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Review Article

An Insight into the Potential Mechanism of Bioactive Phytocompounds in the Wound Management

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ABSTRACT

Skin plays a fundamental role in the protection against mechanical impacts and infections, fluid imbalance, variations in temperature, micro-organisms, radiation, and chemical injury. Wounds are any damage or injury that disturbs the normal structure and function of the skin tissue. Wound healing is a crucial physiological process to maintain the integrity of the skin following injury by tissue repair, regeneration, and remodelling. Routinely, wound healing is a rapid and uncomplicated process, though wounds associated with impairment in host functionality are hard to heal due to diabetes, oxidative stress, chronic infection, immunosuppression, or obesity. Chronic wounds affect millions of patients physically and mentally, drastically reducing their quality of life. Therefore, new treatment strategies are urgently needed. Phytoconstituents are components derived from plants that have been used to treat wounds over the years. Various scientists have reported the crucial role of bioactive phytochemicals in wound healing and promoting skin regeneration. Numerous phytochemical compounds isolated from medicinal plants have been reported to scavenge free radicals, fight infection, and promote faster wound healing. This article aims to review the role of phytochemicals as wound healing agents with a current understanding of mechanisms, molecular targets, and therapeutic efficacy in enhancing wound repair and skin regeneration. Extensive preclinical research and clinical trials are required to understand the mechanism and potential molecular targets responsible for the beneficial impact of phytochemicals in wound healing and skin regeneration.

Keywords: Wound healing, Phytoconstituents, Antioxidant, Antimicrobial, Angiogenesis, Growth factors.

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INTRODUCTION

The skin is the largest organ in the human body comprising 12-15% of body weight, having surface area of approximately 2 meters. The skin protects internal organs from physical injury, pathogens, and fluid loss and has immune-neuroendocrine functions which contribute to maintaining body homeostasis. The two layers of skin are the epidermis and dermis. The epidermis contains various cells like keratinocytes, melanocytes, dendritic, and langerhans. Sensory axons exist in the epidermal and dermal basement membrane. The dermis comprises appendages, mast cells, fibroblasts, antigen-presenting dermal cells, and migrated immune cells. The Extracellular Matrix (ECM) of the dermis supports intercellular connections, cellular movements, cytokine, and growth factors functions.[1] The fibroblast is responsible for collagen deposition, which provides strength, integrity, and structure to normal tissues. The skin possesses excellent regenerative properties supporting the healing of injuries that took place in a highly orchestrated cascade of physiological events. Some conditions can impair and compromise this regenerative property of the skin, and wounds do not heal at the appropriate time, placing the patients at a serious health risk. Normally, wounds that do not heal within three months are called chronic wounds. Treating chronic wounds and severe burns is expensive and tenacious as they are prone to infection and often require surgical intervention.[2]

A wound is a cellular, anatomical, and functional disruption of the living tissue caused by physical, chemical, thermal, microbial, or immunological damage to the living tissue. Wounds may be a simple disruption in the epithelial integrity of the skin, or they can be deeper, prolonging into subcutaneous tissue with impairment to other structures such as tendons, muscles, vessels, nerves, parenchymal organs, and bones. An open wound is a straight cut or puncture, whereas a blunt force trauma creating a contusion is called a closed wound. Burn wounds are caused by fire, heat, electricity, radiation, chemicals, or sunlight.[3,4] The

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focus of the present review is to compile the potential wound healing bioactive phytochemical belonging to the categories like alkaloids, flavonoids, tannins, terpenoids, saponins, essential oils, and phenolic compounds. This review will enable us to understand the biology and the pathogenesis of wound healing. Furthermore, this review thoroughly discusses the vital molecular mechanisms contributing to wound repair and skin regeneration that contribute to effective treatment approaches.

CLASSIFICATION OF WOUNDS

Clinically wounds are categorized according to their etiology, pathogenesis, and time frame required for injury management and wound repair.

Acute wounds

Acute wounds are those which heal within 5 to 10 days, or maximum within 30 days. Acute wounds mostly occur due to traumatic tissue injury or during surgical procedures. Acute skin lesions happen as a result of trauma (e.g., burns, injury), a secondary disease condition (e.g., leg ulcers), or as a combination of both.[5] These wounds repair themselves by following a timely and orderly fashion healing mechanism restoring the functional and anatomical integrity of the skin.[6]

Chronic wounds

Chronic wounds usually do not heal following a normal healing course of wounds and cannot be cured in a timely and orderly manner. Chronic wounds are caused by naturopathic pressure, arterial and venous insufficiency, burns, and vacuities. There are various factors that affect the healing mechanism of chronic wounds, like infection, tissue hypoxia, necrosis, exudate, and excess levels of inflammatory cytokines. Chronic wounds normally accompany intense pain, chronic infection, functional abnormality, and loss of mobility, sometimes leading to amputations and, in some cases, even death. Common chronic wounds include venous leg ulcers, pressure ulcers, and diabetic foot ulcers.[5,6]

Complicated wounds

A complicated wound is characterized by a combination of an infection and a tissue deformity. Infection represents a steady danger to injury healing. The reason for the imperfection resides in the traumatic or post-irresistible etiology or in association with wide tissue resection (tumor management). The manifestation of developed infection depends upon virulence, type of micro-organisms, microbial load, local blood supply, and patient's inherent resistance. As indicated by the level of contamination, complicated wounds are characterized as follows; aseptic injuries (bone and joints), contaminated injuries (stomach, lung), and septic injuries (abscesses in the bowel).[6]

WOUND HEALING

Wound healing is an orchestrated interaction between complex steps of cellular and biochemical processes, leading to rebuilding of injured tissues structural and functional integrity.[4] This process involves activating intercellular pathways, coordinating tissue integrity, and homeostasis.[7] Proper wound healing is achieved by appropriate activation and wound site infiltration of inflammatory cells, neutrophils, and macrophages. Infiltrated cells produce pro-inflammatory cytokines like tumor necrosis factor-α (TNF-α) and interleukin-I (IL-I). These inflammatory cytokines further activate transforming growth factor (TGF)-β and fibroblast growth factors (FGFs), resulting in the proliferation and infiltration of activated fibroblasts at the wound site. However, various factors have an effect on the natural healing processes like aging, obesity, metabolic status, and endocrine abnormalities such as hypothyroidism and diabetes mellitus.[8]

Wound healing is achieved in four interconnected stages, i.e., the hemostasis, inflammatory, proliferative, and the remodelling phase. The healing process is initiated when platelets come into contact with exposed collagen in the wounded tissue. Wound healing in normal conditions is a fast and straightforward process, but it is usually difficult to heal in wounds associated with host dysregulation. Long-standing, complicated chronic wounds affect millions of patients physically and mentally worldwide, causing trauma and reducing the quality of life.[7]

Cascade of wound healing

Hemostasis phase

The first response to a wound is local vasoconstriction within 5 min. Platelets aggregate at the site of injury and activate the coagulation mechanism causing a fibrin clot formation. The fibrin clot functions as an initial temporary matrix initiating the activities that accompany healing. Following clot, the formation of thrombin is responsible for platelet degranulation which leads to the growth factors release. These are platelet-derived growth factor (PDGF), TGF alpha and beta (TGF- α/β), and epidermal growth factor (EGF), as well as adhesive glycoproteins, including fibronectin. Fibrin clot provides hemostasis, acting as a matrix for colonization of inflammatory cells at the wound site attracted via PDGF and TGF-α induced chemotaxis.[9] Vasoconstriction causes surrounding tissues ischemia, inducing sustained vasodilatation. This increases vascular permeability and migration of neutrophils into the wound tissue. Accumulation of fluid, enzymes, and proteins in the extracellular space causes induction of inflammation.

Inflammatory phase

The inflammation phase goes on for around 1-5 days. Neutrophils start to dwindle as monocytes and mast cells reach the wound tissue 24 hr after injury following monocyte-specific

chemotactic signals. Chemotactic signal is induced by monocyte chemoattractant protein-1 (MCF-1) and macrophage inflammatory protein-1 (MIP-1). Chemotactic factors such as kallikrein and fibrinopeptides also play a significant role. These are released from degradation products of fibrinogen and fibrin during coagulation. Monocytes differentiate into a key-wound healing player, the macrophages. Mast cell releases inflammatory mediators like TNF, histamine, proteases, leukotrienes, and ILs. The nature of cells and mediators involved in this phase depends on the type of pathogen, auto-immune response, chemical or physical injury types, and the tissue or organ involved. These mediators upregulate the expression of leucocyte and endothelial cell surfaces adhesion molecules, which further mediate the migration of inflammatory cells. Coordinated cell-cell and cell-matrix interactions enable neutrophils to perform phagocytosis for killing microbes.[10]

The neutrophils have a significant capacity to eliminate microbes, unfamiliar material, damaged matrix proteins, and dead cells by phagocytosis. Neutrophils animate endothelial cells to communicate via specific cell bond particles (CAMs). Leucocytes involved in phagocytosis further release proteases, like matrix metalloproteinase. Leucocytes debride wound, regulate fibrous tissue growth, and degrade collagen in the wound healing process. Proteases are crucial for the initiation of wound healing as they remove damaged ECM components to replace them with new intact ECM molecules. Activated macrophages further secrete TNF-α and IL-1β, stimulates capillary endothelial cells to express cell adhesion molecules, and up-regulate metalloproteinases (MMPs) expression. TNF-α and IL-1β both positively impact collagen deposition in the wound, inducing collagen synthesis by fibroblasts and downregulating the expression of tissue inhibitors of metalloproteinases (TIMPs).[1,11]

Lymphocytes produce Interferon-gamma (IFN-γ), which is the last one to enter the wound area in the inflammatory phase. IFN-γ inhibits fibroblast migration and decreases collagen synthesis. Inflammatory cells secrete TGF- α/β, heparin-binding (HB-EGF), and basic FGF (bFGF). These growth factors stimulate fibroblasts, epithelial cells, and vascular endothelial cells migration into the wound. Moreover, fibroblast production and collagen synthesis further promote induction of the second phase of wound healing. Towards the end of the inflammatory phase, neutrophils are phagocytosed by macrophages, decreasing the population of inflammatory cells and mediators in the injury, demonstrating the initiation of the proliferative phase.[12]

Another important feature of the inflammatory phase is oxidative explosion, releasing reactive oxygen species (ROS). The ROS at high concentrations has profound bacteriostatic effects, while in low concentrations acts as second messenger. If the inflammatory phase is not over within the normal time frame and the high concentration of ROS results in oxidative stress causing excisional dermal wound retardation, incisional wound

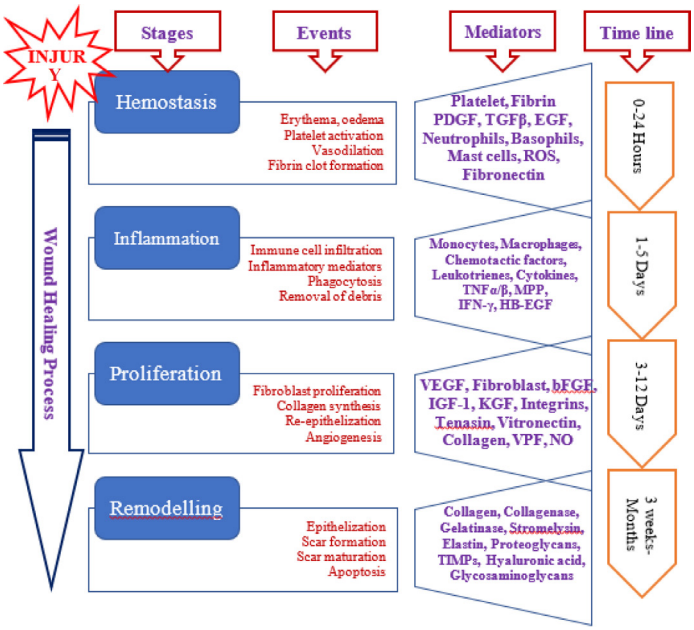


Figure 1: Schematic representation of wound healing phases and mediators involved.

bFGF: Basic fibroblast growth factor, EGF: Epidermal growth factor, HB-EGF: Heparin-binding epidermal growth factor, IFN-γ: Interferon gamma, IGF-1: Insulin-like growth factor-1, KGF: Keratinocyte growth factor, MMP: Matrix metalloproteinase, NO: Nitric oxide, PDGF: Platelet derived growth factor, TGF-β: Transforming growth factor beta, TIMPs: Inhibitors of metalloproteinases, TNF-α: Tumor necrosis factor alpha, VEGF: Vascular endothelial growth.

breaking reduction, decrease in collagen content, and increase glycosaminoglycan synthesis Figure 1.[13]

Proliferative phase

The proliferative phase is the granulation tissue formation stage that occurs between 3-12 days period following injury. This multiplication period of a wound is the point at which the injury is "revamped" by fibroblast proliferation, deposition of ECM, and collagen, supplementing the temporary fibrin lattice. This phase stage superimposes with the inflammatory phase around 3rd day of injury and proceeds until the injury is ready to heal. This phase is characterized by connective tissue deposition, collagen crosslinking, epithelial cell migration across the wound surface, and angiogenesis. Various cytokines control cellular migration and proliferation. TGF-β is the master control growth factor regulating fibroblast functions.[14]

