Review Article

Wound Healing Potential of Some Medicinal Plants

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ABSTRACT

Wound healing is the process by which skin repairs itself. Wound healing can be divided into 4 phases: haemostasis, inflammation, proliferation, and remodelling. In humans, keratinocytes re-form a functional epidermis (re-epithelialization) as rapidly as possible, closing the wound and reestablishing tissue homeostasis. Dermal fibroblasts migrate into the wound bed and proliferate, creating granulation tissue rich in extracellular matrix proteins and supporting the growth of new blood vessels. Ultimately, this is remodelled over an extended period, returning the injured tissue to a state similar to that before injury. Dysregulation in any phase of the wound healing cascade delays healing and may result in various skin pathologies, including non-healing, hypertrophic scarring and chronic ulceration. Various plant products have been used in the treatment of wounds over the years. Recognizing the important role of traditional plants, we have undertaken an extensivesurvey of literature reporting the use of medicinal plants for wounds. We describe the active ingredients, bioactivities, clinical uses of 8 medicinal plant species. Several species including *curcuma longa*, honey, *Terminalia chebula*, *Aloe vera*, *Centella asiatica*, *Arctium lappa*, *Commiphora myrrha*, showing wound healing activities by their anti-inflammatory and antioxidant mechanisms.

Keywords: Transforming growth factor beta 1 ECM, Extracellular matrix, Interleukin-1, Matrix metallo proteases, Tumour necrosis factor-α, Natural factor kappa B, inducible nitric oxide synthase.

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INTRODUCTION

Wounds are disruptions to the continuity of cells due to a physical, chemical, thermal, infectious or immunological injury to the skin. Effective wound healing is defined by the restoration of functional tissue integrity. Proper wound healing is achieved by adequate activation and infiltration of inflammatory cells, neutrophils and macrophages, which produce pro-inflammatory cytokines such as tumor necrosis factor α (TNF-α) and interleukin-1 (IL-1)[1]. These inflammatory cytokines result in the activation of growth factors such as transforming growth factor (TGF)-β, and several fibroblast growth factors, resulting in the proliferation and infiltration of activated fibroblasts to the wound site[1]. However, these natural healing process is impaired with aging, obesity, and endocrine abnormalities such as diabetes mellitus[2].

wound healing is the process by which skin repairs itself following injury caused by surgery trauma and burns. The healing process is classically divided into 4 phases: coagulation (a.k.a. haemostasis), inflammation, proliferation (a.k.a. granulation), and remodelling (a.k.a. maturation)[3]. Upon injury, a fibrin clot rapidly forms to restore haemostasis[4,5]. Platelets present in the blood trigger the clotting cascade and secrete several growth factors, initiating wound healing[6]. In the following inflammation phase, neutrophils migrate into the wound site engulfing foreign debris and killing bacteria by phagocytosis and releasing proteolytic enzymes[6,7]. Coincidently, blood monocytes infiltrate the injury site and differentiate into macrophages, releasing proteases to debride the wound[6], and secrete a mixture of bioactive molecules, including transforming growth factor beta 1 (TGF-β1), that stimulates the migration of fibroblasts and epithelial cells[8]. The proliferation phase usually starts about 3 days after wounding; it involves diverse activities including angiogenesis (by endothelial cells), granulation tissue formation (by fibroblasts), and re-epithelialization (by keratinocytes)[9,10]. In this stage, fibroblasts produce a large amount of extracellular matrix (ECM), mainly collagen, to form the granulation tissue which replaces the damaged tissue. Meanwhile, the keratinocytes migrate, proliferate, differentiate, and re-form a functional epidermis (re-epithelialization), closing the lesion and protecting underlying tissues from further trauma[11]. As the wound matures, the characteristic disorganized ECM of granulation tissue is actively remodeled by the dermal fibroblast cell population[12], whose numbers are progressively reduced through apoptosis[13]. The outcome of wound healing is scar tissue (aka fibrosis) with sparsely distributed fibroblasts within a collagen-rich ECM.

Compared to the original tissue, scar tissue, having distinct texture and reduced biomechanical and functional properties, is characteristically altered[14].

CLASSIFICATION OF WOUNDS

Wounds are generally classified according to the underlying cause of the development of wounds.

Acute wounds

In acute wounds, there is tissue damage/injury that generally occurs through an orderly and time-reparative phase that results in the anatomical and functional integrity being restored sustainably. Acute wounds are typically caused by the cuts or surgical incisions[15].

Closed wounds

The blood escapes from the circulatory system in closed wounds but stays inside the body. Itbecomes evident in the form of bruises.

Open wounds

Blood leaks from the body through an open wound and bleeding is clearly noticeable. The open wound may be further divided into categories according to the source causing the wound.

Incised wounds

This is a wound with no loss of tissue and minor damage to tissue. It is caused primarily by sharp objects like a scalpel or knife.

