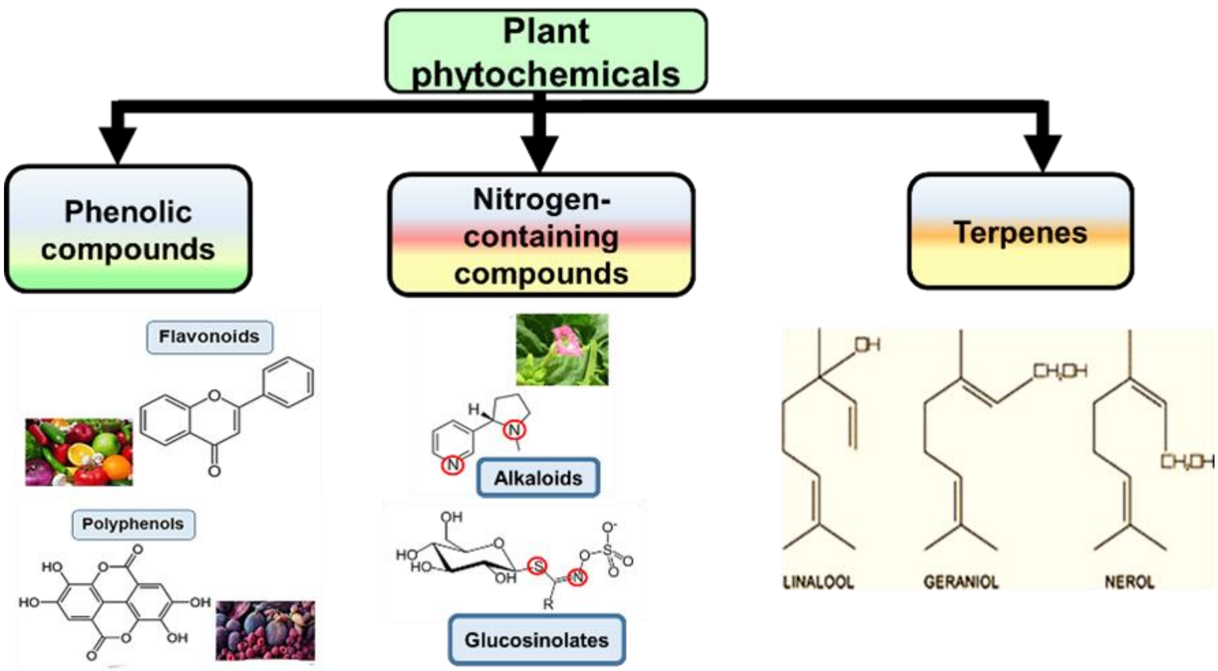

Figure 4. Different plant phytochemicals with wound healing potential.

4.2. Animal-derived natural compounds

4.2.1. Animal-based biopolymers

a. Chitosan

There are numerous polymers from animal sources in nature with diverse pharmaceutical applications. All of these polymers are biodegradable, biocompatible, non-immunogenic and non-toxic [56]. One of the most widely utilized animal-derived polymers is chitosan. It is a co-polymer comprised of N-acetylglucosamine attached to glucosamine via 1–4 glucosidic bond. Chitosan is a derivative of chitin which is abundant in the exoskeleton of marine crustaceans such as crabs and shrimps, beside its existence in yeasts, fungi and insects [57]. It can be used in wound healing owing to its potent antibacterial activity as it is the only positively charged polysaccharide due to presence of amino groups in its structure, which increases its susceptibility to interact with negatively charged molecules found in the bacterial cell membrane [58]. However, chitosan cannot be used in its free form in wound healing as it is only

DOI: 10.62184/tpdd.jtpdd110020242

soluble at pH below 6.5 [59]. As a result, researchers integrated chitosan into different pharmaceutical formulations that can be safely applied on wounds such as hydrogels, nanoparticles, micelles or membranes [60-63].