Fibroblasts further secrete insulin-like growth factor-1 (IGF-1), bFGF, TGF-β, PDGF, and keratinocyte growth factor (KGF). Vascular endothelial growth factor (VEGF), bFGF, and PDGF are released by the endothelial cells, whereas keratinocytes produce TGF-β, TGF-α, and IL-1β. These mediators stimulate cell proliferation, synthesize ECM proteins, and help capillary formation. At the site of injury, fibroblasts and other migrated cells begin to proliferate, and the cellularity of the wound increases. Fibroblasts get attached to the fibrin matrix and begin

biosynthesis of collagen initially by producing procollagen chains and successively hydroxylation of proline and lysine. In the extracellular spaces, crosslinking gives collagen its strength and stability over time required for normal ECM formation. Dermal collagens are naturally strong and highly organized molecules, whereas, in contrast, scar tissue collagen fibers are smaller with random appearance. This, in fact, provides the wound with a maximum of 80% tensile strength compared to normal skin. The number of inflammatory cells begins to decrease after a few days in the non-infected wounds, and re-epithelization starts.[10]

The replacement of dead or damaged tissue with new and healthy ones is called re-epithelialization of the wound. EGF and TGF-α stimulate this process. Re-epithelialization can begin at the wound edges earliest within 24 hr post-injury as the damaged epithelial cells at the wound margin begin to reproduce. Granulation starts around 5th day post-injury. Accelerated epithelial mitosis induces ridge formation around the wound periphery that eventually migrates across the wounded area forming monolayer as overlapping cells migrate from different directions. After the epithelial bridge is complete, 'contact inhibition' eventually results in the cessation of cellular migration. Enzymes are released to dissolve the attachment of the scab at the base resulting in its eventual removal. This occurs due to downregulation in integrins expressed on the cell membranes based on reduction of calcium or increment in magnesium concentrations. An intact epidermal basement membrane is required for cell migration. In wounds with epidermal basement membrane destruction, the cells initially migrate over the provisional fibrin–fibronectin matrix. Following that, epithelial cells can regenerate new basement membrane. Under the migrating cells, reestablishment of basement membrane occurs with the involvement of tenasin, vitronectin, and Type I and V collagens secretion. Further cellular proliferation generates a multi-laminated new epidermis covered by keratin which is thinner than the normal epidermis.[15]

The wound site has an increasing requirement for oxygen and nutrients due to high metabolic activity. Angiogenesis is fundamental for granulation tissue development during the multiplication stage, which promotes new capillary formation as bud-like structures. Angiopoietin-1 (Ang-1), like growth factors released from platelets, stimulates endothelial proliferation, migration, and tube formation. Hypoxia is a crucial driving force for wound angiogenesis, leading to nitric oxide (NO) production, which promotes vasodilation and angiogenesis to improve local blood flow. Angiogenesis is amplified by myriad angiogenic factors released in the wound bed, including PDGF, VEGF, Ang-1, TGF-α, bFGF, IL-8, and TNF-α. Recently framed vessels carry oxygen and supplements to the developing tissues. New blood vessels regenerate in the repairing wound area, maintaining the oxygen tension to normal level. Oxygen binds to hypoxia inducible factor (HIF), decreasing VEGF synthesis. Newly forming blood vessels are stabilized by the influence of Ang-1 released by activated endothelial cells. Ang-1 further promotes PDGF production, which helps recruit smooth muscle cells and pericytes in the newly formed vasculature. At the final stage of wound healing, angiogenesis is suppressed as the tissue becomes normoxic and epidermal production of interferon-β.[14,16]

Remodelling phase

Finally, the process of collagen remodelling occurs via collagen degradation. The final stage of wound recuperating is called the remodelling and rebuilding stage, transforming the immature collagen matrix is transformed into scar tissue. It starts in 3rd week of injury and can last from months to more than a year. After the formation of the initial scar, proliferation and neovascularisation phase stops. Thus, wound healing goes into the remodelling phase. Fibroblasts, neutrophils, and macrophages release specific collagenase enzymes that clip through all three chains of collagen molecule and break it down to characteristic three-quarter and one-quarter pieces. Proteases like gelatinase and stromelysin further denatures and digest fragments of collagen.[12,14]

During this last phase of wound healing, a balance is reached between the synthesis of new scar matrix components and their degradation. Fibroblasts, on the one hand, synthesize ECM components of collagen, elastin, and proteoglycans, and on the other hand, also produces MMPs that degrade the collagen matrix and TIMPs. Fibronectin gradually disappears, and proteoglycans replace hyaluronic acid and other glycosaminoglycans under the influence of PDGF, TGF-β, and FGF. Fibroblasts secrete the lysyl oxidase, which crosslinks ECM components. Macrophages and myofibroblasts are cleared from the wound site by apoptosis. Mitogen-activated protein kinase (MAPK) is an important signal transduction mechanism regulating growth, differentiation, and apoptosis in damaged tissue. Angiogenesis stops as the metabolic activities in the wound site decline. Type III collagen, also known as reticular collagen, is slowly replaced by the predominant type present in the skin (Figure 2).[2]

NATURAL PRODUCTS FOR WOUND MANAGEMENT

There are different ways to heal the wound using oral or topical formulations. In the case of topical formulation, starting from simple ointment to sophisticated dressing, applying negative pressure, use of synthetic polymers, gene therapy, stem cell therapy, and application of growth factors. These sophisticated measures are costly and need a high level of skill and medical care. The use of medicinal plants for wound management is common in most systems of traditional medicine practices worldwide. For more than 5000 years, Egyptians, Africans, Asians, Romans, and indigenous Americans have an ancient history of using medicinal plants as first-line therapy for treating inflammation, burns, ulcers, and surgical wounds. Number of herbs worldwide have been screened for their wound healing activity. Still, we are in

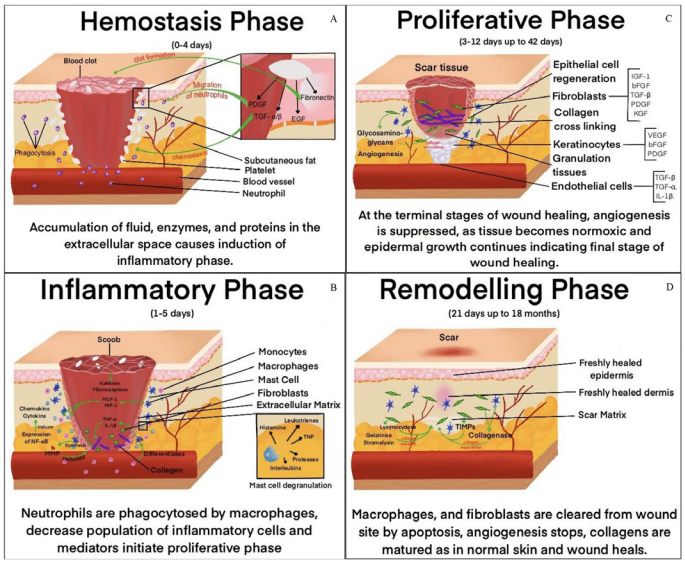


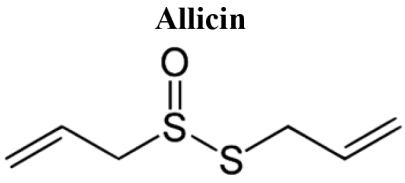
Figure 2: The pathogenesis of wound healing and the mechanism of various mediators involved.

A. Hemostasis phase, B. Inflammatory phase, C. Proliferative phase, and D Remodelling phase. bFGF: Basic fibroblast growth factor, EGF: Epidermal growth factor, IGF-1: Insulin-like growth factor-1, IL-1β: Interleukin-1 beta, KGF: Keratinocyte growth factor, MCF: Monocyte chemoattractant protein, MIP: Macrophage inflammatory protein, MMP: Matrix metalloproteinase, NF-κB: Nuclear factor kappa B, PDGF: Platelet derived growth factor, TGF-α: Transforming growth factor alpha, TGF-β: Transforming growth factor beta, TIMPs: Inhibitors of metalloproteinases and VEGF: Vascular endothelial growth factor.

need of potential, efficacious, and cost-effective wound healing components.[17]

Phytochemicals

Phytochemicals are naturally occurring components biosynthesized by the plants. Approximately half of the new chemical entities introduced in therapy during the last 50 years were derived from natural products, semisynthetic analogs of the natural products or synthetic compounds developed based on natural pharmacophores. Over 70% of the therapeutic agents developed for treating bacterial and fungal infections during this period were derived from natural sources.[18,19] Phytochemicals play a vital role in preventing and treating a number of diseases, along with the potential for wound healing and skin regeneration. The phytochemicals mostly show wound healing properties due to anti-inflammatory, anti-microbial, antioxidative, immunomodulatory, and platelet aggregation inhibition. Some of the noteworthy bioactive phytochemicals with potential wound healing activities are discussed in this review, specifically focusing on the mechanism of action and molecular targets.[4,20] This review focuses on beneficial effects and molecular targets of phytochemicals exerting protective effects on wounds and will also help develop preventive strategies and effective treatment approaches.

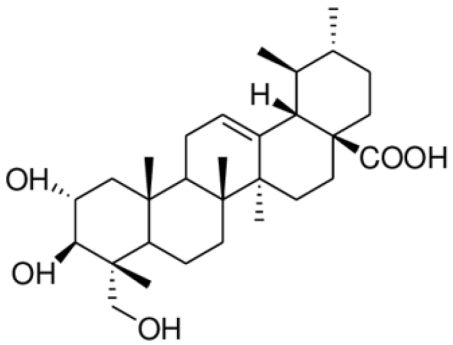


Allicin [S-(Prop-2-en-1-yl) prop-2-ene-1-sulfinothioate] is an organosulfur compound obtained from garlic, and having a wide range of biological activities. Garlic cloves (*Allium sativum*), of the Alliaceae family, produce allicin through enzymatic reactions.[21] Garlic extracts improve wound recovery and diminish the chances of wound contamination.[22] Allicin is released following tissue injury and is catalyzed by the enzyme alliinase from the non-proteinogenic amino acid alliin (S-allylcysteine sulfoxide). Allicin is a reactive sulfur species that undergoes a redox reaction with thiol groups in glutathione and proteins. This redox reaction is essential for its biological activity in the microbial, plant, and mammalian cells. Allicin has antibacterial, antiviral, antifungal, anti-inflammatory, and vasodilating effects.

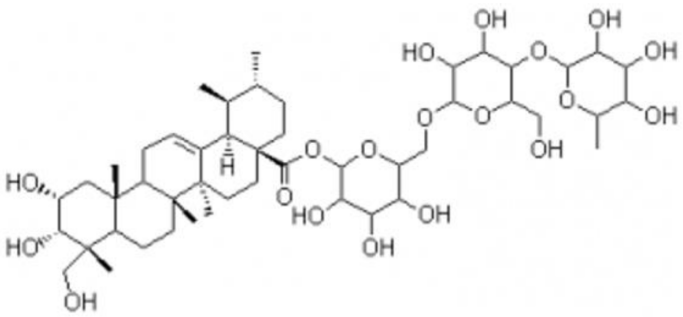
Sardari *et al.*[23] explored the effects of topically applied allicin on second intention wound healing in dogs. Depending on the organism and the antibiotic used, the effectivity of allicin is comparable with conventional β-lactams (penicillin, ampicillin) or glycosidic (kanamycin) antibiotics.[24] Allicin inhibits the proliferation of bacteria and fungi and is lethal on methicillin-resistant *Staphylococcus aureus*. Allicin impels cell destruction and inhibits cell duplication in mammalian cell lines.[25] Toygar *et al.*[26] reported the potential wound healing effect of allicin on diabetes rats. Allicin treated rats showed lower neutrophil and mononuclear cell count with reduced intraepithelial edema and dermal edema density. Fibroblast number, angiogenesis, and collagen density were increased by allicin treatment. Allicin is a very useful topical treatment for full-thickness and excisional wounds basically responsible for a higher density of fibrocytes and fibroblasts in the excisional wound.

Asiatic acid

The medicinal plant *Centella asiatica* is widely used in South Asia. *C. asiatica* contains asiatic acid, asiaticoside and madecassic acid. Asiatic acid (2,3,23-trihydroxy-urs-12-ene-28 -oic-acid; 2α,23-Dihydroxyursolic acid) is an aglycone of ursane type pentacyclic triterpenoids. Asiatic acid is an aglycone of asiaticoside formed during hydrolysis of the sugar moiety in acidic conditions. It is a monocarboxylic acid, a triol, and a pentacyclic triterpenoid. It is isolated from *C. asiatica*, *Symplocos lancifolia,* and *Vateria indica*. Asiatic acid has a role as an angiogenesis modulating agent.[27] Asiatic acid possesses a variety of biological activities, notably anticancer, anti-inflammatory and wound healing, antidiabetic, antioxidant, hepatoprotective, antihepatitis C, and neuroprotective effects.[28]



Asiaticoside



Asiatic acid also reduced incision wound tensile strength and developed epithelialization and keratinization. Triterpenoids of *C. asiatica* and asiatic acid is reported for collagen I synthesis promotion.[29] Using gene microarrays test and real-time reverse transcription polymerase chain reaction (RTPCR) assay asiatic acid was assessed on the expression of 1053 human fibroblasts genes.[30] Asiatic acid was found to activate genes involved in growth factor release, angiogenesis, and extracellular matrix remodelling. All these reports signify the use of asiatic acid in folklore medicine and scientifically validate the claim for wound and microangiopathy treatment.

