Bioactive Topical Platforms for Pressure Ulcer Healing: Mechanisms and Translational Advances

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Abstract

Pressure ulcers, also referred to as decubitus ulcers, are localized injuries to the skin and underlying tissues, typically occurring over bony prominences due to prolonged pressure, friction, or shear forces. Despite being largely preventable, they remain a significant global health concern, affecting approximately 10–15% of hospitalized patients and contributing to prolonged morbidity, elevated mortality risk, and increased healthcare expenditures. Traditional management strategies including frequent repositioning, debridement, infection control, and standard dressings often fail to fully address the complex pathophysiology involving chronic inflammation, oxidative stress, microbial colonization, and impaired angiogenesis. Recent advances in topical therapies incorporating bioactive compounds have shown considerable promise in enhancing pressure ulcer healing. Natural compounds such as phenolics (curcumin, resveratrol), terpenoids (asiaticoside), polysaccharides (chitosan, hyaluronic acid), and growth factor–mimetic peptides demonstrate potent antioxidant, anti-inflammatory, and pro-regenerative effects. Innovative delivery platforms—including nanocarriers, lipid-based systems, hydrogels, and stimuli-responsive polymers—improve solubility, stability, and targeted delivery of these labile compounds to the wound microenvironment. By modulating critical molecular pathways (e.g., NF-κB, MAPK, TGF-β, VEGF), these approaches promote collagen deposition, angiogenesis, and bacterial biofilm disruption. This review provides a comprehensive analysis of the mechanistic basis, formulation strategies, preclinical and clinical outcomes, and translational challenges associated with bioactive compound–loaded topical systems. Special emphasis is placed on smart delivery platforms and personalized wound care strategies, which collectively offer potential to improve healing outcomes and establish next-generation standards in chronic pressure ulcer management.

Keywords: Angiogenesis; Bioactive Compounds; Chronic Wound Healing; Hydrogels; Oxidative Stress; Pressure Ulcer; Wound Dressings

Introduction

Pressure ulcers, also referred to as pressure injuries, remain a major healthcare challenge associated with prolonged immobility, neurological impairment, ageing, critical illness, and chronic systemic disorders [1]. These lesions arise secondary to sustained pressure, shear stress, and microvascular compromise over bony prominences, resulting in localized ischemia, tissue necrosis, and progressive destruction of the skin and underlying soft tissues. Despite substantial advances in preventive care, pressure ulcers continue to contribute significantly to morbidity, prolonged hospitalization, impaired quality of life, and healthcare expenditure worldwide. Their burden is particularly pronounced among elderly individuals, patients with spinal cord injury, critically ill patients, and those requiring long-term institutional care.

Globally, pressure ulcers affect millions of individuals annually, with prevalence varying according to clinical setting, patient population, and healthcare infrastructure. Hospital-based studies report substantially higher prevalence in intensive care units, rehabilitation centers, and neurotrauma facilities where prolonged immobilization and impaired sensory perception predispose patients to chronic wound formation [2-3]. In India and other low- and middle-income countries, the burden remains under-recognized due to inadequate surveillance systems, delayed diagnosis, nutritional deficiencies, limited access to advanced wound care, and inconsistencies in preventive protocols. Importantly, recurrent ulceration, secondary infection, osteomyelitis, and sepsis continue to represent major clinical concerns in advanced-stage disease.

Pressure ulcers are commonly classified into stages according to the depth and extent of tissue involvement, ranging from non-blanchable erythema to extensive full-thickness tissue destruction involving fascia, muscle, or bone. The severity and staging of pressure ulcers are illustrated in Figure 1. Pathophysiologically, pressure ulcer formation is a multifactorial process involving ischemia–reperfusion injury, oxidative stress, mitochondrial dysfunction, persistent inflammation, extracellular matrix degradation, microbial colonization, and impaired angiogenesis. Sustained tissue compression exceeding capillary perfusion pressure disrupts local blood flow and lymphatic drainage, thereby initiating cellular hypoxia and metabolic failure. Subsequent reperfusion further amplifies tissue damage through excessive generation of reactive oxygen species (ROS), inflammatory cytokine release, endothelial dysfunction, and activation of proteolytic pathways. These molecular disturbances collectively impair fibroblast activity, collagen synthesis, keratinocyte migration, and tissue remodeling, ultimately promoting chronic non-healing wounds [4].

Current management strategies primarily focus on pressure redistribution, infection control, debridement of necrotic tissue, exudate management, nutritional optimization, and maintenance of a moist wound environment through conventional dressings. Although these interventions remain clinically essential, therapeutic outcomes are frequently suboptimal in chronic or advanced ulcers because conventional approaches inadequately address the complex biochemical and cellular abnormalities within the wound microenvironment. Furthermore, prolonged treatment duration, recurrent infection, bacterial biofilm formation, antimicrobial resistance, and poor vascularization substantially limit healing efficacy. These limitations have accelerated interest in the development of advanced topical therapeutic systems capable of simultaneously modulating inflammation, oxidative stress, microbial burden, and tissue regeneration [5].

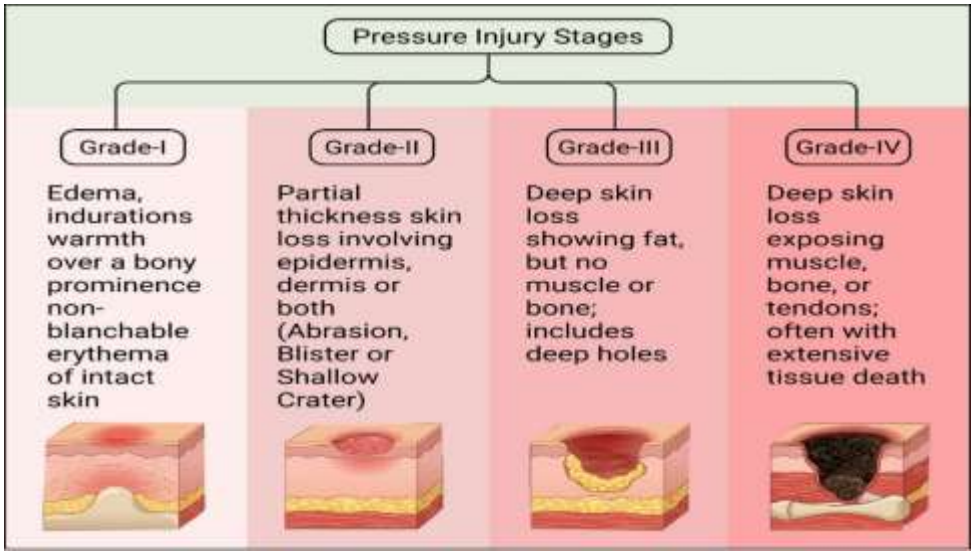
In this context, bioactive compounds derived from natural and biological sources have emerged as promising therapeutic candidates for pressure ulcer management. These compounds include phenolics, flavonoids, terpenoids, alkaloids, polysaccharides, peptides, and growth factor–mimetic biomolecules obtained from plants, marine organisms, microorganisms, and animal-derived matrices. Owing to their antioxidant, anti-inflammatory, antimicrobial, angiogenic, and extracellular matrix-modulating properties, bioactive compounds possess significant potential to target multiple pathological mechanisms associated with chronic wound progression. However, their clinical translation is frequently hindered by poor aqueous solubility, instability, limited tissue penetration, rapid degradation, and insufficient retention at the wound site [6-7, 22].

To overcome these limitations, substantial attention has been directed toward innovative topical formulation strategies incorporating nanotechnology-based carriers, lipidic systems, hydrogels, smart polymers, electrospun matrices, and stimuli-responsive delivery platforms. These advanced systems may enhance bioactive stability, improve penetration into ulcer tissues, prolong local retention, enable controlled release, and optimize therapeutic bioavailability within the hostile wound microenvironment. Consequently, the integration of bioactive compounds with advanced topical delivery technologies represents a rapidly evolving and translationally relevant area in modern wound therapeutics [8].

The present review critically evaluates the mechanistic basis, formulation strategies, therapeutic efficacy, and translational potential of bioactive compound-incorporated topical formulations for pressure ulcer management. Particular emphasis is

placed on molecular pathways involved in wound repair, advanced drug-delivery approaches, preclinical and clinical evidence, and emerging translational challenges that may influence future clinical adoption and personalized wound-care strategies.

Fig: 1 Severity of pressure ulcer



Introduction to Bioactive Compounds: Natural Sources and Therapeutic Potential in Wound Repair

Natural bioactive compounds have been utilized for wound management for centuries within traditional systems of medicine, particularly in Chinese, Indian, Egyptian, and Greco-Arabic therapeutic practices. In recent decades, growing scientific interest has focused on these compounds because of their ability to modulate multiple phases of wound healing simultaneously, including inflammation, oxidative stress, microbial colonization, angiogenesis, extracellular matrix remodeling, and tissue regeneration. Unlike single-target synthetic agents, naturally derived bioactive molecules often exhibit pleiotropic pharmacological activities, making them attractive candidates for the management of chronic and complex wounds such as pressure ulcers [9-10].

Bioactive compounds are biologically active molecules obtained from plants, microorganisms, marine organisms, and animal-derived sources that exert therapeutic effects through biochemical or cellular modulation. These compounds encompass diverse chemical classes including polyphenols, flavonoids, terpenoids, alkaloids, polysaccharides, peptides, and glycosides. Their therapeutic significance in wound repair is primarily attributed to antioxidant, anti-inflammatory, antimicrobial, angiogenic, collagen-stimulating, and immunomodulatory properties. Figure 2 illustrates major classes of bioactive compounds and their mechanistic relevance in pressure ulcer healing [11-12].

Among anti-inflammatory bioactive molecules, myricetin has gained attention due to its ability to suppress inflammatory mediator release and regulate immune responses during tissue repair. This naturally occurring flavonoid, commonly found in fruits and medicinal plants, exhibits anti-inflammatory, anti-allergic, and immunomodulatory activities that may contribute to attenuation of chronic inflammatory responses within the wound microenvironment. Similarly, steroidal glycosides possess significant anti-inflammatory potential through modulation of cytokine-associated signaling pathways, including regulation of interleukins such as IL-2, IL-4, and IL-10, thereby facilitating resolution of persistent inflammation and progression toward tissue remodeling [13-14].