b. Hyaluronic acid

Hyaluronic acid (HA) is a natural polysaccharide that exists abundantly in our bodies. It is a highly anionic and hydrophilic polysaccharide with repeated units of N-acetyl-D-glucosamine and D-glucuronic acid. This interesting biopolymer can be easily modified to give various derivatives according to the required application. In addition, hyaluronic acid is a targeting molecule that can selectively binds to CD44 receptors overexpressed in some disorders [64]. In wound healing, it was found that the function of HA differs according to its size. Large chains are required in the inflammatory phase to act as a porous network, while it can serve as space filler in granulation tissue formation. Conversely light and short HA fragments can stimulate fibroblast migration and proper collagen deposition [65]. Many formulations based on HA or its derivatives blended with other polymers were developed in the form of films, hydrogels or nanocomposites to manage wound healing [66].

4.2.2. Bee products (Apitherapeutics)

Utilization of some bee products in the treatment of some human disorders is called apitherapy [67, 68]. Honey with all its types can be simply defined as an acidic (pH 3.6) concentrated aqueous solution composed of sugars in different ratios (40% glucose, 40% fructose, 20% water) with enzymes, minerals and vitamins [69]. In wound healing, bee honey serves basically as an antibacterial agent through production of hydrogen peroxide by the endogenous enzyme, glucose oxidase. Upon decomposition of hydrogen peroxide, it yields reactive free radicals, which can directly interact with bacteria exerting a killing effect [70]. On the other hand, some honey types are not hydrogen peroxide producers and act as antibacterial agents depending on their low pH and high sugar level [71]. Another component of honeybees is propolis which is composed of 300 or more compounds mainly phenolic compounds, steroids and amino acids [72]. They possess good antibacterial activity due to the presence of phenolic compounds and cinnamic acids [73]. Propolis can also be found in some plant sources such as willow, beech and birch [74].

5. Natural compounds as wound healing stimulators

5.1. Anti-inflammatory activity

Inflammation is a normal physiological response in wound healing which is essential to control hemostasis and help in elimination of damaged tissue and microorganisms [75], but if the inflammation phase is prolonged, it will delay the wound healing process [76]. Compounds with anti-inflammatory effect can prevent a prolonged inflammation phase, and hence can improve the quality of healing [16]. They can inhibit the expression of some pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α, suppress the activity of myeloperoxidase (MPO) and upregulate the M2 macrophage-associated gene expression [16]. In addition, some of these compounds can induce the gene expression of some early inflammatory markers such as IL2, IL4 and IL10 [77].

5.2. Antioxidant activity

Reactive oxygen species (ROS) play an important role in the consortium of a normal healing process. They mainly act as a secondary messenger molecules to many immune cells which are required in the repair process. In addition, they are involved in the regulation of blood vessels formation (angiogenesis) and flow of blood at the wounded area. More importantly, ROS act in the host's defense via bursting onto the pathogens found in the wound, causing their immediate death [78]. In general, ROS are required at low levels to fight any external damage, however, increased oxidative stress is a major factor in the development of non-healing wounds [79], which means that the level of ROS at the wounded site should be strictly controlled. Elevated ROS levels at the wounded site can degrade some proteins of the ECM and can affect the functionality of keratinocytes and fibroblasts [80].

The homeostatic regulation of the ROS levels is mainly the role of a specialized group of protein molecules known as antioxidants or "free radicals scavengers", which are dedicated to eliminating the deleterious side effects of ROS via donating their electrons so as to prevent ROS from capturing electrons from other vital molecules such as proteins, lipids and DNA [78]. Among these protein molecules are superoxide dismutase (SOD), catalase, glutathione peroxidase and glutathione-S-transferase (GST) [81]. Most of phytochemicals with antioxidant activity were found to exert their function mainly via enhancing

DOI: 10.62184/tpdd.jtpdd110020242

the levels of these protein molecules and reducing lipid peroxidation [82].