C. asiatica hexane, ethyl acetate, and methanol extract fractions have been reported to contain asiatic acid, showing wound healing promotion in rats incision and burn wounds model.[31] Asiatic acid enhanced burn wound healing in primary human skin fibroblasts. Orally administered asiatic acid stimulated cell proliferation, promoted collagen synthesis, restored MMP-1/TIMP-1 balance, and regulated the TGF-β/Smad signaling pathway in mice.[32] Yuan *et al.*[33] reported protective effects and mechanism of action of asiatic acid against oxygen-glucose deprivation/re-oxygenation (OGD/R) injury in PC12 cells. Cells pre-treated with asiatic acid showed increased cell survival rate, alleviated lactate dehydrogenase leakage, inhibited lactic acid production, promoted superoxide dismutase activity, reduced malondialdehyde content, decreased apoptosis, and inhibited caspase-3 activity. Protective effect of asiatic acid against OGD/R injury in PC12 cells was possibly due to the elimination of free radicals and inhibition of cell apoptosis. Bian *et al.*[34] reported the usefulness of asiatic acid in keloid management. Asiatic acid inhibited TGF-1-induced collagen and PAI-1 expression in keloid fibroblasts via peroxisome proliferator-activated receptor (PPAR) activation. Asiatic acid induces steady gene expression signifying its preventive effects on connective tissue disorders, such as wound and microangiopathy. Asiatic acid can also protect from skin damage with its antiglycative activity.[35]

Yuyun *et al.*[36] demonstrate novel small molecule inhibitor property of asiatic acid on the Notch signaling pathway. Asiatic acid prevents Notch3 binding to IL-6 promoter, influencing the regulation of mitochondrial function and resulting in the antisepsis effect. Asiatic acid decreases serum levels of IL-1β, IL-6, alanine aminotransferase, and blood urea nitrogen. It alleviates liver, lung, and kidney damage, improving survival of mice with experimental sepsis. Asiatic acid has reduced the expression of nitric oxide, IL-1β, IL-6, and lipopolysaccharide-stimulated proinflammatory mediators in macrophages. Asiatic acid is a novel Notch inhibitor with a promising role in the treatment of sepsis.

Asiaticoside is a triterpene glycoside bioactive compound used traditionally for wound healing applications. Asiaticoside prevents ultraviolet A-dependent photoaging by suppressing oxidative damage induced by ultraviolet A radiation.[37] Various studies have been conducted to ensure the potential benefits of asiaticoside on keratinocytes and dermal fibroblast cells involved in the healing of wounds.[38]

Asiaticoside increased tensile strength of linear skin wounds in the rat tested by local application.[39] Shukla *et al.*[40] investigated asiaticoside treatment against normal and delayed wound healing. Asiaticoside increases collagen content, tensile strength, hydroxyproline content, as well as epithelization in punch wounds of guinea pigs. Asiaticoside is more active orally on the guinea pig punch and chick wound. Asiaticoside wound curative ability is due to increased angiogenesis and collagen formation. Asiaticoside promotes wound healing by enhancing the stretch strength of the newly formed skin. It also decreases the capillary permeability and hypertrophy in abrasions by preventing the inflammatory process.[41] Asiaticoside and retinoic acid were compared for cell proliferation and type I and III collagen synthesis capability in human dermal fibroblast. Human dermal fibroblasts were isolated from foreskin explants. Asiaticoside had significantly increased human dermal fibroblasts proliferation compared to retinoic acid. The type III collagen production was also significantly higher with asiaticoside treatment.[42] Asiaticoside and madecassoside isolated from *C. asiatica* showed burn wound healing property. The cytotoxic nature of the asiaticoside and madecassoside were inspected and found to be non-toxic up to 500 ppm. Asiaticoside and madecassoside increased MCF-1 production but had a non-significant effect on VEGF production.[43]

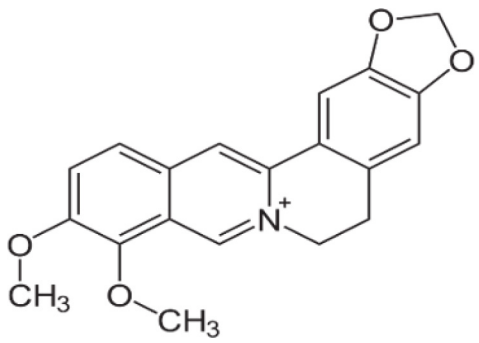
Suriyah *et al.*[44] conducted a study to investigate the healing effect of asiaticoside on human gingival fibroblast cells. The effect of asiaticoside on Collagen Type I Alpha 1 Chain (Col1A1) gene

expression was also analyzed using Real-Time Quantitative Reverse Transcription PCR (qRT-PCR). Col1A1 is reported to have a vital role in wound healing process. Asiaticoside significantly accelerated wound healing, and markedly increased Col1A1 messenger ribonucleic acid (mRNA) expression. These results substantiate potential role of asiaticoside in wound healing. Scarless skin regeneration after wound healing is still a challenge due to complicated microenvironment involved in wound healing. Silk nanofiber hydrogels loaded with asiaticoside were applied as injectable matrices for skin regeneration. Asiaticoside maintained its bioactivity while dispersed in aqueous silk nanofiber hydrogels and regulated inflammatory reactions and vascularization *in vitro*. Asiaticoside-laden hydrogel matrices achieved scarless wound repair following implant in full-thickness wound defects. Asiaticoside hydrogel demonstrated promising benefits toward scarless tissue regeneration.[45]

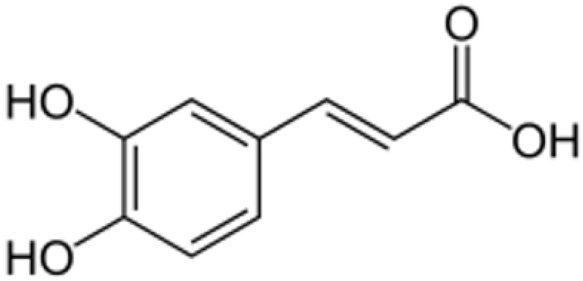
Berberine

Berberine [9,10-Dimethoxy-5,6-dihydro[1,3]dioxolo[4,5-g] isoquinolino[3,2-a]isoquinolin-7-ium] is a benzylisoquinoline alkaloid found in such plants of Berberis, such as *Berberis vulgaris, Berberis aristata, Mahonia aquifolium, Coptis chinensis* etc. The various scientifically reported pharmacological activities of berberine are antifungal, antibacterial, anticholinergic, antiviral, antihypertensive, anti-inflammatory, and antioxidative.[46] Berberine has been efficacy in regulating glucose and lipid metabolism *in vitro* and *in vivo* treating hyperglycemia and dyslipidemia.[47,48]

Traditionally Berberine is used as an anti-infective medicine. Antibacterial activity of Berberine has been found against various bacteria like *Actinobacillus pleuropneumoniae* minimum inhibitory concentration (MIC 0.312 mg/mL), *Streptococcus agalactiae* (MIC 78 µg/mL), most of the strains of *Staphylococcus* (MIC from 16 to 512 µgm/mL) and *Shigella dysenteriae*. Berberine is a deoxyribonucleic acid (DNA) ligand capable of binding both double-stranded and single-stranded DNA *in vitro*. Berberine binds to bacterial DNA and damages it. A recent report shows that the essential system of antibacterial activity of berberine is because of inhibition of the cell division protein FtsZ. Berberine has a synergistic impact with some anti-infection agents, particularly with linezolid, cefoxitin, and erythromycin.



Caffeic acid



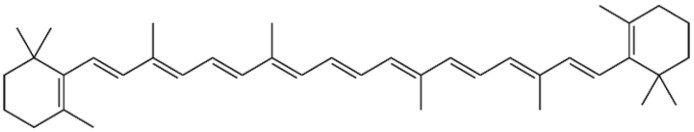
Berberine is a useful therapeutic agent for antibiotic resistant bacterial diseases.[49]

Berberine nano-colloids hydrogel promote wound healing in diabetic rats. Berberine nano-colloids hydrogel inhibits the expression of nuclear factor kappa B (NF-κB), TNF-a, and IL-6 benefiting wound healing in diabetic rats.[50] Topical Berberine treatment accelerates diabetic wound healing by activating Thioredoxin reductases-1 (TrxR1). Targeting TrxR1 is a novel strategy for promoting diabetic wound healing by restoring redox homeostasis.[51]

Caffeic acid (3,4-Dihydroxycinnamic acid) is an orally active polyphenol, hydroxycinnamic acid derivative with potential anti-inflammatory, antioxidant and anticancer activities. Caffeic acid is synthesized in almost all plant species and abundantly present in coffee, wine, tea, and propolis. Caffeic acid prevents oxidative stress preventing free radicals induced DNA damage and acting as an antioxidant.[52]

Serarslan *et al.*[53] reported beneficial effects of caffeic acid phenethyl ester on healing full-thickness incision wound in rats. Caffeic acid treatment significantly increased glutathione and nitric oxide and decreased malondialdehyde and superoxide dismutase levels. Histopathology of the wound tissues displayed rapid epithelium development correlated to antioxidant and ROS-scavenging capabilities. Caffeic acid phenetyl ester was analyzed histologically on bone healing of Critical Size Defect of calvaria in rats. Defect was created in the right side of the parietal bone without damaging the underlying dura mater. Twenty-eight days after the surgery, rats showed new bone areas with regenerated bone. The results indicate that topical and systemic application of caffeic acid phenetyl ester increases bone healing, especially with the systemic application.[54] Song *et al.*[55] investigated the wound healing potential of caffeic acid in skin-incised mice. Anti-inflammatory and wound healing efficacy of caffeic acid is evident as it decreased myeloperoxidase, lipid peroxidation, and phospholipase A2 activity in incised-wound tissue. Caffeic acid significantly stimulated collagen synthesis in fibroblast, inhibiting both silica-induced ROS generation and melittin-induced arachidonic acid release. Caffeic acid inhibited PGE_2 production and histamine release stimulated by melittin and arachidonic acid.

β-carotene



Teke *et al.*[56] investigated caffeic acid phenethyl ester on left colonic anastomoses wound in the presence of intraperitoneal sepsis. This sepsis model was induced by cecal ligation and puncture on rats. Caffeic acid significantly increased colonic anastomotic bursting pressures, tissue Hyp contents, along with enzymatic and nonenzymatic antioxidant markers. Significant decrease in oxidative stress parameters was observed in colonic anastomotic tissues. Caffeic acid phenethyl ester prevented the detrimental effects of sepsis on colonic anastomotic wounds. Caffeic acid phenethyl ester was assessed on the healing of burn injury. Caffeic acid phenethyl ester increased reepithelialization and decreased myeloperoxidase activity and nitrite levels. It also reduced CD68 and platelet endothelial cell adhesion molecule-1 protein expression and carbonyl levels in plasma and lesion tissue. Treatment with caffeic acid improved burn wound healing by decreasing inflammation and oxidative damage.[57] Caffeic acid was explored in laser wound healing in male Wistar rats. The results showed increased wound healing with rise in hydroxyproline levels.[58]

Beta-Carotene is naturally-occurring retinol (Vitamin A) which is a precursor called provitamin A. It is a red-orange colored pigment abundant in fungi, plants, and fruits. The carotenes are terpenoids (isoprenoids), synthesized from 40 carbons containing isoprene units. Distinguishably β-carotene has two beta-rings at both the ends of the molecule. β-Carotene is the most commonly occurring carotene in plants. In plants, β-carotene is the precursor of vitamin A, which is activated by beta-carotene monooxygenase. Beta carotene has powerful antioxidant properties. Beta-carotene antioxidant activity is attributed to preventing free radical damage by singlet oxygen, peroxide, and peroxy radicals scavenging. Vitamin A increases epithelial turnover, which is crucial during wound healing of skin and mucous membranes. Vitamin A is also associated with increased collagen, fibronectin, keratinocytes, and fibroblast, which is important for wound tissue structure.[59]

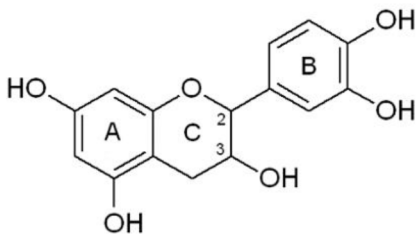
The effects of retinyl acetate, beta-carotene, or retinoic acid feeding on rat skin wound healing were investigated by Gerber and Erdman.[60] Supplemental retinyl acetate, beta-carotene, and trans-retinoic acid can effectively enhance wound strength after surgery in young male rats. Vitamin A can control intra-abdominal sepsis systemically as well as locally. Vitamin A dietary supplementation had a significant protective effect by improving the survival of adult male rats with intra-abdominal sepsis by preventing postoperative hypothermia and maintaining peripheral WBC counts. Dietary supplementation with beta carotene had a lesser protective effect.[61] Vitamin A deficiency retards wound repair, and retinoid treatment can promote wound healing by restoring steroid-retarded delayed repair to normal. Vitamin A can initiate reparative behavior in tissue by suppressing fibroblast proliferation and stimulating steroid-treated macrophages in cell culture. Retinoids play an important role in macrophagic inflammation and controlling wound healing process.[62]