Oxidative stress plays a central role in chronic wound progression by promoting cellular injury, mitochondrial dysfunction, and impaired angiogenesis. Consequently, antioxidant-rich bioactive compounds have emerged as promising therapeutic

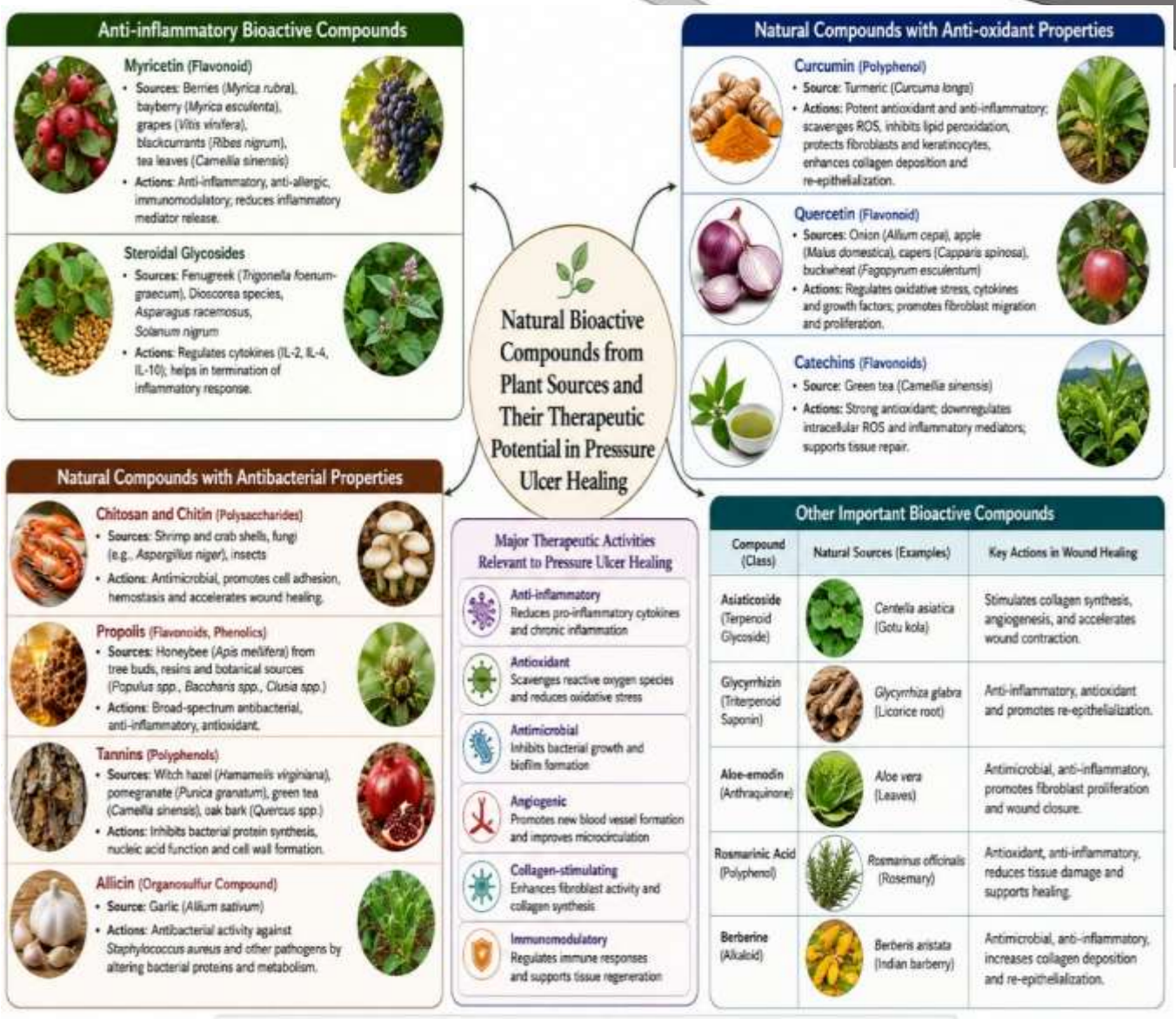
candidates for pressure ulcer management. Curcumin, a polyphenolic compound isolated from *Curcuma longa*, demonstrates potent antioxidant and anti-inflammatory effects by scavenging reactive oxygen species, inhibiting lipid peroxidation, and protecting dermal fibroblasts and keratinocytes from oxidative injury. In addition, curcumin has been reported to enhance collagen deposition and accelerate re-epithelialization during wound healing. Quercetin, another naturally occurring flavonoid, exerts wound-healing activity through regulation of oxidative stress pathways, cytokine signaling, fibroblast migration, and cellular proliferation. Catechins, particularly those derived from green tea, also exhibit substantial antioxidant properties through intracellular ROS suppression and modulation of inflammatory cascades, thereby promoting tissue repair and reducing oxidative tissue damage [15].

Microbial colonization and biofilm formation represent major barriers to successful pressure ulcer healing. Several naturally derived bioactive compounds possess intrinsic antimicrobial properties capable of limiting bacterial proliferation and preventing secondary infection. Chitosan and chitin, naturally occurring polysaccharides primarily derived from crustacean exoskeletons, fungi, and marine organisms, have demonstrated significant wound-healing and antimicrobial activities. Their biocompatibility, biodegradability, and ability to promote cellular adhesion and hemostasis further support their utility in wound-care applications. Propolis, a resinous substance produced by honeybees from botanical sources, contains flavonoids, phenolic acids, amino acids, and aromatic compounds that collectively contribute to broad-spectrum antimicrobial and anti-inflammatory effects. Tannins have also shown antibacterial activity through inhibition of bacterial protein synthesis, disruption of nucleic acid function, and alteration of microbial cell-wall integrity. Similarly, allicin, the principal sulfur-containing compound derived from garlic (*Allium sativum*), demonstrates potent antibacterial activity against common wound pathogens, including *Staphylococcus aureus*, through modification of essential bacterial proteins and metabolic pathways [16-17].

Collectively, these bioactive compounds possess substantial therapeutic potential in pressure ulcer management because of their capacity to target multiple pathological mechanisms involved in chronic wound progression [19-20]. Their multimodal pharmacological activities may facilitate reduction of oxidative injury, modulation of excessive inflammation, suppression of microbial burden, stimulation of angiogenesis, enhancement of collagen synthesis, and acceleration of tissue regeneration. Consequently, incorporation of these compounds into advanced topical delivery systems has emerged as a promising strategy for improving therapeutic efficacy and overcoming the limitations associated with conventional wound-care approaches [20-22].

Figure 2 summarizes the major classes of bioactive compounds and their multifunctional roles in modulating inflammation, oxidative stress, microbial burden, and tissue regeneration during pressure ulcer healing.

Fig:2 Various bioactive compound in pressure ulcer



Phenolic compound

Phenolic compound has showed wound healing activity both in vivo and in vitro by various mechanism. The mechanism includes lowering of oxidative stress, increasing antioxidant activity, inflammatory response adjustment, reducing time of healing and increasing healing rate and mange regeneration of tissues. There are many compounds from endophytic microbes that have biological activity which show effect in wound healing.Neurospora crassa stain from lyceum shawii leaves from Egypt produced benzoic acid which demonstrated strong antimicrobial activity against bacteria of gram positive and gram negative including staphylococcus aureus and Pseudomonas aeroginosa. Benzoic acid show contraction of wound and epithelialisation [22].

Terpenoids

Terpenoids are also called as isoprenoids are structurally diverse product of plant. There are various type of terpenoid like hemiterpenoids, monoterpenoids, iridous, diterpenoids, triterpenoids, tetraterpenoids, sesquiterpenoids and irregular terpenoids. These metabolites may present in plant like family like apocynaceae, Gentianaceae, and many others. In the

management of wound terpenoid have wound dressing capacity in combination with halloysite nanocomposite because of their antimicrobial potential. Iridoid compound have biological activities like anticancer, antiprotozoal, anti-inflammatory with antimicrobial activity in a compound found in scrophulariaceous genus. Another study also suggest extract of iridoid glycoside of laemophloeids rotate may help in wound healing process by performing M2 macrophages polarization [23-24].

Antioxidant Activity

Multiple healing processes occur after injury which utilizes oxygen to synthesize ATP. The main energy source reactive oxygen species concentration consequently. Increased concentration of reactive oxygen species is linked with chronic inflammation which disturb healing process. Balanced level of reactive oxygen species requires in body to keep body functioning normally which help in wound healing. Reactive oxygen species is involved in body haemostasis, re-epithelialization and angiogenesis. Excessive presence of reactive oxygen species can impair healing hence body has an antioxidant system to predict abnormal level of antioxidant that can determine abnormal level of oxidant and react accordingly to maintain balance of ecosystem. Antioxidant is category which act to control the biomolecules oxidation. Which occur due to reaction with reactive oxygen species and behave as chelating agent at site of many injury free radical are generated as byproduct of healing process and antioxidant will alleviate the damage occur due to free radical. Phenolic compound like flavanoid, phenolicacid, tannins, lignanes, stibleneswill be responsible for antioxidant activity which act at different phases of healing to prevent damage. Flavonoids are also contributing for durability of collagen fibres to heal wound contraction. Tannins is the secondary metabolite has wound healing capability by scavenging of reactive oxygen species and free radical. Vitamin E a plant-based antioxidant protects cell membrane from lipid peroxidation by neutralizing peroxyl radical, superoxide and oxygen. Vitamin C also boost antioxidant effect by neutralization of tocopherol radical. Plant derived genistein also has antioxidant activity [25-34].