5.3. Antibacterial activity

Compounds with antibacterial activity can perform their function by either interfering with the mechanisms involved in bacterial resistance or inhibiting the synthesis of vital bacterial components [83]. These compounds are usually required in the inflammation stage of wound healing [16]. Most natural antibacterial agents produce ROS in their defense mechanism, which can directly affect the integrity of bacterial cells found in the wound. Hence, it can be a good alternative for antibiotics administration especially in chronic wounds that might last for a long time [84].

5.4. Collagen activity promotion

Collagen is the most predominant protein in the human body. This protein aids in re-epithelization of new tissues and promotes angiogenesis, so compounds enhancing synthesis of this important protein might be a good choice to promote wound healing [16]. Normally, collagens are synthesized by fibroblasts in their initial form, then they are modified to more complex structures [85]. The type, amount, and orientation of collagen dramatically change during the healing process, determining the extent of the tensile strength of the newly synthesized skin. At the beginning of the healing process, collagen III is synthesized first, then it is replaced by collagen I; the major skin collagen. After that, collagen will be deposited into more complex and mature structures during granulation tissue formation via lysyl oxidase enzyme-induced covalent cross-linking in order to restore the tensile strength for the healed area [86].

Interestingly, it was found that collagen degradation also can affect different phases of wound healing [87]. For example, during inflammation, soluble fragments of collagen can recruit macrophages to eliminate any existing microbes, which accelerates switching to the proliferative phase. In this phase, collagen fragments act as angiogenic signals for the formation of new blood vessels. In addition, collagen fragments can induce keratinocyte migration which helps in re-epithelialization [88]. Collagen degradation is regulated by intracellular and extracellular pathways. Intracellular pathways include internalization of intact collagen fibrils or fragmented collagen into endocytosis, phagocytosis or macropinocytosis pathways, ending up with their enzymatic degradation. Extracellular pathways includes membrane-bound and secreted proteolytic enzymes. Any disturbance in collagen turnover can cause defects in wound healing [89]. Two important enzyme families are included in extracellular degradation of collagen which are the matrix metalloproteinases (MMPs) and serine proteases [90]. MMPs include collagenases and gelatinases which can degrade intact and damaged fibrillar collagen, respectively. MMP-1 (collagenase-1) and MMP-8 (collagenase-2) are responsible for cleaving collagens I and III, respectively, while collagen IV is degraded by MMP-9 [91]. Neutrophil elastase is a serine protease that also aids in managing the level of collagen turnover in wounds. A balance between these enzymes activation and inhibition is vital for a normal wound healing process. Any disturbance in collagen turnover can cause defects in wound healing leading to its chronicity [86].

Some plant or animal-derived compounds can be utilized in wound therapy as they were found to decrease leukocyte infiltration, inhibit the expression of MMP9 and MMP2 and enhance fibroblast translation, which can induce collagen deposition [92]. In addition, they can increase the infiltration of macrophages, which as a result can enhance tissue granulation, re-epithelialization and collagen deposition [93]. Owing to the great importance of collagen in several processes of wound healing, it can be used as an adjuvant therapy in healing as it is non-immunogenic, biocompatible and it has the ability to recruit important cells required in the healing process such as macrophages and fibroblasts [94]. Collagen as a protein can be obtained from different sources. Animal-based collagen (bovine, porcine and avian) was shown to have some disadvantages related to allergic reactions, microbial contamination or disease transfer [95]. As a result, alternative natural sources of collagen from marine sources or recombinant from bacteria was considered [86].

Several wound dressings based on collagen were developed as drug delivery systems. Collagen can be blended with other natural or synthetic polymers such as hyaluronic acid, alginate, elastin, and poly (L-lactic acid). These blends can further incorporate other beneficial components that can help in the healing process such as silver NPs, gold NPs or antibiotics [86, 96-98]. Furthermore, collagen was formulated into nanostructures to be utilized in wound healing. These nanoformulations were found to reduce the particle size to the nanoscale with enhanced surface area-to-volume ratio, resulting

Trends Pharmacol. Drug Deliv., 2025, 1, Iss. X, 1-20
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in increased possible payload [99]. Additionally, the electrospinning technique was also utilized to fabricate collagen nanofibers that can incorporate other active components for topical drug delivery applications [100].