β-carotene contributes to preventing photodamage, inhibiting proliferation and migration in carcinogenesis of epithelial cells. It also inhibits MMPs degradation in collagen deposit in the proliferative and the remodelling phase of wound healing.[63] Vitamin A is crucial for maintaining reproduction, cellular function, growth, immunity, and especially vision. Vitamin A binds with nuclear retinoic acid receptors, retinoid X receptors, and PPAR. Retinoids regulate the growth and differentiation of skin epithelial cells. Deficiency retinoid leads to abnormal skin epithelial keratinization. Vitamin A stimulates epidermal turnover and re-epithelialization restoring epithelial structure in damaged tissue. Retinoids have the special capability to reverse the inhibitory effect of anti-inflammatory steroids on healing wounds. Retinoic acid enhances the production of ECM components such as collagen-I and fibronectin. Proliferation of keratinocytes and fibroblasts is also enhanced by vitamin A along with decrease in matrix MMPs levels.[64]

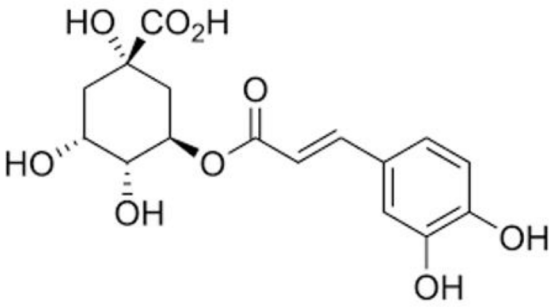
Catechin [2R,3S)-2-(3,4-Dihydroxyphenyl)-3,4-dihydro-2H-chromene-3,5,7-triol] is a flavan-3-ol category natural phenolic compound. Catechin can be harvested from a variety of sources like dietary products, fruits, green tea, red wine, beer, cacao liquor, chocolate, cocoa, etc. A high concentration of catechin is found in tea and red wine, the most popular beverages in the world.[65] The number and position of the hydroxyl groups and the presence or absence of the galloyl moiety significantly impact hydrogen bond capabilities and ultimately impact the ability to affect the biological environment.[66] The antioxidant action of catechin is well-established along with antihypertensive, anti-inflammatory, antiproliferative, anti-thrombogenic, and antihyperlipidemic effects.

Catechin affects the molecular mechanisms of angiogenesis and ECM degradation involved in wound healing. Kapoor *et al.*[67] investigated catechin epicatechin gallate on full-thickness incision wounds in rats. Catechin epicatechin gallate significantly improved scar formation, angiogenesis, inducible nitric oxide synthase, and cyclooxygenase-2 (COX) level. These effects are attributed

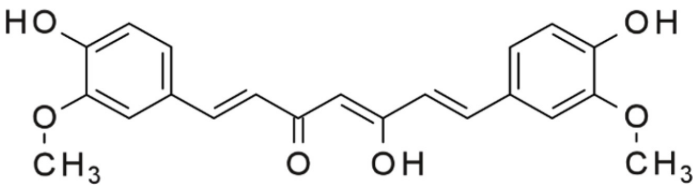
Catechin



Chlorogenic acid



Curcumin



to acceleration of the angiogenesis, up-regulation of nitric oxide synthase, and cyclooxygenase enzymes. Epicatechin-3-O-gallate displayed promising wound-healing effects through inhibition of NF-κB DNA binding and p38α MAPK activity.[68]

Osterburg *et al.*[69] investigated wound healing effects of epigallocatechin-3-gallate both *in vitro* and *in vivo*, with and without infection. *In vitro* assays on normal fibroblasts demonstrated migration, proliferation, and apoptosis inhibition. Epigallocatechin-3-gallate showed an enhanced contraction of full-thickness dorsal wounds, macrophages, neutrophils, myofibroblasts, and reduced quantities of smooth muscle alpha-actin (α-SMA) myofibroblasts in *in-vivo* experiments. Epigallocatechin-3-gallate treatment significantly reduced bacterial load in the infected traumatic wound. Baek *et al.*[70] reported excellent antioxidant and wound healing properties of PCL/(+)-catechin/gelatin film. Catechin isolated from *Dioscorea bulbifera* exhibited potent wound healing activity via cell proliferation promotion, fibroblast migration, and wound closure.[71]

Chlorogenic acid [3-(3,4-Dihydroxycinnamoyl) quinic acid] is a polyphenol. Coffee and black tea predominantly contain this ester of caffeic acid and quinic acid. Chlorogenic acid is one of the amplest polyphenolic compounds in our diet.[72] Chlorogenic acid is a scavenger of free radicals, inhibiting DNA damage and also protecting against carcinogenesis. Chlorogenic acid activates the immune system by proliferation of cytotoxic T-lymphocytes, macrophages, natural killer cells and inhibits matrix MMPs.[73]

Administration of chlorogenic acid on rats induces significant increase in SOD, CAT, and GSH activity and decreases the TBARS level. The wound healing efficacy of chlorogenic acid could be attributed to its antioxidative effect tested on excision wounds model.[74] Chen *et al.*[75] evaluated the effects of topical chlorogenic acid on excision wounds of rats. Chlorogenic acid ointment applied topically once a day for 15 days promoted wound contraction, epithelialization rate, cellular proliferation, and TNF-α levels during the inflammatory phase. It also showed upregulation of TGF-β1 and elevated collagen IV synthesis. Bagdas *et al.*[76] The wound healing activity of chlorogenic acid is attributed to its mechanisms such as enhancing capillary density and collagen production, antioxidative, anti-inflammatory, and free radical scavenging effects on MMPs in wound tissues. Excess chronic chlorogenic acid ingestion during long-term therapy can have a pro-oxidative response on the liver, kidney, and bone marrow.

Chlorogenic acid was explored for wound healing potential in experimental diabetic wounds of streptozotocin-induced diabetic rats that are characterized by delayed healing. This treatment accelerated wound healing by enhancing hydroxyproline production, decreasing malondialdehyde and nitric oxide content, along with elevation of reduced-glutathione levels. Chlorogenic acid decreased lipid peroxidation levels of organs.[77] Chlorogenic acid isolated from *Parrotia persica* (Hamamelidaceae) was assessed for wound repair and regenerative effects on keratinocytes, fibroblasts, and endothelial cells. Chlorogenic acid exhibited complementary pro-healing properties as evident by faster wound closure, keratinocyte turnover, and enhanced capillary-like blood vessel tube formation via endothelial cell regeneration.[78]

Curcumin [1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione] is the major curcuminoid present in many herbs, especially in the well-known Indian zest turmeric (*Curcuma longa* Linn.), which is one of the members from the ginger family (*Zingiberaceae*). Curcumin has been reported to have anticancer, antioxidant, antiviral, anti-inflammatory, and antifungal activities. Curcumin has hepatoprotective, nephroprotective, cardioprotective, neuroprotective, anticancer, antidiabetic, and antirheumatic properties.[79] Curcumin has been used for wound healing for ages in the traditional system of Indian medicine.

Curcumin treatment was demonstrated to increase re-epithelialization, neovascularization, cell migration, and collagen deposition on genetically diabetic mice wounds.[80] Curcumin can potentially reverse the keratinocytes, skin cells, and fibroblasts oxidative damage.[81] The anti-inflammatory and free radical quenching property of curcumin is attributed to NF-κB inhibition.[82] Curcumin can enhance the thermostability of wound collagen by getting integrated into the wound matrix. Curcumin accelerates gastric ulcer healing via reepithelialization, replenishing glutathione, inhibiting lipid peroxidation, and protein oxidation.[83] As reported by Jagetia and Rajanikant.[84-86] curcumin pretreatment enhanced collagen synthesis, hexosamine, and DNA turnover resulting in fast wound healing. Collagen deposition was also enhanced with increased fibroblasts and vascular density, resulting in improved radiation-impaired

wound contraction. Topically applied curcumin on rat full-thickness excision wounds enhances collagen synthesis along with antioxidant effects on cutaneous wounds.[87]

Curcumin at the 100 mg/kg dose induced vascularization in mice wounds.[88] Topical administration of curcumin improved collagen synthesis, epithelialization, wound tissue maturation and contraction, against indomethacin-induced gastric ulceration.[89] Kulac *et al.*[90] showed the Topical application of curcumin increased expression of skin tissues proliferating cell nuclear antigen on rats burn wound. Gadekar *et al.*[91] showed that curcumin transdermal patches effectively increase wound healing in epithelialization and wound contraction rate. Curcumin nanoparticles (lactic-co-glycolic acid) demonstrated potential re-epithelialization, granulation tissue formation, and anti-inflammatory properties on full-thickness excisional wounds.[92] The biodegradable thermosensitive hydrogel of curcumin prepared by Gong *et al.*[93] showed enhanced wound healing.

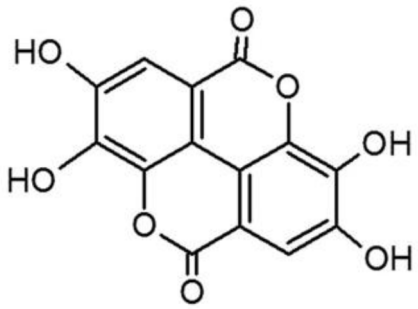
All these wound repair activities of curcumin is primarily attributed to its anti-inflammatory potential caused by inhibition of TNF-α, COX-2, and IL-1b, IL-8, and IL-6 expressions. Curcumin inhibits signal transducer and activator of transcription (STAT), cyclin D1, and NFkB signaling pathways, along with downregulation of the MMP-8 and acute phase proteins expression.[94] Anti-microbial and antioxidant properties of curcumin also contribute towards its wound healing effects. Curcumin induces tissue remodelling and vascular density by promoting granulation tissue formation, collagen deposition, and fibroblast proliferation.[95] Curcumin improves neovascularization, reepithelialization, and relocation of different inflammatory cells (like dermal myofibroblasts, fibroblasts, and macrophages) into the injury bed resulting in higher collagen turnover.[96] Curcumin suppresses the thrombogenic events associated with various pathological complicated wounds suppressing the early growth response-1 gene (Egr-1). Curcumin downregulates Egr-1 expression in endothelial cells and fibroblasts, which is the crucial regulator of vasculature and wound healing genes.[97]

Ellagic acid (4,4′,5,5′,6,6′-hexahydroxydiphenic acid 2,6,2′,6′-dilactone) is a natural polyphenol abundant as ellagitannins in raspberries, strawberries, grapes, pomegranates, nuts, and vegetables. It is the dilactone of hexahydroxydiphenic acid. This heterotetracyclic lactone is a member of catechols and polyphenols derived from gallic acid. Ellagitannins are hydrolyzable tannins that, via hydrolysis under acidic or alkaline conditions, can yield ellagic acid. In the human body, ellagic acid is biotransformed by the gut microflora from ellagitannins. Biological functions of ellagic acid include anti-inflammation, anti-proliferation, anti-angiogenesis, anticancer, antioxidative, inhibition of lipid peroxidation, and anti-apoptosis. Ellagic acid acts as an antioxidant, DNA topoisomerase inhibitor, tyrosinase inhibitor, glycogen phosphorylase inhibitor, glutathione transferase inhibitor, and a skin lightening agent.[98]

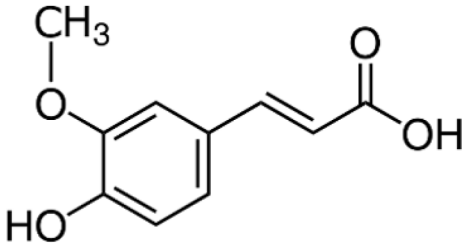
Ellagic acid isolated from standardized pomegranate rind extract was investigated on rat dermal wound models. Both standardized pomegranate rind extract and ellagic acid increased the tensile strength of rat dermal incision wounds. Ellagic acid promoted faster contraction of the excision and burn wound.[99] Primarizky *et al.*[100] reported that ellagic acid treatment has reduced collagen and PMN accompanied by moderate angiogenesis and fibrosis in incision wound healing process of rats. The results concluded that the topical application of ellagic acid ointment has a healing effect on incision wounds. Pomegranate extract containing 40% ellagic acid was evaluated on rat incised wounds by Yuniarti *et al.*[101] Treatment of 7.5% pomegranate for 14 days significantly accelerated the incision wound healing process. This finding was supported by improved collagen deposition, polymorphonuclear neutrophils infiltration in the wound area, angiogenesis, and a high degree of fibrosis.

Gaofu *et al.*[102] studied the effect of modified formulae for ellagic acid on wound healing and macrophage phenotype transformation in diabetic mice. Ellagic acid showed lower wound area and higher IL-12 and TNF-α mRNA with lower VEGF and TGF-βmRNA and protein levels. Inflammatory cytokines were lower in ellagic acid, while the growth factor was significantly higher. Ellagic acid decreases the M1 (macrophage) type inflammatory factors and improves the M2 type growth factors, which might be one of the mechanisms for wound healing. Currently, effective treatment is available for serious pathological hypertrophic scars. Hypertrophic fibroblasts are the primary effector cells for hypertrophic scar formation. The effect of ellagic acid on the fibrotic phenotypes of hypertrophic scar fibroblasts and its downstream signaling mechanism was

Ellagic acid



Ferulic acid



evaluated. Ellagic acid inhibited the proliferation, migration, and contraction of fibroblasts and enhanced collagen expression in hypertrophic scar fibroblasts dose dependently. Ellagic acid suppressed the Smad2/3 pathway and reversed Smad2/3 pathway activation induced by TGF-β1. Up-regulation of the fibrotic cellular phenotypes in hypertrophic scar fibroblasts was also observed. Ellagic acid exerts anti-fibrotic effects on hypertrophic scar fibroblasts by blocking the TGF-β1/Smad2/3 pathway indicating potential therapeutic application of ellagic acid in the treatment of hypertrophic scar.