Anti-Inflammatory Effects

Plant metabolite is known to have anti-inflammatory effect to support wound healing. To protect injured cell against physical injury, microbial attack, defective immunity. While prolonged inflammation can be responsible for non-healing wound. Inflammation can be acute or chronic both play important role in maintaining healing. Anti-inflammatory effect of plant metabolite is useful in inflammatory response for treatment of chronic wound and accelerates healing. Flavonoid, tannins, alkaloid and terpenoids are some important metabolites for wound inflammation control. Flavonoids are plant phenol have in vivo and in vitro inflammatory activity. They show inflammatory activity by acting on molecules like NF-KB, INOS cytokines, cyclooxygenase and metalloproteinases. Wounds are sensitive to contamination and affect surrounding micro-environment which cause down regulation of pro-inflammatory cytokines. Imbalance of ph, release of toxin and high reactive species molecule. This will affect re-epithelization, growth factor regulation and other component of extracellular matrix of pro-healing. Flavonoids triterpenoids tannins have been contributed to improve wound microenvironment by multi action like anti-inflammatory and antimicrobial. However anti-microbial contamination of wound is protected by anti-microbial capacity. These phytochemicals maintain expression of IL-10 and reduce expression of IL-10 and spike of TNF and IL-6 and IL-10. IL-10 reduce expression of profibrotic mediator of pro-inflammation. Which cause decrease infiltration of inflammatory cell at wound site. The TNF reduce production of collagen and hydroxyproline important for wound healing regeneration. Anti-inflammatory phytochemicalpresent chemical structure of natural compound like pathenolide, sesquiterpenes, lactone, which inhibit NF-KB and reduceIL-6 and TNF-a. turmeric active constituent curcumin interact with MAPK and NF-KB to enhance TNF-a, IL-1 and IL-6 release. Quercetin a flavonoid found in fruit vegetable increase IL-10 production and decrease oxidative stress. Derivatives of

caffeic acid and Echinacea polysaccharides maintain activity of immune cell and decrease pro-inflammatory mediator synthesis[35-38].

Antimicrobial Properties

Different phytoconstituent have been studied for their role in various phases of wound healing. This bioactive compound is used as single isolated compound or mixture of plant extract to treat wound. In the management of wound one of the important challenges is contamination by microbial burden. Use of bioactive compound as antimicrobial in treatment of wound has put light on curbing this issue as use of antibiotic can cause antibiotic resistant infection. Infection of wound with antibiotic pathogen resistant can cause high mortality and morbidity. While it is not possiblycreating a wound environment which is sterile without bacteria. It is important to create an environment where bioburden is manageable and favorable for healing. The plant bioactive compound antibacterial application in wound healing has been documented. The lipophilic alkaloid and essential oil have antiseptic properties. Entrapment of bioactive compound in wound dressing has proven to increase wound healing. Enhanced bactericidal activity is observed by infusion of flavonoids and polyphenols in hydrogel. In vivo study shows that quercetin has antimicrobial property which protect injury from bacterial infection and favorable ECM required for proliferation of cell and differentiation in wound closure.

Natural compound shows their antimicrobial effect by interacting with surface of cell to penetrate phospholipid bilayer of cell membrane of bacteria. This action affects permeability of membrane and destroys normal cell physiology which can cause death of cell. The mechanism of bactericidal action of plant metabolite is not specific and variable, thus advantageous to protect bacterial resistance. Bactericidal mechanism of flavonoids is interference in nucleic acid synthesis, energy metabolism, cell membrane porin penetration, attachment of cell and biofilm development and disturb permeability of membrane, and enhancement of bacterial virulence. Antimicrobial activities of Tannins is because of their astringent effect and molecular structure. Tannins disturb the expression of gene of bacteria and disturb fatty acid biosynthesis and act as chelating agent for iron and disrupt membrane by inhibiting synthesis of bacterial wall. Alkaloid mechanism of action is different against different microorganism which include inhibition of nucleic acid synthesis, inhibition of respiratory enzyme, inhibiting gene encoding. A combination of plant extract has pharmacological benefit because of synergistic pharmacological effect [39- 51].

Pro-Angiogenesis

In the proliferation stage of wound repair, angiogenesis is the process which involves formation of blood vessel. In healthy tissue homeostasis is maintain by microvascular system which balanced the oxygen and nutrient supply by the waste and carbon dioxide removal. In injury state dys-functioning of microstructure lead to accumulation of cellular fluid, inflammation and hypoxia. Hypoxia activates endothelial cell and inflammatory cytokines which initiate angiogenesis and stimulate immune cells. Due to the presence of anti-angiogenic factor in non-healing chronic wound angiogenesis is reduced. Many bioactive compound-like polyphenols, flavonoids terpenoids and polysaccharides can inhibit pro inflammatory mediator like TNF alpha, IL-1 and IL-6 which are important in chronic inflammatory disease. Natural product reduces the activation of transcription factor like NF-KB and AP-1 by interfering with regulator like MAPKs, P13K/AKT and ROS generation. This downregulation not only reducing excessive immune activation but protecting tissues from damage because of unresolved inflammation by limiting the transcription and secretion of pro-inflammatory cytokines[52-61].

Collagen Synthesis

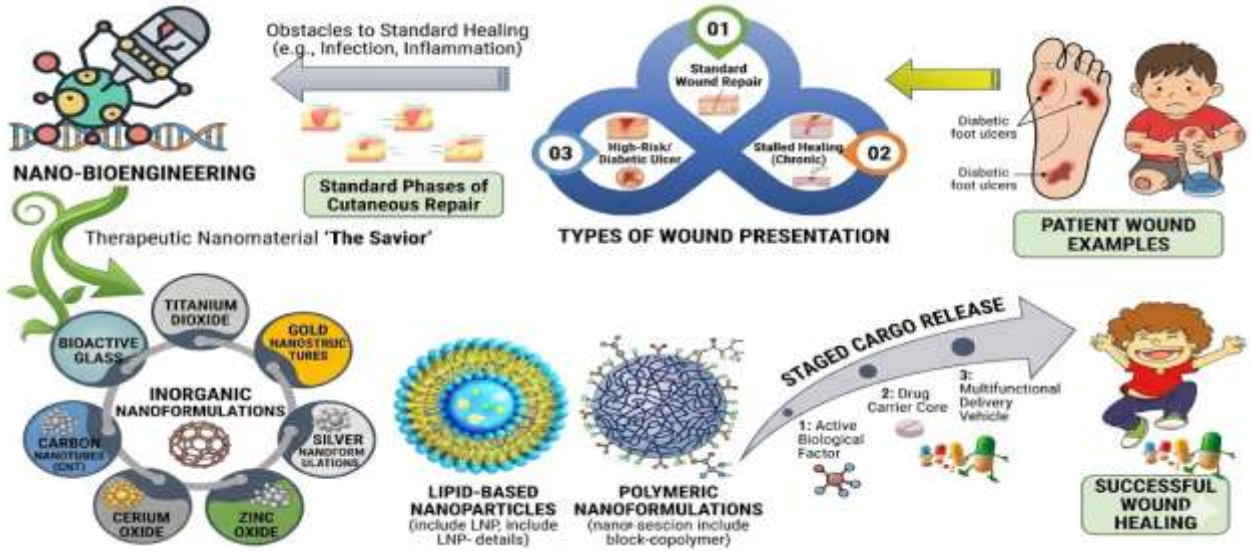
Plant bioactive compounds have long been known to promote collagen synthesis during the tissue repair process. These compounds have been demonstrated to enhance collagen biosynthesis and tissue regeneration, indicating their pro-healing potential. Polysaccharide-rich Aloe vera leaf gel extract encapsulated in liposomes has been shown to increase the synthesis of collagen by 23%. Meanwhile, treatment of A. vera in rats promotes collagen turnover via upregulation of urinary hydroxproline levels and lysyl oxidase activity. Asiatic acid, a triterpenoid derived from Centella asiatica, enhances collagen production in fibroblasts, promotes the accumulation of extracellular matrix, and improves tensile strength of newly formed tissues during the proliferative and remodeling phases.

Flavonoids enhance collagen biosynthesis during tissue repair via multiple mechanisms. Primarily, flavonoids modulate Wnt/β-catenin, TGF-β, and MAPK/ERK pathways, which results in cellular proliferation and differentiation, thus improving the synthesis of collagen [**72**]. Antioxidant properties of the flavonoid protect newly formed collagen fibers from degradation effects from residual ROS, thus maintaining extracellular matrix integrity, while its anti-inflammatory activity impedes inflammatory cytokines against collagen production. Quercetin is a flavonoid known to upregulate the expression of collagen type III via modulation of SIRT3/TGF-β/Smad3 axis signaling pathways [62-66].

Nanotechnology

Nanotechnology is important in by pass the limitation of conventional wound care with the use of nanomaterial of size range 1 to 100 nanometre, which can interact at molecular level with biological system. Which provide high surface area, increased bioavailability and targeting of specific tissues, which make it ideal for wound healing. Nanotechnology is important in antimicrobial wound care. Nanoparticle like silver, zinc, oxide, gold have broad spectrum antimicrobial activity because of their ability to disrupt bacterial membrane and interact with microbial DNA [67-68].

Fig 3: Nanotechnology in pressure ulcer management



Lipid nanoparticle

Lipid nanoparticle has gain importance in drug delivery due to unique properties like biocompatibility, capability to incorporate both hydrophilic and hydrophobic drug. Lipid nanoparticle isdivided into two main class solid lipid nanoparticle and nanostructured carrier contain core of solid lipid at room temperature stabilized by surfactant. [21] role of lipid nanoparticle in wound healing is due to their capability to increase drug penetration by skin. The lipidic part of nanoparticle mix with lipid bilayer of skin. The layer is stratum corneum allow deeper delivery of drug to wound. This is required for chronic wound where long term growth factor treatment anti-inflammatory and antimicrobial compound is required. Lipid nanoparticles provide protection of drug encapsulated from enzymatic degradation and external environmental factor like heat and light[69-70].

Solid lipid nanoparticle

Consist of solid lipid at room temperature which gives higher physical stability and offer controlled and sustained release of drug. Solid lipid nanoparticle has advantage to protect drug from degradation as they are stabilized by surfactant. Solid lipid nanoparticle is use in topical use in topical use like wound healing as they can increase drug penetration and prolong drug release. Solid lipid nanoparticle allows effective drug delivery by skin and reduced systemic side effect[70].

Nanostructured lipid carrier

They are type of nanoparticle that is advanced which combined solid and liquid. This mixture createsa lipid mixture which is imperfect which provide high loading of drug and improved stability. Nano structured lipid carrier allows improve release of therapeutic agent and provide better sustained and controlled drug delivery. Nanostructured carrier is useful in topical application for wound healing because of their ability to increase drug delivery and improved outcomes[69].