6. Recent approaches in using natural wound healing materials with an integrated bioactivity

The market of advanced wound care products is rapidly expanding and is expected to reach about $22 billion by 2030. The main focus of this global market is to develop multifunctional dressings which can perform many functions across all integrated wound healing phases [16]. Natural compounds usually have multiple therapeutical activities, which make them ideal candidates to develop advanced wound care dressings. However, many natural compounds have limitations which prevent them from reaching clinics. Most of them have very low bioavailability, low aqueous solubility and very low stability [16]. Consequently, in order to use these compounds efficiently, they should be formulated into a suitable form that can overcome all these challenges. Nanotechnology paved the road to fabricate natural compounds-based nanoformulations with enhanced aqueous solubility and improved biocompatibility [101]. There are various nanocomposites with integrated functions that can be included in wound healing such as hydrogels, film membranes and nanofibers.

6.1. Hydrogels

Hydrogels fabricated from natural polymers are a good choice as they exhibit good efficiency in encapsulating natural compounds with enhanced potency in managing wounds owing to their water absorption properties, hydrophilicity, non-adhesiveness and the ability to mimic the skin microenvironment [51]. They can be incorporated directly with active molecules or active molecules-loaded nanoparticles. Gelatin is a natural protein derived from collagen and it is well known for its activity in cellular migration, proliferation and adhesion, which makes it a suitable material for fabrication of wound dressings [102]. However, its weak mechanical properties hinder using it solely in fabrication of wound dressings, and instead, it should be crosslinked or blended with other biomaterials such as nanoparticles or plasticizers to improve its mechanical properties [103]. In this regard, thyme essential oil as an antibacterial and anti-inflammatory material was encapsulated into self-assembled sodium caseinate micelles which were further incorporated into a gelatin nanocomposite hydrogel [40]. In vitro drug release study revealed that incorporation of thyme oil-micelles within the hydrogel matrix resulted in a more sustained release profile in comparison to both free thyme oil and thyme oil micelles. More importantly, in vivo studies in a rat full excision wound model showed that the prepared nanocomposite hydrogel was able to enhance wound contraction with reduced inflammation and induced proliferation and angiogenesis when compared to a blank hydrogel without micelles [40].

Another integrative hydrogel based on natural components and polymers was fabricated in which gum arabic/pectin hydrogel was used to incorporate naringin (plant flavanone glycoside) within its matrix. The hydrogel was prepared via $CaCl_2$ crosslinking. Results indicated good encapsulation efficiency and high drug loading efficiency, associated with low hemolytic effect. Moreover, when this natural hydrogel was topically applied on full excision wounds in rats, there was a notable increase in wound contraction, as well as reduced inflammation, improved angiogenesis, increased collagen deposition and antioxidant effect [104].

Functionally Graded Scaffolds (FGSs) are another class of composites which can be designed in a manner to mimic the anisotropic structure of native skin tissue with all its layers, and hence they can enhance efficient and fast wound healing [105]. κ-carrageenan (κCG), a polymer extracted from sea red weeds, can be used in the preparation of different wound dressings such as films, membranes hydrogels, freeze-dried matrices as well as FGSs. The polymer shows excellent biocompatibility, biodegradability, good water absorption and similarity to the native ECM [106]. This polymer has negative charge per its disaccharide unit which can form hydrogels at low temperature after cooling (<50 °C) in the presence of low concentrations of cations [107]. Under these conditions and in aqueous medium, the coiled chains of κCG are converted to helix aggregation with brittle physical gel formation [108]. Physically-formed gels are preferred over the chemically-formed ones in tissue regeneration applications as their formation mainly depends on hydrogen bonding or electrostatic interactions with no covalent bonds, and hence they usually possess suitable biodegradation rate [109].