Phenolic compound ferulic acid (4-hydroxy-3-methoxy cinnamic acid) is present in grains and fruits conjugated with mono, di, or polysaccharides. Ferulic acid is responsible for maintaining the color tone of green peas, protecting green tea from discoloration, and prevent oxidation of bananas from turning black and also reduce bacterial contamination.[103] Ferulic acid can inhibit melanin formation through competitive inhibition with tyrosine. The structure of ferulic acid is similar to tyrosine, enabling it to act as a potential pigmentation inhibitor. Ferulic acid can interrupt UV radiation induced peroxidative chain reactions in membrane phospholipids like Vitamin E. Ferulic protects human skin from UV irradiation. Ferulic acid is widely used in cosmetic formulations like sunscreen and whitening agents.[104]

Diabetic patients are more susceptible to skin infections and ulcers, which can cause gangrene. In diabetic patients, wound healing is compromised due to impairment of angiogenesis, neovascularisation, matrix metalloproteinases, keratinocyte, and fibroblast functions. Ferulic acid was evaluated for excision wound healing capability on streptozotocin-induced diabetic rats using. Ferulic acid treatment causes fast epithelization and increased hydroxyproline and hexosamine content. Ferulic acid effectively inhibited lipid peroxidation and increased catalase, superoxide dismutase, glutathione, and nitric oxide level, along with the serum zinc and copper content.[105]

Dwivedi *et al.*[106] explored the healing potential of ferulic acid on diabetic animal dermal wounds. The wound contraction percentage in rats treated with ferulic acid ointment was higher and was almost completely healed in 16 days. Ferulic acid also showed faster onset of granulomas and epithelialization. Ferulic acid is very safe to use with low toxicity. Prominent physiological actions of ferulic acid are anti-inflammatory, antioxidant, antimicrobial, anticancer, and antidiabetic effects. Ferulic acid has a protective function on skin keratinocytes, fibroblasts, collagen, and elastin.[107]

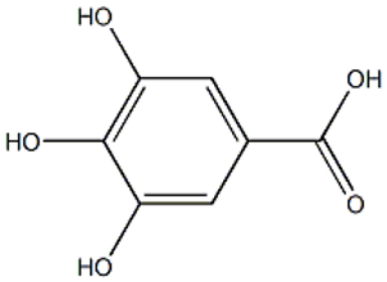
Gallic acid (3,4,5-trihydroxy benzoic acid) is classified as phenolic acid. Gallic acid exists both in free condition and also as a constituent of tannins, such as gallotannin. Gallic acid and its complexes commonly occur in every part of plants, i.e., bark, wood, leaf, fruit, root, and seed. Gallic acid is a secondary polyphenolic metabolite and a reputed natural antioxidant. It is a very important common antioxidant in tea and Ayurvedic herbal products. Gallic acid is useful in treating gastrointestinal, neurological, metabolic, and cardiovascular disorders.[108]

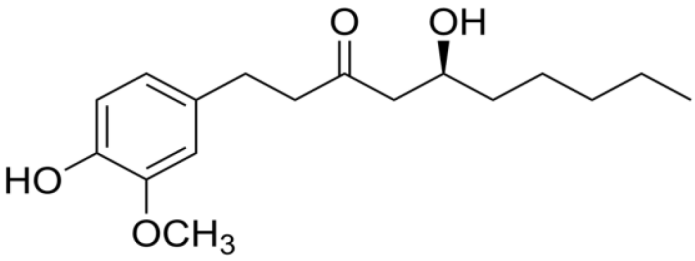
Yang *et al.*[109] studied gallic acid on normal and hyperglucidic conditions wound healing mimicking diabetic conditions in human keratinocytes and fibroblasts. This study revealed the potent antioxidant effect of gallic acid as it can upregulate the expression of antioxidant genes. Gallic acid accelerated keratinocytes and fibroblasts migration in both normal and hyperglucidic conditions. Gallic acid also activated the hallmarks of wound healing like focal adhesion, c-Jun N-terminal, and extracellular signal-regulated kinases. Effects of gallic acid were evaluated on an experimental palatal wound in rats. The Gallic acid treated group showed significantly lower wound area, and fibroblast cell counts. Gallic acid has decreased inflammatory cell counts and increased TGF-βl levels. Gallic acid in powder and liposome formulations increased fibroblast count and TGF-β expression and decreased the late inflammatory process in healing wounds.[110] *Terminalia bellerica* fruit extract and gallic acid showed healing properties in experimental hyperglycemic excision and dead space wound models. Oral gallic acid significantly improved wound contraction, scar size, and re-epithelialization period in the excision wound of streptozotocin induced diabetic rats. The hydroxyproline level was also enhanced with gallic acid treatment in diabetic dead space wounds.[111]

Gingerol

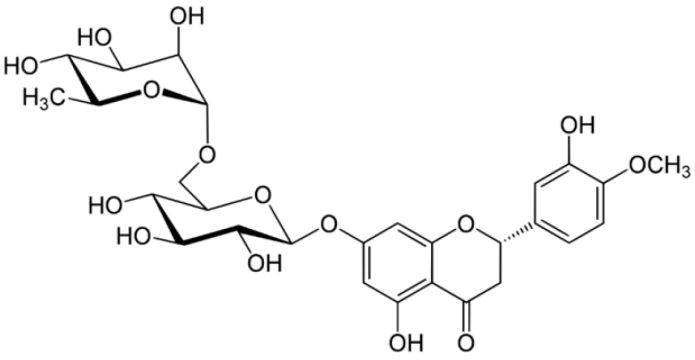
Ginger contains many phenolic compounds such as gingerol, shogaol, and paradol reported to exhibit antioxidant, anti-tumor, and anti-inflammatory properties. Gingerols are the most abundant pungent aromatic compounds in the fresh rhizome that can be of various chain lengths (6 to 10), with the most abundant being 6-gingerol. Gingerol [5-hydroxy-1-(4-hydroxy-3-methoxyphenyl) decan-3-one] is an active

Gallic acid

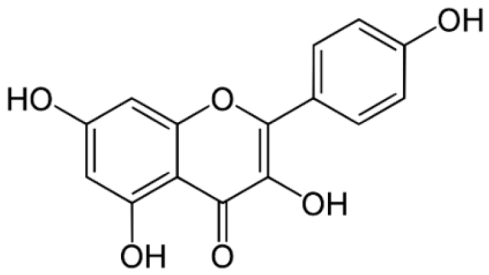




Hesperidin



Kaempferol



inhibitor of *M. avium* and *M. tuberculosis in vitro*. Gingerol isolated from ginger rhizome demonstrated antibacterial activity against periodontal bacteria.[112]

Topical treatment of curcumin–ginger extract increased collagen and decreased matrix metalloproteinase production in the recently healed skin of rats.[113] Orally administered 6-gingerol, 8-gingerol, and 10-gingerol at the dose of 35 mg/kg showed moderate reduction of wound size in the mice excisions wound model. The most effective one was 10-gingerol.[114] Two weeks of oral treatment of gingerol fraction has significantly shortened diabetic wound healing duration. Gingerol activated vascularization, fibrin deposition, and myofibroblasts in healing wounds, which helped in new tissue turnover and scar formation. Gingerol treatment is significantly associated with fibrin deposition, vascularization, and reepithelialization events. Anti-inflammatory property of gingerol promotes vascularization and new tissue formation during wound repair.[115]

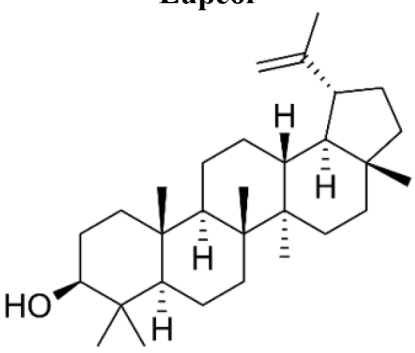
Hesperidin [(2S)-5-Hydroxy-2-(3-hydroxy-4-methoxyphenyl)-4-oxo-3,4-dihydro-2H-chromen-7-yl 6-O-(6-deoxy-α-L-manno-pyranosyl)-β-D-glucopyranoside] is chemically known as a flavanone glycoside. It is richly found in citrus fruits like lemon, sweet orange (*Citrus sinensis*), and grapefruits. Hesperidin has various biological and pharmacological actions like antioxidant, anti-inflammatory, antidiabetic and anti-carcinogenic activities.[116]

Topical application of different concentrations of hesperidin ointment in mice accelerated the healing of irradiated wounds DPPH, hydroxyl, superoxide, $ABTS^{\bullet+}$ and nitric oxide radical.[117] Hesperidin accelerates angiogenesis and vascularization in chronic diabetic foot ulcers by virtue of VEGF-c, Ang-1/Tie-2, TGF-β, and Smad-2/3 mRNA up-regulation, enhancing the healing process.[118] Hesperidin act as a radioprotector initiating angiogenesis by VEGF gene induction. Hesperidin stimulates epithelialization, collagen deposition, and enhanced cellular proliferation, accelerating wound healing on radiation-induced skin damage.[119] Jagetia and Rao[120] reported accelerated healing of irradiated wounds following oral hesperidin treatment. This response is mediated via enhanced collagen deposition, hexosamine, DNA, and nitric oxide synthesis. Increased densities of fibroblasts and blood vessels were also associated with wound tissue regeneration.

Studies have demonstrated multiple beneficial effects of hesperidin in wound repair. Hesperidin has UV protection, anti-inflammation, antioxidant, antimicrobial, anticancer, and skin lightening properties. Hesperidin improves epidermal homeostasis in young and aged skin, maintaining barrier permeability. Hesperidin activates cutaneous tissue functions by inhibiting MAPK-dependent signaling pathways and stimulating epidermal proliferation, differentiation, and lipid production.[121] Modulating VEGF, TNF-α, and IL-6 expression is reported to enhance angiogenesis following hesperidin treatment in foot ulcers[122] and incision wounds in diabetic rats.[123] Hesperidin loaded into alginate and chitosan hydrogels enhanced cell proliferation with better wound closure on the full-thickness dermal wound in the rat model.[124]

Kaempferol [3,5,7-Trihydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one], is a flavonoid also known as kaempferol-3 or kaempferide. Kaempferol is naturally present in tea, common vegetable, and fruits, including beans, gooseberries, broccoli, cabbage, citrus fruits, grapes, kale, strawberries, tomatoes, apple, brussel sprouts, and grapefruit. Kaempferol has a beneficial role in treating various acute and chronic inflammatory diseases and has antioxidative properties. Antioxidant activity of kaempferol is attributed to the inhibition of superoxide radical at low concentrations, which is associated with producing the most reactive oxygen and nitrogen species concerned with oxidative stress. The synergistic effect of kaempferol and its glycosides with antibiotics like methicillin,

Lupeol



rifampicin, clindamycin, erythromycin, and vancomycin against antibiotic-resistant bacteria is well known. Therefore, kaempferol could be used along with these drugs in the treatment of antibiotic resistance.[125]

Kaempferol decreases lipopolysaccharide induced TNF-α and IL-1 expression by escalating activated macrophages count and suppressing TNF-α mediates translocation of nuclear NF-κB p65.[126] Kaempferol is an effective topical wound repair drug effective in treating both nondiabetic and diabetic wounds.[127] Kaempferol can bind with VEGF, probably in the heparin binding domain. This binding potentiates the angiogenic functions of VEGF.[128]

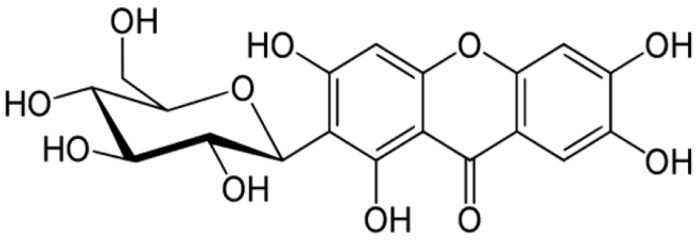
Lupeol [(3β,13ξ)-Lup-20(29)-en-3-ol; Clerodol] is a pentacyclic triterpenoid in which a hydroxy group substitutes the hydrogen at the 3 beta position. Lupeol is found in lupin seed skin, fig tree latex, and rubber plants. Lupeol occurs in a wide variety of plants, like mango, red alder (*Alnus rubra*), *Acacia visco,* or *Abronia villosa*. It is also found in many edible fruits, vegetables, and dandelion coffee. Lupeol is a lupine type triterpene that possesses several biological activities. Lupeol is a bioactive triterpenoid with complex pharmacology that displays different biological activities like antiprotozoal, antimicrobial, anti-inflammatory, antioxidant, antidiabetic, antitumor, chemopreventive, and wound healing.[129]