Liposome

Liposome is made up of cholesterol and phospholipid, phospholipid like phosphatidylcholine or phosphatidyl serine which incorporate hydrophobic and hydrophilic drug. Cholesterol increases membrane fluidity and stability. Desired characteristic for specific application can be achieved by proper selection of phospholipid and cholesterol. Liposomal structure contains one and more bilayer of lipid surrounding an aqueous core. The bilayer of phospholipid arranged in double layer configuration with hydrophobic tails and hydrophilic heading facing inward and outward. This liposomal arrangement facilitates encapsulation of both hydrophilic and hydrophobic substances. Liposome is versatile carrier for no of therapeutic agent. Size of liposome varies from 20 nanometre to micrometre.

Hydrogel

Hydrogel are biomaterial used in biomedicine because of high water content, soft nature and breathability. Hydrogel are effective for utilization such as pressure ulcer, delivery of drug, healing of wound because of unique properties of hydrogel. The most important property of hydrogel is high water content due to their three-dimensional structure. This three-dimensional structure allows absorption of large water suitable for growth of cells and regeneration of tissue in wound healing. Hydrophilic nature of hydrogel enhances process of repair by maintaining condition for proliferation and migration of cells. Hydrogel has softness and elasticity which is beneficial allowing them to conform wound bed. The texture of hydrogel minimizes irritation and friction of healthy surrounding tissue, pain reaction and improve comfort of patient. Excellent breathability of hydrogel allow air, water, vapour to pass through which manage moisture level and avoid complication caused by excess fluid and change in temperature. Hydrogel is safe for many clinical applications like wound healing, burn and skincare. Use of hydrogel in pressure ulcer dressing has various benefit like hydration of wound, pressure relief and high

healing. The moist nature of hydrogel not only reduce time of healing but provide optimal condition of repair of wound. Hydrogel biocompatibility guarantee adherence to surface of wound creating ideal environment for healing [71].

The Marvelous healing power of curcumin is long known and its role in the improvement of several types of topical skin wounds is due to its antioxidant activity, improvement of the production of granulation tissue and new vascularization and increasing the process of reepithelialization of wound damage, but unfortunately all of those useful applications are limited by its bad solubility and stability. Tailoring suitable drug delivery systems for carrying curcumin improves its pharmaceutical and pharmacological effects. In brief, curcumin is a natural molecule separated from the rhizomes of Curcuma longa and is used topically for many wound healing applications. Table demonstrate Different examples of curcumin-loaded dosage forms for wound healing purposes [72-80].

Table. 1. Different examples of curcumin-loaded dosage forms for wound healing purposes.

Formulation type	Used polymer	Findings
Hydrogel	Chitosan and sodium alginate	Hydrogel membrane based on chitosan and sodium alginate with curcumin prepared by physical cross linking by microwave is useful in wound healing[81]
Thermo sensitive hydrogel	Poloxamer	Hydrogel prepared by cold swelling method have capacity to enhance human fibroblast proliferation. Hydrogels enhance wound healing in rat by regeneration of epithelium and rearrangement of connective tissues[82].
Films	Bacterial cellulose, gelatin	Thin film with bioadhesive properties and high fluid uptake upto 70% with good antibacterial activity. Films are nontoxic to human[83]
Scaffolds	Collagen, sodium alginate	Curcumin loaded sodium alginate and collagen scaffolds hydrogel system for wound healing is used because of their hydrophobic nature. Wound healing is achieved due to unique properties like permeability, bioavailability, and solubility as well reduced destruction by immune system[84].
Sponge	Cellulose, chitosan, cyclodextrin	Complexation of curcumin with cyclodextrin improve aqeous solubility. Sponge prepared by cellulose has porous structure and improved mechanical properties. Due to complexation with chitosan antimicrobial properties get enhanced and improved. Sponges are compatible with NCTCL929 and NHDF cells. This formulation can be used in chronic wound[85].
Liposome	Liposome augmented with pluronic F127	Curcumin loaded liposome with additional pluronic 127 studied in human keratinocytes shows safety. This liposome improves migration of cells and expression factor, erythroid related factor2. This liposomal formulation has better healing properties as compared to pure curcumin powder and non-medicated liposomes[86].
Nanoemulgel	Tween 80, PEG400, Labrafac PG	Nanoemulgel prepared by method of ultrasonic emulsification by incorporation of nanoemulsion into carbopol. Nano emulsion particle size is 50nm using least concentration of surfactant. This nano emulsion has promising wound healing capacity due to excellent penetrability to skin[87].

Carbon dots	Protease responsive hydrogel, carbon dots	Curcumin carbon dot improves solubility and stability of free curcumin. Carbon dots are good for wound healing properties because of high proliferative and antibacterial activity. Use of crosslink protease provides sustain release. Carbob dot with protease responsiveness shows high and fast wound contraction due to high rate of angiogenesis and formation of full epithelium[88].

Mechanistic Insights into Bioactive-Enhanced Healing

Wound healing is a biological process which involves constriction of blood vessel and formation of clot, inflammation, cell growth and wound remodeling. Wound healing process required oxygen in every phase because energy required in various phases of wound repair like biosynthesis, intracellular transport, synthesis of ATP, the main source of energy is presence of oxygen. In wound healing process there is increase cell growth and extracellular matrix generation causes increases energy need. Oxygen is important in healing process as it's required for enzymatic reaction and supply energy. Various sources of reactive oxygen species are mitochondria, endoplasmic reticulum, peroxisomes, various oxidase, metabolism of phospholipid. In addition, reactive oxygen species can be generated by specific enzyme action on NADPH. Nitrous oxide enzyme is present in cell membrane and help electron to pass through biofilms, which reduce superoxide production and oxygen reduction. Various reactive oxygen species like hydrogen peroxide, peroxide radical and hydroxy radical react with superoxide. Cellular function like differentiation, proliferation, apoptosis are affected by reactive oxygen species. Group of reactive oxygen species include hydroxyl radical, peroxide radical, hydrogen peroxide, superoxide anion. In non-healing phase of wound high reactive oxygen species produced and these reactive oxygen species oxidize other component of cells and molecules which cause cellular damage. Higher concentration of reactive oxygen species has negative effect on wound healing. In inflammatory phase neutrophils and macrophages produced superoxide and H2O2 which play important role in killing of bacteria and prevent wound infection. ROS also support cell migration by stimulating tumor necrosis factor and platelet derived growth factor. Tissue growth factor pathway also mediated by ROS which improve fibroblast growth factor expression and facilitate proliferation and migration of fibroblast. Hence for fighting with micro-organism and survival of cell optimal level of reactive oxygen species is required.

A high concentration of ROS at the wound cause formation of inflammation, stimulate functioning of transcription factor like AP-1 activator protein, nuclear factor kappa(NF-KB) and nuclear factor erythroid 2-like2 (NrF2). NrF2 is important in preventing against high level of oxidative stress and heal wound. ROS inhibit recovery of wound and increases damage of tissue by block the effect of cytokines like vascular endothelial growth factor [89-97].

In chronic inflammatory disease and cellular injury. The inflammatory cytokines like IL-6, IL-8, TNF-a and IL-1B play important role in stimulating the destructive events by activation of transcription factor NF-KB which activate various proinflammatory genes. The pro-inflammatory pathway is regulated by mitogen activated protein kinase. In the chronic inflammatory disease and homeostasis of skin three MAPK protein C-jan N-terminal play key role[98-100].

Important factor of angiogenesis includes vascular endothelial growth factor and it's receptor, angiogenesis a process critical for pathology and physiology. Angiogenesis is base of VEGF-VEGFR based proliferation of endothelial cell, survival and migration, which allow new blood vessel development in organized way. For wound healing vascular development is important. If VEGF signaling is not regulated can cause various diseases. Effect of VEGF is unique in multiple phases of wound healing specially angiogenesis. Role of VEGF in wound healing is by angiogenesis stimulation, involve various steps like vasodilation, degradation of vascular membrane and proliferation of endothelial cells. An important part of wound healing is

granular tissue formation i.e. fibrovascular tissue made up of fibroblast, blood vessel and collagen, which is main step in healing.VEGF involves multiple mechanism in wound healing include collagen deposition, epithelization and angiogenesis[101-105].

In pressure ulcer healing hemostasis, inflammation, proliferation are four important phases. All of the phases can be altered and can slow down the healing process and increase patient complications. Mesenchymal stem cells obtained from bone marrow have ploripotency. These stem cell with extracellular vesicles and exosomes have important role in repairing of wound because of their therapeutic property. Mesenchumal stem cells can affect inflammatory and immune reaction. Mesenchymal stem cell can stimulate tissue regeneration and increases re-epitheliliazation and enhances neovascularisation [106].

Biofilm infection management in wound healing may be divided into three classes on the basis of lifecycle of biofilm includes inhibitor of adhesion: material of biofilm, disruption of promoters. Various physical, chemical and biological method are adopted to achieve this at infection site microbes can exist into two state planktonic or biofilm. Planktonic can attach to a surface and form biofilm aggregates of polymicrobial nature. Various strategies for biofilm are as follow.