In an interesting study, κCG was selected as the main structural component of a recently prepared FGS [110]. A porous three-

DOI: 10.62184/tpdd.jtpdd110020242

layered FGS was fabricated from physical hydrogel of κCG using a single freeze-drying step. The lower layer was composed of κCG (1% w/v) and $CaCl_2$ (0.05% w/v) to mimic the dermal layer and it will be also suitable to be in direct contact with the wound bed with suitable pore size and elasticity to promote cellular migration and re-epithelization. The intermediate and the superficial layers were formed from the same components of the lower layer with the addition of 0.5% w/v arginine and 5% w/v whey protein isolate (WPI), respectively [110]. Pore size and hydration properties of the intermediate layer were suitable to mimic the deeper layers of epidermis. Regarding the superficial layer, it was dense enough to mimic the stratum corneum with small pore size to resist the external stress produced during freeze-drying. Results showed that this three-layered scaffold was formed with a pore size gradient resembling the native layers of skin, with improved in vitro cell proliferation, migration and adhesion towards normal fibroblasts and good in vivo healing potential in an animal model [110].

Arginine and WPI were involved in the preparation as multifunctional materials. Both of them can contribute in some phases of wound healing [111]. WPI is a mixture of biodegradable proteins including; bovine serum albumin, α-lactalbumin and β-lactoglobulin [112], which are a rich source of glutamine required for cellular growth [28]. Arginine is a positively charged and biocompatible amino acid with antimicrobial properties. It can interact with the negatively charged sulfate groups of κCG affording stability to the formed hydrogel layers. Moreover, it can modulate inflammatory responses and induce proper collagen deposition [113]. Arginine is an amino acid which is not produced in the body with adequate amounts. As its metabolic products are required in the healing process, it can be used to impregnate wound dressing matrices [114]. Another function for arginine in this FGS is its effective cryoprotectant properties [115].

6.2. Film membranes

Multifunctional membranes or films synthesized from natural polymers or plant resins have indeed shown great potential as wound dressings due to their ease of fabrication, high payload capacity, biocompatibility and good mechanical properties. In an interesting study, essential oil, plant resin and animal-derived polymer were simultaneously utilized to fabricate a membrane for wound healing with antimicrobial, anti-inflammatory and proliferative effects [28]. First, frankincense (FRK) essential oil was extracted from *Bosolica papyrifera* oliogum resin and encapsulated into whey protein NPs using a spray drying method. Afterwards, the same FRK resin used to extract the essential oil was further used to prepare a composite membrane and FRK-loaded whey protein nanoparticles were incorporated into the film using solvent casting technique. The fabricated membrane composite showed sustained release of the essential oil with good hemocompatibility and improved *in vitro* antimicrobial activity. In addition, *in vivo* wound healing study in a rat model revealed that the prepared composite membrane was able to reduce the gene expression of IL-6 with increase in the gene expression of transforming growth factor-β1 (TGF- β1), which confirms the potential of this composite as an efficient and easy to fabricate wound dressing [28].

A multifunctional gelatin-based film was fabricated using a solvent casting method in which gelatin was blended with Shekar tighal manna (St) as a pharmaceutical polysaccharide, persian gum (Pg) and essential oil of Anghozeh (EOA). Morphological examination revealed successful incorporation of oil droplets within the film matrix. Moreover, the obtained film with all components displayed good tensile strength with improved cytocompatibility and anti-inflammatory effect. In addition, blending of all components with gelatin resulted in the production of a film composite which could be used as an efficient microbial barrier for managing chronic wounds [116]. Shekar tighal (St) or Trehala manna is cocoon-shaped manna produced by the larval activity of the Curculionidae family on some species of Echinops. About 67.5% of this manna is water-insoluble and gel-forming molecules including cellulose, hemicellulose A and hemicellulose B, while 32.5% is water-soluble components [117]. Persian gum is another polysaccharide biopolymer originating from the bark of wild almond tree and it is useful in films fabrication especially wound dressings because of its safety and biodegradability [118]. The essential oil of Asafetida resin oleogum was incorporated in this gelatin film because of its antifungal and antibacterial activity against a wide spectrum of bacteria including methicillin-resistant bacteria [119].