Chitosan-gelatin hydrogel film with entrapped lupeol was prepared by solution cast method crosslinking with glutaraldehyde. Antioxidant activity study confirmed that, like isolated lupeol, the lupeol entrapped chitosan-gelatin hydrogel film also has excellent antioxidant properties. The hydrogel can scavenge free radicals at a steadily increasing rate with time following the release of lupeol. Antibacterial activity of lupeol was retained while entrapped chitosan-gelatin hydrogel film, as evident by significant MIC in disc diffusion and cell viability with NIH/3T3 fibroblast assay. Chitosan/gelatin hydrogel film acted as an ideal delivery system for sustained release of lupeol, enhancing wound healing.[130]

Lupeol cream effectively enhanced the wound repair process in hyperglycemic rats. This activity was attributed to an anti-inflammatory response initiated via decreased inflammatory mediators like IL-6 (proinflammatory cytokine) and an increase in IL-10 levels (anti-inflammatory cytokine) on NF-κB signaling pathways. Histopathology also substantiated decreased inflammation with enhanced neovasculogenesis and fibroblasts proliferation. Lupeol enhanced the involvement of HIF-1α, FGF-2, and TGF-β1 in the repair site crucial for angiogenesis. Lupeol efficiently mediated fibroblast infiltration, proliferation, and migration at wound sites returning the wound tissue to its original state. In addition, lupeol also minimized oxidative stress by increasing Ho-1 and Sod-2 mRNA expression.[131]

Pereira Beserra *et al.*[132] investigated topically treated lupeol based cream on excision wound healing in the thoracolumbar area. Lupeol reduced the level of proinflammatory cytokines (TNF-a, IL-1β, and IL-6), NF-κB gene, and protein expression, whereas

Mangiferin

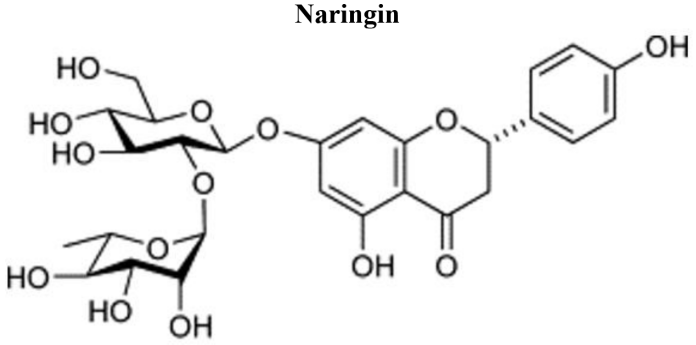


it positively altered IL-10 levels signifying anti-inflammatory effects. Lupeol promoted the proliferative phase by stimulating angiogenesis, VEGF, EGF, and increased TGF-β1 and Ki-67 gene expression. Lupeol aggravated tissue regeneration increasing collagen fibers synthesis. Lupeol cream showed potential cutaneous wound healing by regulating mechanisms involved in the inflammatory, proliferative, and tissue-remodelling phases.

Mangiferin [1,3,6,7-tetrahydroxyxanthone-C2-β-D-glucoside] is a xanthone glycoside predominantly obtained from the mango tree. Mangiferin has many pharmacological effects, including antioxidant, analgesic, anti-inflammatory, antidiabetic, neuroprotective, hepatoprotective, cardioprotective, antibacterial, antiviral, immunomodulatory, and anticancer action.[133] Mangiferin showed antibacterial activity against gram positive (*Bacillus pumilus*) and gram-negative bacteria (*Salmonella agona*) and also protected from harmful effects of *Enterococci* and *Mycobacterium tuberculosis*. Mangiferin possesses antifungal action against *Thermoascus aurantiacus*, *Aspergillus flavus*, and *Trichoderma reesei*.[134]

Mangiferin can permeate the stratum corneum and pass through the epidermis and dermis by reducing elastase and collagenase activity. The lipid and water distribution coefficient of mangiferin is relatively high, suggesting better absorption through the skin, while oral absorption is low.[135] Topical mangiferin reduces wound size and increases skin thickness surrounding the wound site. Topical mangiferin increased the expression of EGF, FGF, TGF-β, VEGF, MMP, and Nuclear factor erythroid 2-related factor 2 (Nrf2). Whereas expression of TNFα and NF-κB were decreased in diabetic wounds.[136] Mangiferin incorporated transfersomes, and glycoltransfersomes topical formulation protected fibroblasts

Naringin



from oxidative stress and stimulated proliferation on skin wounds *in vitro* and *in vivo*.[137]

Naringin (4',5,7-trihydroxy flavonone-7-rhamnoglucoside) is a flavanone-7-O-glycoside formed by the combination of flavanone naringenin and disaccharide neohespiridose. Naringin naturally exists in citrus fruits, especially in the skin of grapefruit and orange giving it the characteristic bitter taste. Naringinase enzyme widely occurs in nature, like in plants, yeasts, and fungi. Naringinase present in the human liver rapidly metabolizes naringin into naringenin. Naringin supplementation is beneficial for the management of obesity, diabetes, hypertension, cancer, and metabolic syndrome. Naringin is reported to have various pharmacological effects such as antioxidant, antimicrobial, anti-inflammatory, and antimutagenic activities.[138]

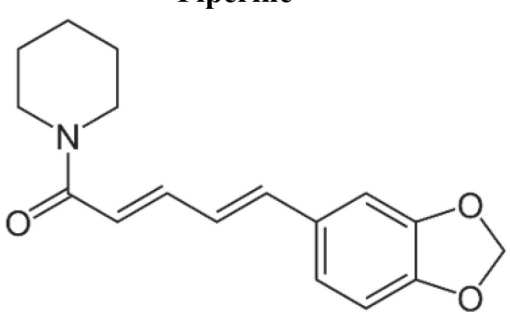
Soft paraffin-based cream containing naringin was evaluated for topical excision and incisions wound healing. Naringin balm application showed reduction in injury area and shortened epithelization period with enhanced wound contraction. Treatment significantly increases tensile strength, hydroxyproline content, and protein content. Treatment also causes down regulation of inflammatory (TNF-α, ILs, NF-κB) and apoptotic (pol-γ and Bax) mediators with upregulation of growth factor (VEGF and TGF-β) modulating collagen expression and angiogenesis.[139] Okur *et al.*[140] reported the wound healing potential of naringin gel on alloxan induced diabetic mice. The results also substantiate the weak antimicrobial effect of naringin. *In vivo* studies revealed enhanced wound contraction, re-epithelialization, granulation tissue thickness, and angiogenesis. Naringin gel effectively enhanced diabetic wound healing.

Piperine [(2E,4E)-5-(Benzo[d][1,3]dioxol-5-yl)-1-(piperidin-1-yl) penta-2,4-dien-1-one piperoylpiperidine] is a tertiary carboxamide and a piperidine alkaloid isolated from oleoresin part of *Piper nigrum* fruit. This alkaloid is responsible for the characteristic pungent taste of black pepper and long pepper. Piperine is widely used in the traditional Indian system of medicine. It is an NF-κB inhibitor, a plant metabolite, a food product, and a human blood serum metabolite. Piperine belongs to the vanilloid family of phytocompounds, including capsaicin, the pungent substance present in hot chili peppers. It has putative anti-inflammatory activity and can also promote digestive processes. Piperine exhibits antioxidant, anti-inflammatory, immunomodulatory, antiasthmatic, antiepileptic, antibacterial, antiamoebic, and anticancer activities. Various studies have reported the chemopreventive efficacy of piperine against cancer cells.[141,142]

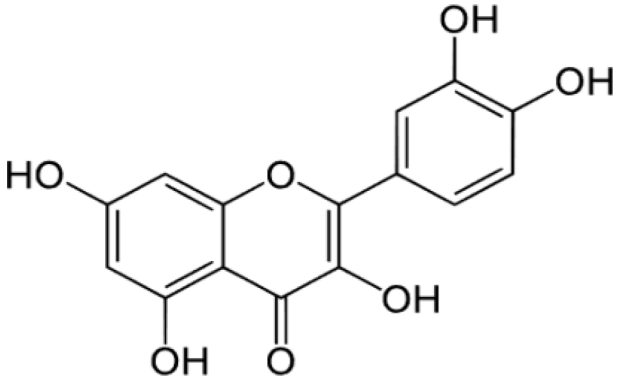
Pepper plants can be utilized as wound recuperating specialist as it has antibacterial, calming, cancer prevention agents, and antifungal movement. The injury recuperating capability of the pepper could be ascribed to the presence of flavonoids and triterpenes. Wound mending measure comprises a few phrases, in particular, i.e., intense irritation, cell multiplication, and development stage. During intense irritation, the expanding number of fibroblasts in the sore has a focal job in starting the recuperating interaction. Expanding the number of fibroblasts in the dermal tissue showed its mending capacity. The mending interaction of the wound region might be hampered by receptive oxygen stress delivered by micro-organisms or neutrophils in the injury region through a system that leads to DNA harm. Thus, antimicrobial and cell reinforcement specialists in the injury region significantly advance the mending interaction.[143] Nanofibrous dressings having structural resemblance with ECM were engineered by electrospinning and loaded with natural extracts of curcumin and piperine. This formulation endowed efficient antimicrobial, anti-inflammatory, and antioxidant activity to effectively treat chronic wounds. The antimicrobial efficacy of nanofibrous biomolecule load dressing was evaluated against *S. aureus* where it showed a minimum inhibitory concentration of 31.2-125 μg/mL.[144]

Quercetin [2-(3,4-dihydroxy phenyl)-3,5,7-trihydroxychromen-4-one] is the most abundant dietary flavonoid and an antioxidant flavonol generally present as Que glycoside. The Que aglycone conjugates with xylose, glucose, or rutinose in one of the Ques' hydroxyl groups and forms Que glycoside. Nutritional Que is available mainly as glycosides rather than as aglycones. It shows comparatively higher bioavailability compared to other glycosidic phytochemicals.[145] Quercetin is the most widely distributed and broadly found flavonoid in food sources, including natural products like vegetables, nuts, grapes, apples, onion, green tea, and

Piperine

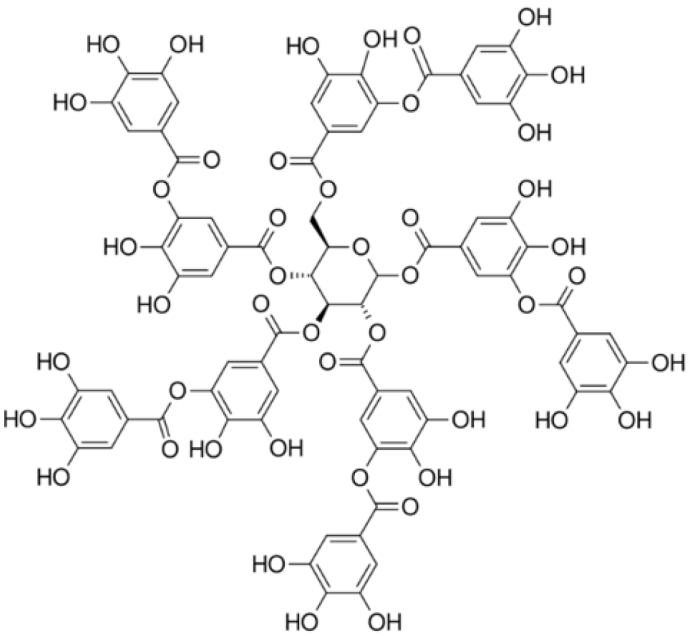


Quercetin



seeds. Pharmacological properties of quercetin are adaptogenic, antistress, anticancer, antidiabetic, anti-inflammatory, antimicrobial, antimutagenic, antinociceptive, antioxidant, antiulcer, cardio-protective, cytoprotective, hepatoprotective, hypolipidemic, neuroprotective and vasoprotective effects.[146]

Anjaneyulu and Chopra[147] reported the application of quercetin in pain management, particularly thermal hyperalgesia and cold allodynia. Quercetin upregulated VEGF via activating the key transcription factor of the VEGF gene, the HIF-1α.[148] Application of quercetin-incorporated collagen increases hydroxyproline contents of rat dermal excisional wounds[149] and rabbit bone regeneration.[150] Quercetin is effective for healing common mouth ulcers.[151] The antiallergic property of quercetin is attributed to histamine and other proinflammatory cytokines release inhibition from basophils and mast cells.[152] Quercetin alters cell interactions with the ECM via integrin expression regulation, in turn decreasing fibrosis.[153] Quercetin can suppress the MAPK pathway in pressure ulcers showing improved wound repair in ischaemia-reperfusion lesions.[154] Quercetin is a naturally-occurring antifibrotic agent, very efficient in diminishing scars after healing.[155] Quercetin can switch M1 macrophage to M2 phenotype polarization, which is responsible for its anti-inflammatory effect on repair of diabetic wound in rats.[156] Quercetin has the potential to alleviate atopic dermatitis related symptoms by virtue of its anti-inflammatory and antioxidant activities. Acceleration of wound healing was initiated via ERK1/2 MAPK and NF-κB pathways on *in vitro* immortalized human HaCaT keratinocytes.[157] Topical quercetin efficiently improves wound repair by reversing oxidative damage in wounds and modulating cytokines, growth factors, proteins, and inflammatory cells involved in healing.[158]