Fig 4.: stages of bioactive enhance healing

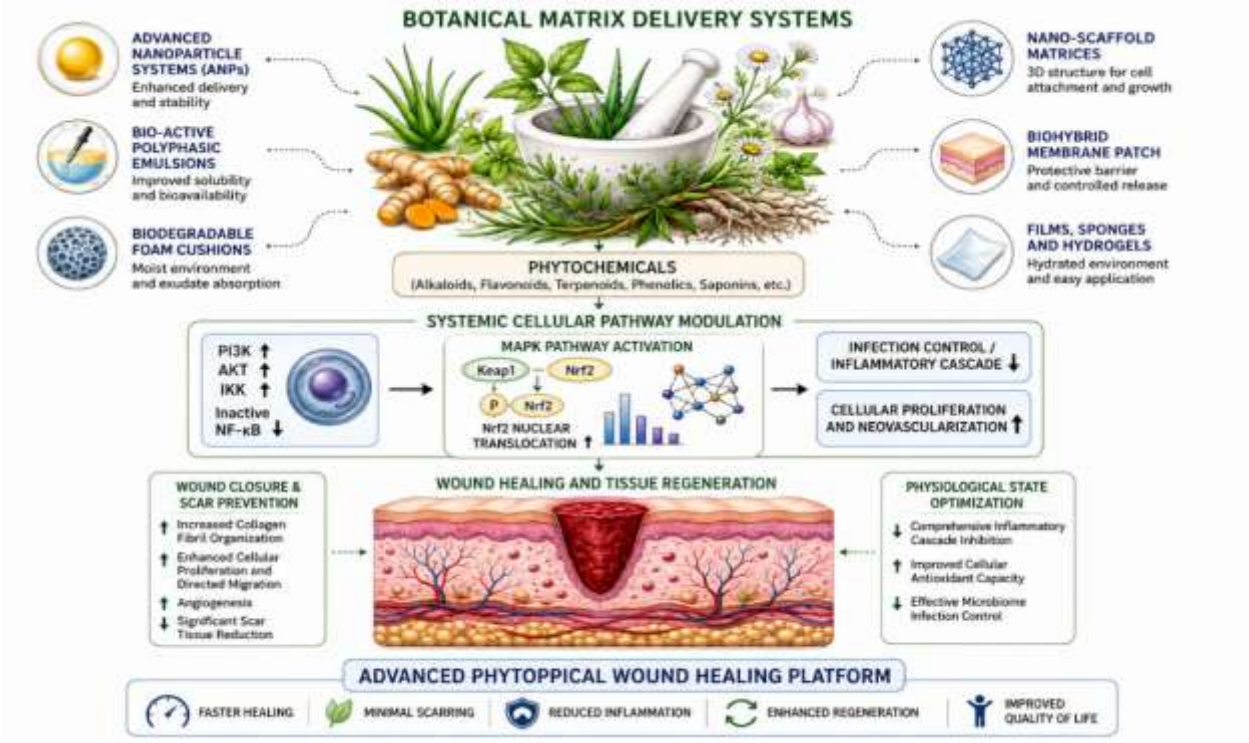


Table: Mechanism of bioactive enhanced healing

Strategies	pro	Cons
Debridement	Most surgeon used this standard technique Can be used with othe therapies also	Debridement can push fragment of biofilm into deeper wound tissue and enhance wound infection [107].
Silver based treatment	It is more effective in preventing starting of stem of formation of biofilm can be used in	Effect is less for biofilms [108]

	with other therapies that release planktonic or disruption.	
Iodine	Iodine has a inhibitory effect with broad spectrum Despite the use of iodine over a period of decade iodine has less resistance as compared to antibiotics.	[109]
Physical method	Involve use of surface abiotic like catheters Available in wide variety	Inhibition is narrow spectrum[109] Negative effect against host may occur.
Electroneuticals	Can treat a broad variety of pathogen either alone or in combination with antibiotics and others.	It has limited clinical approach[110]
Probiotics	With low resistance and broad spectrum Low toxicity and inexpensive.	Not sufficient clinical evaluation data available[111]
Antimicrobial peptides	Can inhibit a large range of gram positive and negative bacteria Additional bioactive properties can achieve by modifications.	Poor bioavailability Sensitive to protease[111]

Cytokinase are main signalling molecule involved in inflammatory response and regulation of immune system. Cytokines are divided into interleukin, chemokines, tumor necrosis factor, growth factor, interferon, and colony stimulating factor. One of most important pro-inflammatory cytokines is TNa have various effect on different cells. TNFa is activated by two pathway canonical and noncononical. TNF is made up of two unit which is inactive and located in cytoplasm on stimuli from external environment it get activated. Then get bind with various genes at the promoter region and initiate transcription of inflammatory response.

Jak/Stat pathwaya signalling pathway use by cytokines, growth factor, and interferon. The binding of mediator at receptor cause phosphorylation of Jak and STAT protein, initiate expression of gene which are cytokine responsive. This pathway play key role in inflammatory process suppression and initiation of immunity. Flavonoid, curcumin and quercetin act at different stages of this pathway[112].

MAPK pathway mitogen activated protein kinase are serine/theronine protein kinase, that has various kinase like ERK (Extra cellular signal regulated) and JNK(Jan-N-Terminal kinasr). The binding of proinflammatory stimuli to tyrosine cause activation of pathway. It cause transcription of factor CREB (CAMP response element binding protein), some flavonoid phenolics and terpenoid, alkaloid can regulate this pathway MAPK pathway regulate proliferation, apoptosis, inflammation and differentiation [113].

Preclinical and Clinical Efficacy Evidence

Cell motility is important in so many diseases of human and normal cellular process for wound healing cell migration is important as inflammatory cell and fibroblast initiate the re-epitheliasation. However, in regulated migration of cells can cause cell invansion and metastasis. Agent which affects motility can promote wound healing because their positive and negative effect. For discovering agent which can affect cell motility, cell-based technology especially high content. screening is important and promosing. The most popularly used assay is transmigration assay by the use of boyden chamber, scratch wounding assay and assay that allow accurate timing of cell migration, through porous membrane transwell assay. In drug discovery most

widely used assay is cell motility assay, but they are limited due to complex set up some promising alternatives are also available[114].

Animal models of pressure ulcers: wound contraction rates, histological and immunohistochemical analyses

Animal model- to study the complex cellular and biochemical process of wound healing. Animal model are developed which evaluate the safety and efficacy of therapeutic agent. Animal model should be able to achieve reproducibility, quantitative, detection, relevance and use various model are as follow.

Model for acute healing model for acute healing includes excisional, incisional and burn model. These models are useful for studying the process of natural healing and discovery of drug.

Model for impaired healingacute wound can convert into chronic wound by diabetes, mechanical pressure, ischemia and perfusion injuryinduction. It includes.

- Diabetic wound models
- Pressure ulcer models

- **Diabetic wound model-** they are of two types

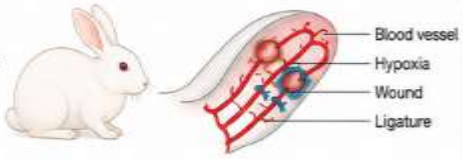
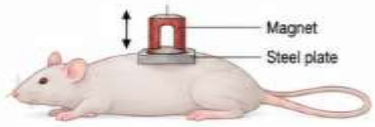
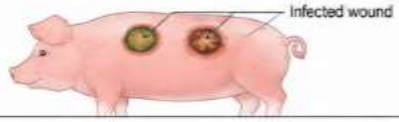
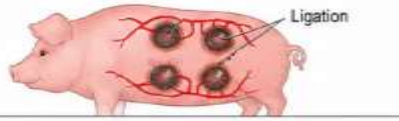
a) Streptozotocin induced model

b) Alloxan induced model

No animal model predict chronic problem which cause type2 diabetes ulcer.

- **Pressure ulcer model-**Pressure ulcer is caused by repeated ischemia-reperfusion injury due to long mechanical pressure. Pressure ulcer model can include loose skin animal with little subcutaneous fat and greyhound dogs due to thin skin. Pig are also better option [115].

Fig 5: various animal model of pressure ulcer

ANIMAL MODEL	SCHEMATIC REPRESENTATION	CLINICAL RELEVANCE	BENEFITS	LIMITATIONS
A Rabbit ear ischemic ulcer model		Clinically relevant to ischemic ulcers	• Suture-induvant ischemia recreates human wounds • Accessible and suitable for pharmacological testing	• Does not fully replicate human hypoxic wounds; not genetically tractable
B Diabetic mouse model		Clinically relevant to diabetic ulcers	• Diabetic mice are chemically or genetically induced • Enables testing of antidiabetic agents and multiple wounds	• Does not fully reflect human diabetic complications; high variability
C Excision wound splinting model in mouse		Clinically relevant to acute and chronic wounds	• Splinting reduces contraction, mimicking human healing • Useful for studying excisional wound healing	• Anatomical differences in skin and healing mechanisms
D Rat pressure ulcer model		Clinically relevant to pressure ulcers	• Controlled pressure induces ischemia and ulceration • Mimics chronic pressure conditions	• Skin and perfusion differences from human skin
E Pig infected wound model		Clinically relevant to infected ulcers	• Closely resembles human skin structure and immunity • Suitable for testing antimicrobials and dressings	• Expensive and not genetically tractable
F Pig ischemic ulcer model		Clinically relevant to ischemic ulcers	• Surgical ligation induces localized ischemia • Similar to human ischemic ulcer pathology	• Expensive and not genetically tractable
G Mouse tail full-thickness wound model		Clinically relevant to delayed wound healing	• Simple and reproducible excision model • Useful for studying delayed healing and scar formation	• Differences in skin structure and healing relative to humans

- **Source bioavailability and side effect of major bioactive compounds.**

Due to failure of tissue and organ caused by injury healthcare industry facing many challenges. Therapy used such as drug therapy surgery and implantation, these therapies are affected by many factor such as rejection of host tissue. Use of various pro healing plant bioactive compounds into biomaterial has been a prime factor to increase tissue regeneration at various target sites. Utilization of bioactive material over traditional is advantageous as it stabilize delivery of medication on site of wound show prolong and sustain delivery of bioactive compound, provide maximum bioavailability and make sure effect last throughout the therapeutic processes [116].

Table various bioactive compound with source, bioavailability and side effect

Compound	Source	Bioavailability	Side effect
Curcumin	Rhizomes of Zingiberaceae	Low bioavailability and solubility	At high dose curcumin can associate with nausea, diaeehea and can increase alkaline phosphatase and lactate[117].
Resveratrol	Grapes and wine	Poor bioavailability due to high rate of metabolism	At short dose reseveratrol does not cause any side effect but at high dose nausea, vomiting, diarrhea, and liver dysfunction may occur[117].

Luteolin	Chamomile tea, green pepper	Poor solubility and bioavailability	At the dose of 10-20 micro gram per ML luteolin can cause sister chromatid exchanges. Luteolin at dose 2-5 microgram reduce cell viability ATP content and TK6 cells[117].
Catechins	green tea, cocoa products (chocolate), and various fruits	Low Absorption	Gastrointestinal Issues: High doses, particularly in supplements (e.g., 1,200 mg), can cause nausea, especially when fasting[118].
Asiaticoside,	Dried whole grass and leaves	Low Oral Bioavailability	In rare cases, high doses may cause mild, transient, and non-specific side effects, including nausea, dizziness, headaches, stomach pain, or diarrhea [118].
Glycyrrhizin	Root and rizhome of liquorice	Poor oral bioavailability	Hypertension, edema and hypokalemia [119].