6.3. Nanoparticles-in-nanofibers

Another recent approach in wound dressings is nanoparticles-in-nanofibers composites, in which the release of the encapsulated active compounds can be controlled to be

DOI: 10.62184/tpdd.jtpdd110020242

sequential according to the assigned application. In addition, the presence of nanoparticles within the nanofibers matrix was found to improve the mechanical properties of these composites [120]. In two recent studies, tadalafil (TDF)-loaded zein NPs were incorporated into electrospun nanofibers either made from pectin/polyvinyl alcohol blend [121] or Withania somnifera extract/polyvinyl alcohol blend [122]. In both nanofibers composites, NPs were able to afford sustained drug release for more than one week. In case of Withania somnifera extract-based nanofibers, there was a sequential release of the extract first from the nanofibers matrix during its decomposition, which might have a vital anti-inflammatory effect in the early phase of wound healing. Tadalafil was released later to serve as an angiogenic enhancer. This delay in the release was due to the double barrier effect afforded by the nanoparticles-in-nanofibers composites [122]. Different wound dressings based on natural materials with integrated approaches are listed in Table 2 and different types of nanocomposites including nanoparticles-in-nano/microgel, nanoparticles-in-membranes or films, and nanoparticles-in-nanofibers are illustrated in figure 5.

Table 2. Different wound dressings based on natural materials with integrated approaches.

Formulation	Composition	Incorporated active components	Fabrication technique	Key features	Reference
Hydrogel	Gelatin	Thyme essential oil-loaded caseinate micelles	Solvent evaporation/ thermal gelation	- Sustained thyme oil release with good *in vivo* wound healing, associated with reduced inflammation and increased angiogenesis.	[40]
Hydrogel	Gum arabic/pectin	Naringin	$CaCl_2$ crosslinking	- High drug loading with enhanced in vivo wound healing and potent antioxidant effect.	[104]
Three layered Graded hydrogel Scaffolds	κ-carrageenan	0.5 %w/v arginine in intermediate layer 5% w/v, whey protein in superficial layer	$CaCl_2$ crosslinking/ freeze-drying	- Good in vitro cellular proliferation, migration and adhesion. - Increased *in vivo* wound healing potential due to suitable pore size gradient resembling the native layers of skin.	[110]
Film	Frankincense (FRK) resin, guar gum	FRK essential oil-loaded whey protein NPs	Spray drying/Solvent casting	- Good hemocompatibility and improved *in vitro* antimicrobial activity. - Reduction in inflammation and improvement in proliferation in a rat full excised wound model.	[28]
Film	Gelatin, Shekar tighal manna polysaccharide, persian gum	Anghozeh essential oil	Solvent casting	- Successful incorporation of oil droplets within the film matrix with good tensile strength and cytocomptability. - An efficient microbial barrier for wound management.	[116]
Nanoparticles-in-nanofibers	pectin/ polyvinyl alcohol NFs	Tadalafil-loaded zein NPs	Anti-solvent/ electrospinning	- Sustained tadalafil release due to double barrier effect associated with improved *in vivo* wound healing in diabetic rat model.	[121]
Nanoparticles-in-nanofibers	*Withania somnifera* extract/ polyvinyl alcohol NFs	Tadalafil-loaded zein NPs	Anti-solvent/ electrospinning	- Enhanced *in vivo* anti-inflammatory effect due to sequential release of the extract first from the NFs matrix, followed by sustained tadalafil release. - Superior wound healing with increased angiogenesis.	[122]