Tannic acid

Tannic acid [1,2,3,4,6-penta-O-{3,4-dihydroxy-5-[(3,4,5-trihydroxy benzoyl) oxy] benzoyl}-D-glucopyranose] is a polyphenolic compound. Tannic acid is a specific form of tannin called gallotannin, having weak acidity due to numerous phenol groups present in the chemical structure. This gallotannin is obtained by acylation of the hydroxy groups present in D-glucose by 3,4-dihydroxy-5-[(3,4,5-trihydroxy benzoyl) oxy] benzoic acid. Tannic acid is a mixture of polygalloyl glucose or polygalloyl quinic acid esters depending on the plant source used to extract the tannic acid. Commercially tannic acid is obtained from plant parts like pods of Tara (*Caesalpinia spinosa*), gallnuts of *Rhus semialata* or *Quercus infectoria* , and leaves of Sicilian sumac (*Rhus coriaria*). Tannic acid is commonly used for treating diarrhea, topically to dress burns, and in rectal diseases.[159]

Several mechanisms are responsible for the wound healing potential of tannins like free radical and reactive oxygen species scavenging, promotion of wound contraction, regeneration of capillary vessels, and fibroblast proliferation.[160] Water-soluble tannic acid can complex with macromolecules and metal ions, enabling its antioxidant, antimicrobial, and healing properties. These properties are targeted for developing technologies related to wound healing formulations.[161]

A carboxylated agarose/tannic acid hydrogel scaffolds cross-linked with zinc were fabricated, targeting a pH-controlled release of tannic acid. The hydrogels released very less tannic acid at neutral and alkaline pH, whereas acidic pH showed maximum swelling with sustained tannic acid release. The hydrogels exhibited antibacterial and anti-inflammatory activities and were free of cytotoxicity on fibroblast cell lines. Fibroblast cell lines exposed to tannic acid hydrogel expressed higher cell migration and proliferation in simulated wound assays. The hydrogel suppresses stimulated human macrophage production in a concentration-dependent manner, indicating potential anti-inflammatory activity. The cytocompatibility, antibacterial, and anti-inflammatory properties of this novel pH-sensitive tannic acid hydrogel signify its promising role in wound dressings.[162]

Tannic acid silver nanoparticles exhibited antibacterial activity against *Pseudomonas aeruginosa*, *S. aureus,* and *E. coli*. Nanoparticles stimulated *in vitro* keratinocytes migration. It has enhanced epithelialization, angiogenesis, and granulation tissue formation in splint wounds of mice, along with fast wound closure. Tannic acid silver nanoparticles prompted expression of VEGF-α, PDGF-β, and TGF-β1 cytokines involved in wound repair. Lymph node assay further substantiates that tannic acid nanoparticles have strong anti-inflammatory response during wound healing applied topically on damaged skin.[163] Multifunctional hemostatic tannic acid microparticles were prepared using tannic acid as an effective cross-linker. Microparticles showed rapid hemostasis and excellent antibacterial activity over the healing process. Microparticles

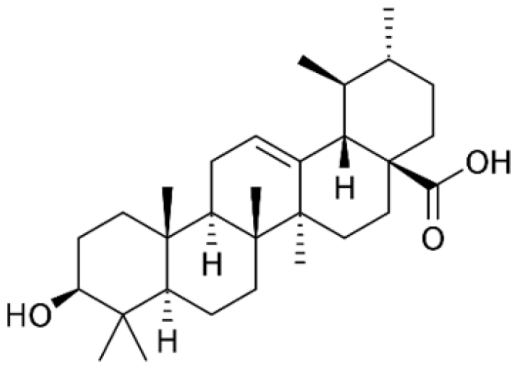
exhibited broad-spectrum antibacterial activity against *E. coli* and *S. aureus*.[164] Rat cutaneous skin wounds were topically treated with purified tannic acid until closure to explore dose specific response on fibroblast proliferation and protein expression. Tannic acid caused faster wound healing, accelerated re-epithelialization, and increased growth of hair follicles. The levels of growth factors like bFGF, TGF-β, and VEGF increased, whereas IL-1 and IL-6 content decreased.[165]

A multifunctional silk fibroin and tannic acid hydrogel exhibited advantages in the wound repair process, such as short gelation time, low gelation concentrations, good adhesiveness, shear-thinning, and self-recovery properties. The incorporation of tannic acid in the hybrid hydrogel enables it with remarkable antimicrobial and antioxidant bioactivity to heal wounds. Hybrid hydrogel significantly accelerated wound repair process in mice with full-thickness skin defects.[166] A biocompatible composite hydrogel was developed by incorporating tannic acid and $MgCl_2$ into bacterial cellulose. The Mg^{2+} cross-link impedes tannic acid released from bacterial cellulose matrix, while a composite of bacterial cellulose-tannic acid can lack Mg^{2+} ionic cross-links releasing more tannic acid from the hydrogel. The bacterial cellulose-tannic acid-Mg composites showed profound antibacterial activity against *S. aureus*, *E. coli,* and *P. aeruginosa*. The bacterial cellulose-tannic acid-Mg composites came out to be a very promising alternative for combating biofilm-associated infections.[167]

Aliabadi *et al.*[168] investigated the regenerative properties of chitosan-tannic acid incorporated bleach kraft nanocellulose. The rigidity of this film was increased with the formation of lamellar structure when incorporated with tannic acid due to strong hydrogen bonding. Complexing with chitosan presented a good release profile of tannic acid compared to pure cellulose. In addition, the film exhibited good thermal stability with antibacterial activity against *S. aureus* and *E. coli*. It also showed good cellular viability while inhibiting NF-κB activity. A tannic acid-thioctic acid supramolecular hydrogel was formed with successful intermolecular crosslinking. X-ray photoelectron spectroscopy confirmed the formation of successful intermolecular crosslinking. The formation of multiple hydrogen bonds between polyphenol and carboxyl groups enabled the hydrogel with self-healing and injectable properties. Applied as an adhesive for skin wounds, the tannic acid–thioctic acid hydrogel exhibited faster healing time and enhanced regeneration in wound tissue compared with suture application. Hydrogel showed antibacterial activity against Methicillin-resistant *S. aureus* in burn wound infection.[169]

Li *et al.*[170] developed a multifunctional tannic acid-chelated iron-molybdenum disulfide nanosheets based hydrogel for treating infected wounds. This nanosheet hydrogel showed potent antibacterial activity against *E. coli* and *S. aureus*. The response is attributed to photothermal therapy like peroxidase and catalase activity, glutathione loss, and abundant oxygen supplementation.

Ursolic acid



Peroxidase like activity was primarily due to molybdenum disulfide nanosheets, while tannic acid /iron complex was responsible for catalase like activity. Tannic acid chelation with iron and conjugation with molybdenum disulfide nanosheets provided the hydrogel with outstanding anti-oxidant ability. The hydrogel was able to scavenge redundant reactive oxygen and nitrogen species under a neutral environment maintaining antioxidant systems balance, thus preventing inflammation. Moreover, tannic acid boosted the hydrogels with anti-inflammatory activity, inhibiting inflammatory factors released from macrophages. The dynamic boron ester bonds between tannic acid-chelated Fe-decorated molybdenum disulfide nanosheets, polyvinyl alcohol, dextran, and borax provided the hydrogel with multiple biological functions. These include excellent tissue-adhesive ability, fast self-healing, and rapid adaptivity with wound shape. The hydrogel facilitated infected wound healing by killing bacteria, promoting cell proliferation, reducing inflammation, enhancing oxygenation, scavanging free radicals, and angiogenesis during the wound healing cascade.

Ursolic acid (3β-hydroxyurs-12-en-28-oic acid) is a triterpenoid widely found in apple, bilberry, cranberry, elderflower, peppermint, lavender, oregano, thyme, hawthorn, prunes, spices, leaves, blossoms, and many other natural products. It is especially abundant in apple peel. Ursolic acid is a lipophilic pentacyclic triterpenoid, a hydroxy monocarboxylic acid. It derives from a hydride of a ursane. It shows a variety of potential pharmacologic activities such as cell regeneration, antibacterial, antifungal, hepatoprotective, immunomodulatory, antitumor, chemopreventive, cardioprotective, antihyperlipidemic, and hypoglycemic effects. Ursolic acid can benefit muscle atrophy wasting, acting as small-molecule inhibitor of skeletal muscle in mice.[171]

Leaves of *Lantana camara* L. are traditionally used for healing cuts, swellings, and burns. Ursolic acid stearoyl glucoside (isolated from *L. camara*) treated animals exhibited a significant reduction in wound area in excision and incision wounds of rats.

Wounds showed faster epithelization as compared to controls. A significant increase in granuloma breaking strength was observed when compared with the control group. The Ursolic acid stearoyl glucoside had considerable wound healing activity.[172] Ursolic acid isolated from *Clematis gouriana* Roxb. was subjected to *in silico* glycogen synthase kinase 3-β protein kinase inhibition ability. Ursolic acid showed significant excision, incision, and dead space wound healing activity in rats. Skin-breaking strength, granulation tissue weight, tensile strength, and hydroxyproline content were increased. Ursolic acid showed decreased accumulation of macrophages at the site of injury.[173] Wound healing activity of ursolic acid isolated from *Plantago major* was assessed on hyperglycemic rats applied topically on dorsal wounds. Ursolic acid increases the percentage of the healed area and accelerates healing time.[174]

Poly (L-lactic acid) lipid-core nanocapsules containing ursolic acid were evaluated for the healing potential of skin damage caused by a hormonal deficiency in ovariectomized rats. Treatment with ursolic acid nanocapsules resulted in faster wound contraction, angiogenesis, and collagen deposition with a reduced inflammatory response. Ursolic acid entrapped lipid-core nanocapsules are a suitable option for treating skin damage triggered by decreased estrogen levels in menopause.[175] Babu *et al*.[176] prepared ointment with ursolic acid rich chloroform extract of *H. herbacea*. Healing efficacy was assessed on incision and excision wounds of rats. The high rate of wound contraction, tensile strength, total protein, hydroxyproline, hexosamine, and hexuronic acid content was found in animals treated with ointment. Histopathological studies of the wound tissue of the ointments treated animals revealed the effectiveness of ursolic acid in wound repair Table 1.

Wound healing is a multifaceted and complex process involving several inflammatory cells like neutrophils, macrophages, lymphocytes, keratinocytes, fibroblasts, and endothelial cells in conjugation with various components of proinflammatory and anti-inflammatory mediators. The impacts of these elements may not be distinctive at the same time, but disruption with one or more elements can impair wound restoration timeline by affecting different phases of wound healing and, in general, the final results of the healing cascade. Naturally derived substances and photochemical have promising impacts on wound repair and enhance the skins natural regeneration mechanisms. Phytochemicals are very useful for managing and treating microbial contaminated infectious wound repair.

Flavonoid and polyphenolic compounds like curcumin, hesperidin, quercetin, caffeic acid, catechin, and chlorogenic acid are the most widely investigated natural wound healing compounds. They accelerate angiogenesis, vasculogenesis, epithelialization, collagen deposition, hexosamine, growth factors, and epidermal proliferation along with antioxidant, anti-inflammatory, and antimicrobial properties. Tannic acid (tannin), asiatic acid, and asiaticoside (triterpenoid) found in Brahmi are very potent wound healers extensively studied on the molecular level of various wound models.

When an injury is covered with a dressing, it constantly helps the damaged tissue to get exposed to proteinases, chemotactic, supplements, and development factors. So during the late twentieth century, the use of occlusive dressing started to provide moist climate in the wounds. These dressings help in quicker re-epithelialization, collagen deposition, advancement of angiogenesis, and decrease wound bed pH, which promptly decreases the chances of wound infection. Modern interactive dressings, including films, foams, hydrogels, and semi-occlusive or occlusive hydrocolloids loaded with bioactive components offer excellent wound hydration. Phytocompounds are well known for their chemopreventive activity and are beneficial for treating various skin diseases. Phytochemicals applied topically have the potential to augment tissue remodelling and also act as proangiogenic. The extensively studied pathway through which bioactive phytochemicals exert potential wound healing effect is modulation of NF-κB expression. NF-κB induces various pro-inflammatory genes responsible for the expression of cytokines and chemokines. NF-κB plays crucial role in regulating the survival, activation, and differentiation of immune and inflammatory cells in wound tissue. Inhibiting NF-κB pathway, phytochemicals reduce inflammation and promote wound healing by increasing collagen content and decreasing glycosaminoglycan synthesis. Phytochemicals also affect *TGF*-β, TGF-β, and FGFs expression resulting in enhanced proliferation and infiltration of activated fibroblasts in the wound areas.

Asiaticoside silk nanofiber hydrogels, biodegradable thermosensitive hydrogel of curcumin, hesperidin loaded alginate and chitosan hydrogels, lupeol entrapped in chitosan-gelatin hydrogel films, pH-sensitive tannic acid hydrogels, and tannic acid multifunctional hemostatic microparticles, all have shown remarkable wound healing activity due to antibacterial and anti-inflammatory properties. Tannin was the most extensively explored phytocomponents incorporated in various types of state-of-the-art wound dressing like supramolecular hydrogel and chelated iron-decorated molybdenum disulfide nanosheets hydrogel, having excellent infected wound healing property.