Conclusion

Bioactive compound–incorporated topical formulations represent a promising and rapidly evolving strategy for the management of pressure ulcers. These advanced therapeutic systems offer multifunctional benefits through modulation of inflammation, oxidative stress, microbial burden, angiogenesis, and extracellular matrix remodeling, thereby addressing key limitations associated with conventional wound-care approaches. Incorporation of bioactive molecules into nanocarriers, hydrogels, lipid-based systems, and smart biomaterials has further enhanced drug stability, tissue penetration, controlled release, and overall wound-healing efficacy.

Despite encouraging preclinical and early clinical outcomes, several translational challenges remain, including biocompatibility concerns, variability in patient response, optimization of mechanical strength and flexibility, controlled biodegradation, large-scale manufacturing, and long-term safety evaluation. Addressing these limitations through rational biomaterial engineering, surface modification strategies, and standardized clinical validation will be essential for successful clinical translation. Future integration of smart responsive systems, biomarker-guided therapies, and regenerative wound technologies may significantly improve therapeutic outcomes and establish next-generation standards for chronic pressure ulcer management.

References

1. Edsberg, L.E., Black, J.M., Goldberg, M., McNichol, L., Moore, L., and Sieggreen, M. (2016). Revised national pressure ulcer advisory panel pressure injury staging system: revised pressure injury staging system. J. Wound Ostomy Continence Nurs. 43, 585–597.
2. Gefen, A., Brienza, D., and Edsberg, L. (2019). Prevention and Treatment of Pressure Ulcers/Injuries: Clinical Practice Guideline European Pressure Ulcer Advisory Panel (EPUAP), National Pressure Injury Advisory Panel (NPIAP) and the Pan Pacific Pressure Injury Alliance (PPPIA).
3. Kruger, E.A., Pires, M., Ngann, Y., Sterling, M., and Rubayi, S. (2013). Comprehensive management of pressure ulcers in spinal cord injury: current concepts and future trends. J. Spinal Cord Med. 36, 572–585.
4. Shiferaw, W.S., Akalu, T.Y., Mulugeta, H., and Aynalem, Y.A. (2020). The global burden of pressure ulcers among patients with spinal cord injury: a systematic review and meta-analysis. BMC Musculoskelet. Disord. 21, 334.
5. Goossens RH, Snijders CJ, Holscher TG, Heerens WC, Holman AE. Shear stress measured on beds and wheelchairs. Scand J Rehabil Med. 1997;29:131–6.
6. Allman RM. Pressure ulcer prevalence, incidence, risk factors, and impact. Clin Geriatr Med. 1997;13:421–36.

7. Bansal C, Scott R, Stewart D, Cockerell CJ. Decubitus ulcers: a review of the literature. Int J Dermatol. 2005 Oct;44(10):805-10.
8. van Marum RJ, Meijer JH, Ribbe MW. The relationship between pressure ulcers and skin blood flow response after a local cold provocation. Arch Phys Med Rehabil. 2002 Jan;83(1):40-3.
9. Padula WV, Delarmente BA. The national cost of hospital-acquired pressure injuries in the United States. Int Wound J. 2019 Jun;16(3):634-640.
10. Gefen A, Ousey K. COVID-19: pressure ulcers, pain and the cytokine storm. J Wound Care. 2020 Oct 02;29(10):540-542.
11. Whittington K, Patrick M, Roberts JL. A national study of pressure ulcer prevalence and incidence in acute care hospitals. J Wound Ostomy Continence Nurs. 2000;27(4):209-215.
12. Agyare C., Akindele A.J., Steenkamp V. Natural Products and/or Isolated Compounds on Wound Healing. Evid.-Based Complement. Altern. Med. 2019;2019:4594965.
13. Elshamy A.I., Ammar N.M., Hassan H.A., El-Kashak W.A., Al-Rejaie S.S., Abd-ElGawad A.M., Farrag A.-R.R.H. Topical Wound Healing Activity of Myricetin Isolated from Tecomaria Capensis v. Aurea. Molecules. 2020;25:4870.
14. Di R., Murray A.F., Xiong J., Esposito D., Komarnytsky S., Gianfagna T.J., Munafo J.P. Lily Steroidal Glycoalkaloid Promotes Early Inflammatory Resolution in Wounded Human Fibroblasts. J. Ethnopharmacol. 2020;258:112766.
15. Gadekar R., Saurabh M.K., Thakur G.S., Saurabh A. Study of Formulation, Characterisation and Wound Healing Potential of Transdermal Patches of Curcumin. Asian J. Pharm. Clin. Res. 2012;5:225–230.
16. Bains R., Bains V. The Antioxidant Master Glutathione and Periodontal Health. Dent. Res. J. 2015;12:389.
17. Baek S., Park H., Kim M., Lee D. Preparation of PCL/(+)-Catechin/Gelatin Film for Wound Healing Using Air-Jet Spinning. Appl. Surf. Sci. 2020;509:145033.
18. Ueno H., Mori T., Fujinaga T. Topical Formulations and Wound Healing Applications of Chitosan. Adv. Drug Deliv. Rev. 2001;52:105–115.
19. Czyżewska U., Konończuk J., Teul J., Drągowski P., Pawlak-Morka R., Surażyński A., Miltyk W. Verification of Chemical Composition of Commercially Available Propolis Extracts by Gas Chromatography–Mass Spectrometry Analysis. J. Med. Food. 2015;18:584–591.
20. Su X., Liu X., Wang S., Li B., Pan T., Liu D., Wang F., Diao Y., Li K. Wound-Healing Promoting Effect of Total Tannins from Entada phaseoloides (L.) Merr. in Rats. Burns. 2017;43:830–838.
21. Fujisawa H., Watanabe K., SUMA K., Origuchi K., Matsufuji H., SEKI T., ARIGA T. Antibacterial Potential of Garlic-Derived Allicin and Its Cancellation by Sulfhydryl Compounds. Biosci. Biotechnol. Biochem. 2009;73:1948–1955.
22. Taher Tan, W.-N.; Chear, N.J.-Y.; Leong, C.-R.; Rashid, S.A.; Tong, W.-Y. Metabolites Characterisation of Endophytic Phyllostictafallopiae L67 Isolated from Aloe vera with Antimicrobial activity on diabetic wound microorganism. Nat.prod.res. 2023, 37, 1674-9
23. Marinelli, L.; Cacciatore, I.; Eusepi, P.; Dimmito, M.P.; Di Rienzo, A.; Reale, M.; Costantini, E.; Borrego-Sanchez, A.; Garcia-Villen, F.; Viseras, C.; et al. In Vitro Wound-Healing Properties of Water-Soluble Terpenoids Loaded on Halloysite Clay. Pharmaceutics 2021, 13, 1117.
24. Pasdaran, A.; Hamedi, A. The genus Scrophularia: A source of iridoids and terpenoids with a diverse biological activity. Pharm. Biol. 2017, 55, 2211–2233.
25. Kurutas, E.B. The importance of antioxidants which play the role in cellular response against oxidative/nitrosative stress: Current state. Nutr. J. 2015, 15, 71.

26. Moghadam, M.; Salami, M.; Mohammadian, M.; Khodadadi, M.; Emam-Djomeh, Z. Development of antioxidant edible films based on mung bean protein enriched with pomegranate peel. Food Hydrocoll. 2020, 104, 105735.
27. Krishnaiah, D.; Sarbatly, R.; Nithyanandam, R. A review of the antioxidant potential of medicinal plant species. Food Bioprod. Process. 2011, 89, 217–233.
28. Ambika; Singh, P.P.; Chauhan, S. Activity-guided isolation of antioxidants from the leaves of Terminalia arjuna. Nat. Prod. Res. 2014, 28, 760–763.
29. Fernandez, O.; Capdevila, J.Z.; Dalla, G.; Melchor, G. Efficacy of Rhizophora mangle aqueous bark extract in the healing of open surgical wounds. Fitoterapia 2000, 73, 564–568.
30. Tie, L.; An, Y.; Han, J.; Xiao, Y.; Xiaokaiti, Y.; Fan, S.; Liu, S.; Chen, A.F.; Li, X. Genistein accelerates refractory wound healing by suppressing superoxide and FoxO1/iNOS pathway in type 1 diabetes. J. Nutr. Biochem. 2013, 24, 88–96.
31. Savoia, P.; Raina, G.; Camillo, L.; Farruggio, S.; Mary, D.; Veronese, F.; Graziola, F.; Zavattaro, E.; Tiberio, R.; Grossini, E. Anti-oxidative effects of 17 β-estradiol and genistein in human skin fibroblasts and keratinocytes. J. Dermatol. Sci. 2018, 92, 62–77.
32. Duchnik, E.; Kruk, J.; Baranowska-Bosiacka, I.; Pilutin, A.; Maleszka, R.; Marchlewicz, M. Effects of the soy isoflavones, genistein and daidzein, on male rats' skin. Adv. Dermatol. Allergol./Postępy Dermatol. I Alergol. 2019, 36, 760–766.
33. Maier, C.M.; Chan, P.H. Book review: Role of superoxide dismutases in oxidative damage and neurodegenerative disorders. Neuroscientist 2002, 8, 323–334.
34. Zhang, L.; Ma, Y.; Pan, X.; Chen, S.; Zhuang, H.; Wang, S. A composite hydrogel of chitosan/heparin/poly (γ-glutamic acid) loaded with superoxide dismutase for wound healing. Carbohydr. Polym. 2018, 180, 168–174.
35. Talhouk, R.; Karam, C.; Fostok, S.; El-Jouni, W.; Barbour, E.K. Anti-Inflammatory Bioactivities in Plant Extracts. J. Med. Food 2007, 10, 1–10.
36. Scalise, A.; Bianchi, A.; Tartaglione, C.; Bolletta, E.; Pierangeli, M.; Torresetti, M.; Marazzi, M.; Di Benedetto, G. Microenvironment and Microbiology of Skin Wounds: The Role of Bacterial Biofilms and Related Factors; Seminars in Vascular Surgery; Elsevier: Amsterdam, The Netherlands, 2015; pp. 151–159.
37. Chen, W.C.; Liou, S.S.; Tzeng, T.F.; Lee, S.L.; Liu, I.M. Wound repair and anti-inflammatory potential of Lonicera japonica in excision wound-induced rats. BMC Complement. Altern. Med. 2012, 12, 226.
38. Ferrante, C.J.; Leibovich, S.J. Regulation of Macrophage Polarization and Wound Healing. Adv. Wound Care 2012, 1, 10–16.
39. Sandar, W.-P.; Saw, S.; Kumar, A.M.; Camara, B.S.; Sein, M.-M. Wounds, antimicrobial resistance and challenges of implementing a surveillance system in Myanmar: A mixed-methods study. Trop. Med. Infect. Dis. 2021, 6, 80. [Google Scholar] [CrossRef] [PubMed]
40. Geoff, S. Antimicrobial resistance relating to wound management and infection. Wound Pract. Res. 2016, 24, 224–227. [Google Scholar]
41. Piskláková, L.; Skuhrovcová, K.; Bártová, T.; Seidelmannová, J.; Vondrovic, Š.; Velebný, V. Trends in the Incorporation of Antiseptics into Natural Polymer-Based Nanofibrous Mats. Polymers 2024, 16, 664.
42. Liakos, I.L.; Holban, A.M.; Carzino, R.; Lauciello, S.; Grumezescu, A.M. Electrospunfiber pads of cellulose acetate and essential oils with antimicrobial activity. Nanomaterials 2017, 7, 84.
43. Rashid, N.; Khalid, S.H.; Ullah Khan, I.; Chauhdary, Z.; Mahmood, H.; Saleem, A.; Umair, M.; Asghar, S. Curcumin-loaded bioactive polymer composite film of pva/gelatin/tannic acid downregulates the pro-inflammatory cytokines to expedite healing of full-thickness wounds. ACS Omega 2023, 8, 7575–7586.