DOI: 10.62184/tpdd.jtpdd110020242

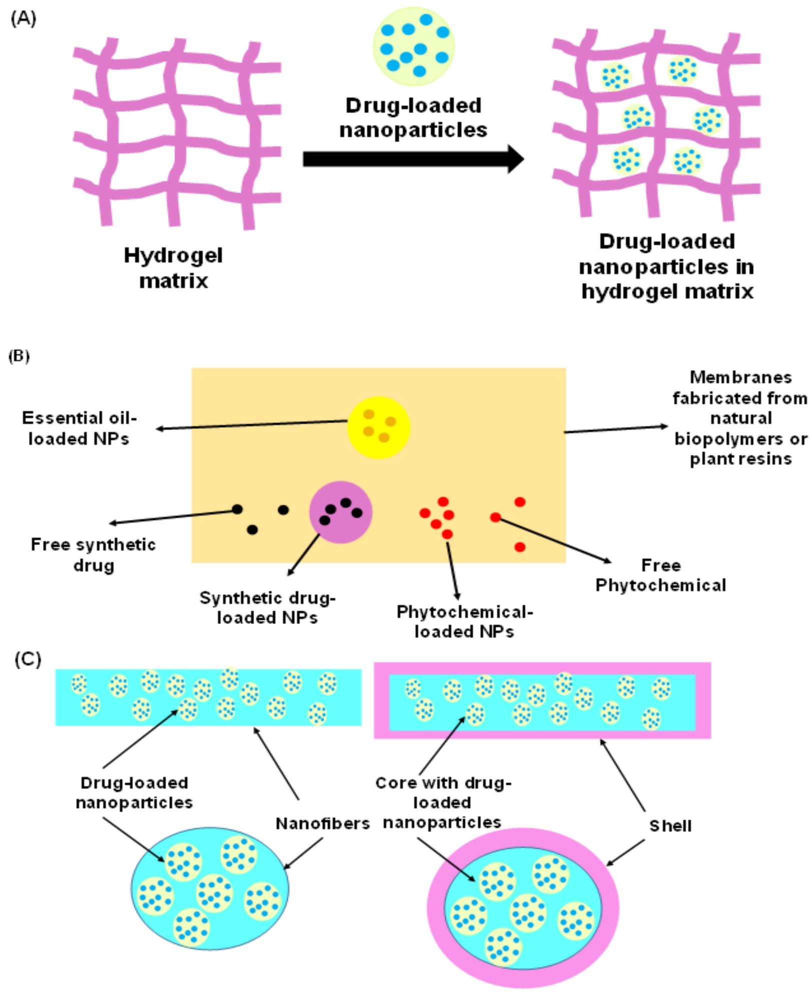

Figure 5. Different approaches in the fabrication of nanocomposites. (A) nanoparticles-in-hydrogels, (B) nanoparticles-in-membranes or films, (C) nanoparticles-in-nanofibers.

7. Conclusion and future perspectives

Wound healing is a normal physiological overlapping process that occurs simultaneously as a response to injury or cut in the skin. Traditional wound dressings are usually made from inert materials that just serve as a barrier to minimize bacterial infections without any activity towards the healing process. Nowadays, natural materials are attracting concern as wound healing materials owing to their low cost, safety and more importantly their unique multifunctionality and bioactive properties. These natural materials can have anti-inflammatory, antioxidant, antibacterial or collagen synthesis promoting activities. However, there are some limitations that might face researchers to use these compounds in wound healing. There was a massive progress in the development of natural materials-based formulations that can efficiently manage the healing of different wound types. Among these formulations are plant resin-based films, natural polymers-based hydrogels and nanoparticles-in nanofibers composites. In the future, the clinical potential of these polymer-based formulations should be clinically examined before their transfer to the clinic. However, there is an important challenge which is the scaling up of these formulations as large amounts are required to be produced in a reproducible manner and successfully complete all formulation stages and clinical evaluation before eventually reaching the market.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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DOI: 10.62184/tpdd.jtpdd110020242

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