Huge popularization of herbs and phytoconstituents is warranting to explore clinical efficacy from the therapeutic point of view. More clinical studies are needed to be conducted to assess the safety and therapeutic efficacy of these wound healing phytoconstituents as these compounds can have splendid preventive and curative utilization in wound repair. Considering the current scenario, future studies should focus on isolation, characterization, and pharmacological evaluation of phytoconstituents for the treatment of various types of wounds and injury and, more specifically, incorporated in dressings. The perfect blending of conventional and modern knowledge will be beneficial in developing novel and effective therapeutic delivery systems for skin regeneration and wound repair. Wound

Table 1: Diverse wound healing mechanism of plant derived bioactive phytocompounds.

Chemical class	Phyto-compound	Source	Wound healing mechanism	Reference
Alkaloid	Berberine	Plants of Berberis (*Berberis vulgaris*, *B. aristata*, *Mahonia aquifolium*, *Coptis chinensis*)	Antifungal, antibacterial, antiinfective, anti-inflammatory, antioxidative, inhibit expression of NF-κB, TNF-a and IL-6, activate TrxR1, restore redox homeostasis.	[49]
	Piperine	*Piper nigrum* (Black Pepper, Kali mirch)	Antioxidant, anti-inflammatory, antimicrobial, immunomodulatory, NF-κB inhibition, fibroblast proliferation.	[143,144]
Flavonoid	Hesperidin	Citrus fruits like *Citrus sinensis* (orange), Suchas lemon, grapefruits, lemon, tangerines	Anti-oxidant, anti-inflammatory, antimicrobial, accelerate angiogenesis and vasculogenesis, up-regulation of VEGF-c, Ang-1/Tie-2, and Smad-2/3 mRNA expression, promote angiogenesis, stimulates epithelialization, collagen deposition, and enhanced cellular proliferation, hexosamine, and DNA, increase density of fibroblasts and blood vessels, inhibition of MAPK-dependent signalling pathways, stimulation of epidermal proliferation.	[117-124]
	Kaempferol	Tea, beans, gooseberries, broccoli, cabbage, citrus fruits, grapes, kale, strawberries, tomatoes, apples, brussel sprouts, grapefruit	Antioxidant, activate macrophages, suppression of NF-κB p65, promote angiogenesis via VEGF.	[126-128]
	Quercetin	Vegetables, nuts, grapes, apple, onion, green tea and seeds.	Antioxidant, anti-inflammatory, antimicrobial, upregulate VEGF and HIF-1α, increase hydroxylproline content, inhibition of proinflammatory cytokines, decrease in fibrosis via regulation of integrin expression, suppress MAPK pathway, antifibrotic, diminishes scar formation, accelerate expression of ERK1/2 MAPK and NF-κB, promote keratinocyte proliferation.	[147,148,150-158]
Glycoside	Mangiferin	Mango tree	Antioxidant, anti-inflammatory, antimicrobial, antifungal, fibroblasts proliferation, increase expression of EGF, FGF, VEGF, MMP and Nrf2, decrease NF-κB.	[136,137]
	Naringin	Citrus fruits especially in the skin of grapefruit and orange	Antioxidant, antimicrobial, anti-inflammatory, antimutagenic, increases tensile strength, hydroxyproline content, and protein content, modulate collagen expression, angiogenesis, re-epithelialization.	[139,140]
Organo-sulfur compound	Allicin	*Allium sativum* (Garlic cloves)	Fibrocytes and fibroblasts proliferation, angiogenesis, increased collagen density, increased mononuclear cell infiltration, antibacterial, antifungal.	[24-26]

Table 1: Cont'd.

continued...

Chemical class	Phyto-compound	Source	Wound healing mechanism	Reference
Polyphenol	Caffeic acid	Espresso, wine, tea, and famous medications, for example, propolis	Antioxidant, anti-inflammatory, increase collagen synthesis, fibroblast proliferation, inhibited PGE_2 production and histamine release.	[53-58]
	Catechin	Green tea, fruits, red wine, beer, cacao liquor, chocolate, cocoa	Antioxidant, anti-inflammatory, antibacterial, promote angiogenesis, promote cell proliferation, inhibition of fibroblasts migration, fibroblasts proliferation, promote apoptosis.	[67-71]
	Chlorogenic acid	Coffee and black tea	Antioxidant, immune stimulant, proliferation of cytotoxic T-lymphocytes, macrophages, and natural killer cells, increase epithelialization rate, promote cellular proliferation, upregulate TGF-β1, elevate collagen IV synthesis, increase collagen production, enhanced hydroxyproline content, enhance capillary-like tube formation of endothelial cells, promote angiogenesis.	[73-78]
	Curcumin	*Curcuma longa* Linn. (curcumin, haldi)	Anti-microbial, antioxidant, anti-inflammatory, antifungal, increase re-epithelialization, increase neovascularization, increase deposition of collagen, NF-κB inhibition, increase thermostability of collagen, promote re-epithelialization, enhances synthesis of collagen, hexosamine, DNA, and nitrate, improved collagen deposition, increase fibroblasts, improve vascular density, improved collagen synthesis and maturation, wound contraction, proliferating cell nuclear antigen, downregulation of MMP-8 expression and acute phase proteins, improved neovascularization, increased relocation of dermal myofibroblasts, fibroblasts, and macrophages, downregulation of early growth response-1 gene.	[80-97]
	Ellagic acid	Raspberries, strawberries, grapes, pomegranates, nuts and vegetables	Anti-inflammatory, antioxidant, promote angiogenesis and fibrosis, improvement of collagen deposition and polymorphonuclear neutrophils infiltration, promote fibrosis, lower VEGF, TGF-βmRNA and proteins levels, inhibited proliferation, migration, and contraction of fibroblasts and collagen expression, suppress Smad2/3 pathway, up-regulation of the fibrotic cellular phenotypes.	[99-102]

Table 1: Cont'd.

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Chemical class	Phyto-compound	Source	Wound healing mechanism	Reference
	Ferulic acid	*Ferula communis* L. (fennel), grains, fruits, and vegetables	Antioxidant, anti-inflammatory, antimicrobial, promote epithelization, increase hydroxyproline and hexosamine content, protective role on keratinocytes, fibroblasts, collagen, and elastin, increment in the serum zinc and copper levels.	[105,107]
	Gallic acid	Bark, wood, leaf, fruit, root and seed of bearberry, pomegranate, gallnuts, sumac, witch hazel, tea, oak	Antioxidant, anti-inflammatory, accelerate cell migration of keratinocytes and fibroblasts, promote re-epithelialization, increase hydroxyproline, activate focal adhesion kinases, c-Jun N-terminal kinases, and extracellular signal-regulated kinases.	[109,111]
	Gingerol	Rhizome of *Zingiber officinale* (ginger)	Antioxidant, anti-inflammatory antimicrobial, increase collagen and decrease matrix metalloproteinase production, activated vascularization, fibrin deposition, and myofibroblasts synthesize, fibrin deposition, vascularization, and re-epithelialization process.	[113-115]
Tanin	Tannic acid	*Caesalpinia spinosa* (Tara pods), *Rhus semialata* (gallnuts), *Quercus infectoria* (Aleppo oak), *Rhus coriaria* (Sicilian sumac leaves)	Antioxidant, anti-inflammatory, antimicrobial, promote angiogenesis, proliferation of fibroblasts, migration and proliferation of macrophages, promote tissue proliferation, stimulated migration of keratinocytes, promote epithelialization, increase bFGF, TGF-β, and VEGF levels, inhibit NF-κB activity.	[118,160-170]
Tri-terpenoid	Asiatic acid	*Centella asiatica* (Bhahmi, Mandukparni)	Anti-inflammatory, increase proinflammatory mediators, antioxidant, promote superoxide dismutase, reduce malondialdehyde, fibroblasts proliferation, promote angiogenesis, remodelling of extracellular matrix, apoptosis inhibition, inhibition of caspase-3, inhibition of TGF-1-induced collagen expression, promote collagen I synthesis, inhibit PAI-1 expression, antiglycative activity, promote epithelization, hydroxyproline synthesis.	[30-36]

continued...

Table 1: Cont'd.

Chemical class	Phyto-compound	Source	Wound healing mechanism	Reference
	Asiaticoside	*Centella asiatica* (Bhahmi, Mandukparni)	Anti-inflammatory, promote angiogenesis, increases collagen content, improves tensile strength, increases hydroxyproline content, promote epithelization, proliferation of collagen inducing cell, induces type I and III collagen synthesis fibroblasts proliferation, increase monocyte chemoattractant protein-1 production, vascular endothelial growth factor, increased Col1A1 mRNA expression.	[39-44]
	β-carotene	Provitamin A (red-orange pigmented fungi, plants, and fruits)	Antioxidant, increase epithelial tissue turnover, collagen synthesis, protect collagen degradation, increase fibronectin activity, stimulate macrophages, control macrophagic inflammation, regulate growth and differentiation of skin epithelial cell, stimulates epidermal turnover, increases rate of re-epithelialization, restores epithelial structure, promote collagen-I and fibronectin, induce proliferation of keratinocytes and fibroblasts.	[59-61,64]
	Lupeol	Lupin seeds, latex of fig tree, rubber plant, fruits like mango, red alder (*Alnus rubra*), *Acacia visco*, *Abronia villosa*, dandelion coffee, vegetables	Antioxidant, antiprotozoal, antimicrobial, anti-inflammatory, promote NIH/3T3 fibroblasts, increase proinflammatory cytokine and inhibit anti-inflammatory cytokine, promote neovasculogenesis, proliferation of fibroblasts, angiogenesis, decrease NF-κB expression, immunostaining of Ki-67 gene expression, immunolabeling VEGF and EGF, increase synthesis of collagen fibers.	[130-132]
	Ursolic acid	Apples, bilberries, cranberries, elder flower, peppermint, lavender, oregano, thyme, hawthorn, prunes, spices, leaves, blossoms and many other natural products	Antibacterial, antifungal, promote granulation tissue growth, inhibit glycogen synthase kinase 3-β protein kinase, increase skin-breaking strength, increase weight of granulation tissue and hydroxyproline content, increase collagenation, decrease accumulation of macrophages, elevate total protein, hydroxyproline, hexosamine, and hexuronic acid content.	[172-176]

healing studies on phytocompounds were extensively reviewed, unraveling the effect on wound modulation pathways, molecular targets, and novel mechanisms through which phytochemicals induce affect on wound repair and skin regeneration. Identifying molecular targets for phytochemicals and exploring interaction mechanisms with complex wound related mediators will help future clinical studies to develop bioactive phytochemicals as therapeutic agents.

CONCLUSION

Therefore, it is imperative to study potential photycomponents available in the vast natural resources to explore therapeutically in the best possible way. Phytomedicines are comparatively affordable and safe than synthetic drugs. Bioactive phytochemicals should be identified and formulated to treat and manage wounds. However, it is also associated with a need for standardization, safety evaluation, and scientific validation before recommending phytochemicals for therapeutic purposes. This review comprehensively investigates different phytocompound categories, including individual potential compounds with wound healing efficacy and mechanism. Phytocompounds reported for wound healing properties have antimicrobial, antioxidant, and anti-inflammatory properties, encouraging faster healing, fighting infection, and accelerating tissue proliferation. Impairment of pro-oxidant/antioxidant balance in chronic wounds occurs due to extensive oxidative stress leading to harmful delays in healing process. Delicate balance is vital between oxidative stress and endogenous antioxidant defense system for natural wound healing with redox control. Phytocompounds like curcumin, caffeic acid, chlorogenic acid, lupeol, and tannic acid can act as excellent wound healers due to their superb antioxidant capacity.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest

ABBREVIATIONS

Ang: Angiopoietin; **bFGF:** Basic FGF; **CAM:** Cell bond particles; **Col1A1:** Collagen Type I Alpha 1 Chain; **COX:** Cyclooxygenase; **DNA:** Deoxyribonucleic acid; **ECM:** Extracellular matrix; **EGF:** Epidermal growth factor; **Egr-1:** Early growth response-1 gene; **FGF:** Fibroblast growth factor; **HB-EGF:** Heparin-binding; **HIF:** Hypoxia inducible factor; **IFN:** Interferon-gamma; **IGF:** Insulin-like growth factor; **KGF:** Keratinocyte growth factor; **IL:** Interleukin; **MAPK:** Mitogen-activated protein kinase**; MCP:** Monocyte chemoattractant protein; **MIC:** Minimum inhibitory concentration; **MIP:** Macrophage inflammatory protein; **MMP:** Metalloproteinase; **mRNA:** Messenger ribonucleic acid; **NF-κB:** Nuclear factor kappa B; **NO:** Nitric oxide; **Nrf2:** Nuclear factor erythroid 2-related factor 2; **OGD/R:** Oxygen-glucose deprivation/re-oxygenation; **PDGF:** Platelet-derived growth factor; **qRT-PCR:** Real-Time Quantitative Reverse Transcription; **ROS:** Reactive oxygen species; **RT:** Reverse transcription; **STAT:** Signal transducer and activator of transcription; **TGF:** Transforming growth factor; **TIMP:** Tissue inhibitors of metalloproteinase; **TNF:** Tumor necrosis factor; **TrxR1:** Thioredoxin reductases; **VEGF:** Vascular endothelial growth factor; **α-SMA:** Smooth muscle alpha-actin.

Authors' contributions

Papiya Bigoniya conceived the idea, Manisha Khaire researched the literature and wrote the manuscript, Papiya Bigoniya reviewed and revised the manuscript, Jagriti Bigoniya performed visualisation duties and graphical work. All authors read and approved the manuscript.

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