44. Yaseen, H.S.; Asif, M.; Saadullah, M.; Mahrukh; Asghar, S.; Shams, M.U.; Bazmi, R.R.; Saleem, M.; Yousaf, H.M.; Yaseen, M. Methanolic extract of Ephedra ciliata promotes wound healing and arrests inflammatory cascade in vivo through downregulation of TNF-α. Inflammopharmacology 2020, 28, 1691–1704.
45. Kováč, J.; Slobodníková, L.; Trajčíková, E.; Rendeková, K.; Mučaji, P.; Sychrová, A.; Bittner Fialová, S. Therapeutic potential of flavonoids and tannins in management of oral infectious diseases—A review. Molecules 2022, 28, 158.
46. Farha, A.K.; Yang, Q.-Q.; Kim, G.; Li, H.-B.; Zhu, F.; Liu, H.-Y.; Gan, R.-Y.; Corke, H. Tannins as an alternative to antibiotics. Food Biosci. 2020, 38, 100751.
47. Othman, L.; Sleiman, A.; Abdel-Massih, R.M. Antimicrobial activity of polyphenols and alkaloids in middle eastern plants. Front. Microbiol. 2019, 10, 911.
48. Sumayya, S.S.; Lubaina, A.S.; Murugan, K. Bactericidal Potentiality of Purified Terpenoid Extracts from the Selected Sea Weeds and its Mode of Action. J. Trop. Life Sci. 2020, 10, 197–205
49. Huang, W.; Wang, Y.; Tian, W.; Cui, X.; Tu, P.; Li, J.; Shi, S.; Liu, X. Biosynthesis investigations of terpenoid, alkaloid, and flavonoid antimicrobial agents derived from medicinal plants. Antibiotics 2022, 11, 1380.
50. Vadhana, P.; Singh, B.R.; Bharadwaj, M.; Singh, S.V. Emergence of herbal antimicrobial drug resistance in clinical bacterial isolates. Pharm. Anal. Acta 2015, 6, 434.
51. Atta, S.; Waseem, D.; Fatima, H.; Naz, I.; Rasheed, F.; Kanwal, N. Antibacterial potential and synergistic interaction between natural polyphenolic extracts and synthetic antibiotic on clinical isolates. Saudi J. Biol. Sci. 2023, 30, 103576.
52. Ferrante, C.J.; Leibovich, S.J. Regulation of Macrophage Polarization and Wound Healing. Adv. Wound Care 2012, 1, 10–16.
53. Monteforte, A.J.; Lam, B.; Das, S.; Mukhopadhyay, S.; Wright, C.S.; Martin, P.E.; Dunn, A.K.; Baker, A.B. Glypican-1 nanoliposomes for potentiating growth factor activity in therapeutic angiogenesis. Biomaterials 2016, 94, 45–56.
54. Eming, S.A.; Koch, M.; Krieger, A.; Brachvogel, B.; Kreft, S.; Bruckner-Tuderman, L.; Krieg, T.; Shannon, J.D.; Fox, J.W. Differential Proteomic Analysis Distinguishes Tissue Repair Biomarker Signatures in Wound Exudates Obtained from Normal Healing and Chronic Wounds. J. Proteome Res. 2010, 9, 4758–4766.
55. Kimura, Y.; Sumiyoshi, M.; Samukawa, K.; Satake, N.; Sakanaka, M. Facilitating action of asiaticoside at low doses on burn wound repair and its mechanism. Eur. J. Pharmacol. 2008, 584, 415–423.
56. Phaechamud, T.; Yodkhum, K.; Charoenteeraboon, J.; Tabata, Y. Chitosan-aluminum monostearate composite sponge dressing containing asiaticoside for wound healing and angiogenesis promotion in chronic wound. Mater. Sci. Eng. C Mater. Biol. Appl. 2015, 50, 210–225.
57. Liu, C.; Yang, Q.; Hu, W. Flavonoids accelerate wound healing of pressure sore by promoting angiogenesis: Potential mechanism. Pak. J. Pharm. Sci. 2022, 35, 1647–1654.
58. Li, W.; Kandhare, A.D.; Mukherjee, A.A.; Bodhankar, S.L. Hesperidin, a plant flavonoid accelerated the cutaneous wound healing in streptozotocin-induced diabetic rats: Role of TGF-ß/Smads and Ang-1/Tie-2 signaling pathways. EXCLI J. 2018, 17, 399.
59. Ghaisas, M.M.; Kshirsagar, S.B.; Sahane, R.S. Evaluation of wound healing activity of ferulic acid in diabetic rats. Int. Wound J. 2014, 11, 523–532.
60. Lin, C.-M.; Chiu, J.-H.; Wu, I.H.; Wang, B.-W.; Pan, C.-M.; Chen, Y.-H. Ferulic acid augments angiogenesis via VEGF, PDGF and HIF-1α. J. Nutr. Biochem. 2010, 21, 627–633.
61. Cai, H.-A.; Huang, L.; Zheng, L.-J.; Fu, K.; Wang, J.; Hu, F.-D.; Liao, R.-Y. Ginsenoside (Rg-1) promoted the wound closure of diabetic foot ulcer through iNOS elevation via miR-23a/IRF-1 axis. Life Sci. 2019, 233, 116525.

62. Chithra, P.; Sajithlal, G.; Chandrakasan, G. Influence of Aloe vera on collagen characteristics in healing dermal wounds in rats. Mol. Cell. Biochem. 1998, 181, 71–76.
63. Diniz, L.R.L.; Calado, L.L.; Duarte, A.B.S.; de Sousa, D.P. Centella asiatica and Its Metabolite Asiatic Acid: Wound Healing Effects and Therapeutic Potential. Metabolites 2023, 13, 276.
64. Zulkefli, N.; Che Zahari, C.N.M.; Sayuti, N.H.; Kamarudin, A.A.; Saad, N.; Hamezah, H.S.; Bunawan, H.; Baharum, S.N.; Mediani, A.; Ahmed, Q.U.; et al. Flavonoids as Potential Wound-Healing Molecules: Emphasis on Pathways Perspective. Int. J. Mol. Sci. 2023, 24, 4607.
65. Vitale, S.; Colanero, S.; Placidi, M.; Di Emidio, G.; Tatone, C.; Amicarelli, F.; D'Alessandro, A.M. Phytochemistry and Biological Activity of Medicinal Plants in Wound Healing: An Overview of Current Research. Molecules 2022, 27, 3566.
66. Lin, D.-W.; Jiang, Y.-W.; Wu, C.; Zhang, H.; Li, Y.-Z.; Wang, Y.-S. Quercetin Alleviates Cardiac Fibrosis via Regulating the SIRT3 Signaling Pathway. Cardiovasc. Drugs Ther. 2025, 39, 737–748.
67. Kaur, K., & Khatri, M. Role of nanotechnology in wound care. Indian Journal of Clinical and Experimental Dermatology, 2018; 4(2): 119-123.
68. Singh, P., Pandit, S., Mokkapati, V. R. S. S., Garg, A., Ravikumar, V., &Mijakovic, I. Gold nanoparticles in diagnostics and therapeutics for human cancer. International Journal of Molecular Sciences, 2018; 19(7): 1979.
69. Muller, R. H., Radtke, M., & Wissing, S. A. Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) in cosmetic and dermatological preparations. Advanced Drug Delivery Reviews, 2002; 54: S131-S155.
70. Souto, E. B., & Müller, R. H. Lipid nanoparticles: Effect on bioavailability and pharmacokinetic changes. Handbook of Experimental Pharmacology, 2008; 197: 115-141.
71. Cascone, S., and Lamberti, G. (2020). Hydrogel-based commercial products for biomedical applications: a review. Int. J. Pharm. 573, 118803.
72. Ahmad N., Ahmad R., Al-Qudaihi A., Alaseel S.E., Fita I.Z., Khalid M.S., Pottoo F.H., Bolla S.R. A novel self-nanoemulsifying drug delivery system for curcumin used in the treatment of wound healing and inflammation. 3 Biotech. 2019;9:1–20.
73. Albarqi H.A., Alqahtani A.A., Ullah I., Khan N.R., Basit H.M., Iftikhar T., Wahab A., Ali M., Badar M. Microwave-Assisted Physically Cross-Linked Chitosan-Sodium Alginate Hydrogel Membrane Doped with Curcumin as a Novel Wound Healing Platform. AAPS PharmSciTech. 2022;23:1–13.
74. Zhang Z., Chen H., Shen W., Deng J., Bai C., Xiao Y., Lyu L. Localized delivery of curcumin by thermosensitive hydrogels for promoting wound healing. J. Cosmet. Dermatol. 2022;21:5081–5091.
75. Chiaoprakobkij N., Suwanmajo T., Sanchavanakit N., Phisalaphong M. Curcumin-Loaded Bacterial Cellulose/Alginate/Gelatin as A Multifunctional Biopolymer Composite Film. Molecules. 2020;25:3800.
76. Mobaraki M., Bizari D., Soltani M., Khshmohabat H., Raahemifar K., AkbarzadeAmirdehi M. The Effects of Curcumin Nanoparticles Incorporated into Collagen-Alginate Scaffold on Wound Healing of Skin Tissue in Trauma Patients. Polymers. 2021;13:4291.
77. Kiti K., Suwantong O. The potential use of curcumin-β-cyclodextrin inclusion complex/chitosan-loaded cellulose sponges for the treatment of chronic wound. Int. J. Biol. Macromol. 2020;164:3250–3258.
78. Zhou Q., Cai X., Huang Y., Zhou Y. Pluronic F127-liposome-encapsulated curcumin activates Nrf2/Keap1 signaling pathway to promote cell migration of HaCaT cells. Mol. Cell. Biochem. 2022
79. Algahtani M.S., Ahmad M.Z., Nourein I.H., Albarqi H.A., Alyami H.S., Alyami M.H., Alqahtani A.A., Alasiri A., Algahtani T.S., Mohammed A.A. Preparation and characterization of curcumin nanoemulgel utilizing ultrasonication technique for wound healing: In vitro, ex vivo, and in vivo evaluation. Gels. 2021;7:213.

80. Sharma A., Panwar V., Salaria N., Ghosh D. Protease-responsive hydrogel, cross-linked with bioactive curcumin-derived carbon dots, encourage faster wound closure. Biomater. Adv. 2022;139:212978.
81. Albarqi H.A., Alqahtani A.A., Ullah I., Khan N.R., Basit H.M., Iftikhar T., Wahab A., Ali M., Badar M. Microwave-Assisted Physically Cross-Linked Chitosan-Sodium Alginate Hydrogel Membrane Doped with Curcumin as a Novel Wound Healing Platform. AAPS PharmSciTech. 2022;23:1–13.
82. Zhang Z., Chen H., Shen W., Deng J., Bai C., Xiao Y., Lyu L. Localized delivery of curcumin by thermosensitive hydrogels for promoting wound healing. J. Cosmet. Dermatol. 2022;21:5081–5091.
83. Chiaoprakobkij N., Suwanmajo T., Sanchavanakit N., Phisalaphong M. Curcumin-Loaded Bacterial Cellulose/Alginate/Gelatin as A Multifunctional Biopolymer Composite Film. Molecules. 2020;25:3800.
84. Mobaraki M., Bizari D., Soltani M., Khshmohabat H., Raahemifar K., AkbarzadeAmirdehi M. The Effects of Curcumin Nanoparticles Incorporated into Collagen-Alginate Scaffold on Wound Healing of Skin Tissue in Trauma Patients. Polymers. 2021;13:4291.
85. Kiti K., Suwantong O. The potential use of curcumin-β-cyclodextrin inclusion complex/chitosan-loaded cellulose sponges for the treatment of chronic wound. Int. J. Biol. Macromol. 2020;164:3250–3258.
86. Zhou Q., Cai X., Huang Y., Zhou Y. Pluronic F127-liposome-encapsulated curcumin activates Nrf2/Keap1 signaling pathway to promote cell migration of HaCaT cells. Mol. Cell. Biochem. 2022.
87. Algahtani M.S., Ahmad M.Z., Nourein I.H., Albarqi H.A., Alyami H.S., Alyami M.H., Alqahtani A.A., Alasiri A., Algahtani T.S., Mohammed A.A. Preparation and characterization of curcumin nanoemulgel utilizing ultrasonication technique for wound healing: In vitro, ex vivo, and in vivo evaluation. Gels. 2021;7:213.
88. Sharma A., Panwar V., Salaria N., Ghosh D. Protease-responsive hydrogel, cross-linked with bioactive curcumin-derived carbon dots, encourage faster wound closure. Biomater. Adv. 2022;139:212978.
89. Bedard, K., and Krause, K.-H. (2007). The NOX family of ROS-generating NADPH oxidases: physiology and pathophysiology. Physiol. Rev. 87 (1), 245–313.
90. Beckman, K. B., and Ames, B. N. (1998). The free radical theory of aging matures. Physiol. Rev. 78 (2), 547–581.
91. Dassarma, B., Nandi, D. K., Gangopadhyay, S., and Samanta, S. (2018). Hepatoprotective effect of food preservatives (butylated hydroxyanisole, butylated hydroxytoluene) on carbon tetrachloride-induced hepatotoxicity in rat. Toxicol. Rep. 5, 31–37.
92. An, Y., Liu, W. J., Xue, P., Ma, Y., Zhang, L. Q., Zhu, B., et al. (2018). Autophagy promotes MSC-mediated vascularization in cutaneous wound healing via regulation of VEGF secretion. Cell Death Dis. 9, 58.
93. Hunt, T. K., Zederfeldt, B., and Goldstick, T. K. (1969). Oxygen and healing. Am. J. Surg. 118 (4), 521–525.
94. Hoffmann, M. H., and Griffiths, H. R. (2018). The dual role of Reactive Oxygen Species in autoimmune and inflammatory diseases: evidence from preclinical models. Free Radic. Biol. Med. 125, 62–71.
95. Jones, R. E., Foster, D. S., and Longaker, M. T. (2018). Management of chronic wounds-2018. Jama-Journal Am. Med. Assoc. 320 (14), 1481–1482.
96. Koike, Y., Yozaki, M., Utani, A., and Murota, H. (2020). Fibroblast growth factor 2 accelerates the epithelial-mesenchymal transition in keratinocytes during wound healing process. Sci. Rep. 10 (1), 18545.
97. Lord, M. S., Ellis, A. L., Farrugia, B. L., Whitelock, J. M., Grenett, H., Li, C., et al. (2017). Perlecan and vascular endothelial growth factor-encoding DNA-loaded chitosan scaffolds promote angiogenesis and wound healing. J. Control. Release 250, 48–61.

98. Damjanov N, Vojinovic J. Biologic therapy of rheumatoid arthritis. Srp Arh Celok Lek. 2009;137:205–210. doi: 10.2298/sarh0904205d. [DOI] [PubMed] [Google Scholar]
99. Ding C, Cicuttini F, Li J, Jones G. Targeting IL-6 in the treatment of inflammatory and autoimmune diseases. Expert OpinInvestig Drugs. 2009;18:1457–1466.
100. Kovarikova M, Hofmanova J, Soucek K, Kozubik A. The effects of TNF-alpha and inhibitors of arachidonic acid metabolism on human colon HT-29 cells depend on differentiation status. Differentiation. 2004;72:23–31.
101. Carmeliet, P. Angiogenesis in life, disease and medicine. Nature 438, 932–936 (2005).
102. Ferrara, N. & Kerbel, R. S. Angiogenesis as a therapeutic target. Nature 438, 967–974 (2005).
103. Apte, R. S., Chen, D. S. & Ferrara, N. VEGF in signaling and disease: beyond discovery and development. Cell 176, 1248–1264 (2019).
104. Stephenson, J. A., Goddard, J. C., Al-Taan, O., Dennison, A. R. & Morgan, B. Tumour angiogenesis: a growth area—from John Hunter to Judah Folkman and beyond. J. Cancer Res. 2013, 895019 (2013).
105. Lenzi, P., Bocci, G. & Natale, G. John Hunter and the origin of the term "angiogenesis". Angiogenesis 19, 255–256 (2016).
106. Junjie Tang, Penglei Zhang, Yadong Liu, Dingyu Hou, You Chen, Lili Cheng, Yifang Xue, Jie Liu, Revolutionizing pressure ulcer regeneration: Unleashing the potential of extracellular matrix-derived temperature-sensitive injectable antioxidant hydrogel for superior stem cell therapy, Biomaterials, Volume 314, March 2025, 122880.
107. Wolcott RD, Kennedy JP, Dowd SERegular debridement is the main tool for maintaining a healthy wound bed in most chronic wounds. Journal of wound care2009;18:54–56.
108. Chen X, SchluesenerHJNanosilver: a nanoproduct in medical application. Toxicology letters2008;176:1–12.
109. Fitzgerald DJ, Renick PJ, Forrest EC, et al.Cadexomer iodine provides superior efficacy against bacterial wound biofilms in vitro and in vivo. Wound repair and regeneration : official publication of the Wound Healing Society [and] the European Tissue Repair Society2017;25:13–24 iodine
110. Sultana ST, Atci E, Babauta JT, et al.Electrochemical scaffold generates localized, low concentration of hydrogen peroxide that inhibits bacterial pathogens and biofilms. Scientific reports2015;5:14908.
111. Chandan K., roysashwati., s shomita, 2021, biofilm management in wound care, Plast Reconstr Sur., 148(2), 275-88.
112. Boyle D.L., Soma K., Kavanaugh A., The JAK inhibitor tofacitmib suppresses synovial JAK1-STAT signalling in reheumatoid arthritis, Ann. Rheam. Dis, 2015, 74.
113. Shi A., LiuL., Li S., Qi B., natural product targeting th MAPK signalling pathway in cancer overview, J. Cancer Res. Clin. Oncol, 2024, 150, 6.
114. Hanahan D., Wenberg R.A., 2000, The hallmarks of cancer cells, 100, 51-70.
115. Aryman Grada, Joshua Meris, research technique made simple animal model of wound healing, journal of investigative dermatology, 138(10), 2018, 2095-2105.
116. Chouhan, D.; Chakraborty, B.; Nandi, S.K.; Mandal, B.B. Role of non-mulberry silk fibroin in deposition and regulation of extracellular matrix towards accelerated wound healing. Acta Biomater. 2017, 48, 157–174.
117. Xiaoxuan Deng [1], Jithendra Ratnayake [2], Azam Ali [1,2,*] Curcumin-Loaded Drug Delivery Systems for Acute and Chronic Wound Management: A ReviewBioengineering (Basel)2025 Aug 11;12(8):860.
118. Anna-Lisa Pignet [1,2,*], Marlies Schellnegger [1], Andrzej Hecker [1,2], Michael Kohlhauser [1], Petra Kotzbeck [1,2], Lars-Peter Kamolz [1,2] Resveratrol-Induced Signal Transduction in Wound Healing, nt J Mol Sci 2021 Nov 23;22(23):12614.