Tear or laceration wounds

This is the non-chirurgical injury in conjunction with other types of trauma which results in tissue loss and damage.

Puncture wounds

These are caused by an object like a nail or a needle, which punctures the skin. Since dirt may penetrate deep into the wound, chances of infection are common on them.

Abrasive or superficial wounds

Sliding slip onto a rough surface induces abrasion. During this time, abrasion is scrapped off the top layer of the skin, i.e., epidermis which exposes nerve endings resulting in a painful injury.

Penetration wounds

Penetration wounds are chiefly caused by an object like a knife going in and out of the skin.

Gunshot wounds

They are typically produced by bullet or similar projectile which drives through or into the body.

Chronic wounds

Chronic wounds are the wounds that have not gone through the usual healing stages and hence reach a state of pathologic inflammation. They need extended healing time[16].

FACTORS AFFECTING WOUND HEALING

Oxygenation

Oxygen is essential for the metabolism of cells, particularly the production of energy through ATP, and is necessary for almost all wound healing processes. It protects wounds from infection, causes angiogenesis, increases differentiation of keratinocytes, migration and re-epithelialization, improves proliferation of fibroblasts and synthesis of collagen, and facilitates contraction of wounds. The microenvironment of the early wound is deprived of oxygen and is very hypoxic owing to ingestion by metabolically active cells. several systemic disorders will produce reduced vascular flow, including advancing age and diabetes, thereby setting the stage for inadequate oxygenation of the tissue. This superposition of inadequate perfusion produces a hypoxic wound in the sense of recovery. Chronic wounds are hypoxic in particular; tissue oxygen concentrations were measured transcutaneous in chronic wounds of 5 to 20 mm Hg, relative to control tissue concentrations of 30 to 50 mm Hg.

Infections

Micro-organisms that are typically sequestered on the skin surface gain access to the underlying tissues until the skin is wounded. If the wound is listed as having inflammation, colonization, local invasion/critical colonization, and/or spreading invasive infection determines the state of infection and replication status of the micro-organisms. Contamination is the presence of non-replicating microbes on a wound, while colonization is characterized as the presence without tissue damage of replicating micro-organisms on the wound. An intermediate stage is local infection/critical colonization, with proliferation of micro-organisms and the beginning of local tissue responses. The involvement of replicating organisms inside a wound with subsequent damage to the host is known as invasive infection. Inflammation is a natural part of the wound healing process and is necessary for the elimination of micro-organisms that are infected. However, inflammation can be prolonged in the absence of successful decontamination, because microbial clearance is incomplete. The sustained elevation of pro-inflammatory cytokines such as interleukin-1 (IL- 1) and TNF-α will contribute to both bacteria and endotoxins and elongate the inflammatoryprocess. The wound can reach a chronic state and refuse to heal if this persists. In addition, this prolonged inflammation contributes to an elevated level of matrix metallo-proteases (MMPS), a protease family that can degrade the ECM. A decreased level of the naturally occurring protease inhibitors occurs in combination with the increased protease content. This change in protease equilibrium may cause the rapid deterioration of growth factors that occur in chronic wounds.

Age

The elderly population (people over 60 years of age) is growing more than any other age group (a significant risk factor for delayed wound healing). Several cellular and

molecular- level clinical and animal studies have explored age-related changes and delays in wound healing. It is widely accepted that the impact of aging induces a transient pause in wound healing in stable older people, but not a genuine disability in terms of the consistency of healing.

Stress

Stress has a considerable influence on human well-being and social behaviour. Stress is associated with multiple disorders, such as cardiovascular disease, cancer, compromised wound healing, and diabetes. Several studies have reported that stress-induced neuroendocrine immune equilibrium dysfunction is critical for well-being. Stressed people are more likely to have risky behaviours, including irregular sleep schedules, insufficientdiet, less exercise, and a higher risk for the consumption of alcohol, nicotine, and other medications, in addition to the direct effects of anxiety and depression on endocrine and immune function.

Body type

Body form can also influence the healing of wounds. For instance, an obese patient can experience a compromise in wound healing due to low adipose tissue blood supply. In addition, there is some protein malnutrition in some obese patients, which further impedes recovery. Conversely, the absence of oxygen and nutrition stores can interfere with wound healing when a patient is thin and weak.

Chronic diseases

A few of chronic conditions that can compromise wound healing are coronary heart disease, stroke, peripheral vascular disease, and diabetes mellitus. To have the right plan, patients with chronic illness should be monitored closely through their course of care.

Vascular insufficiency

Various wounds or ulcers such as arterial, diabetic pressure, and venous ulcers can affect the lower extremities. Decreased blood supply is the common cause of these ulcers. The clinician must identify the type of ulcer to ensure appropriate topical and supportive therapies.

Nutrition

Food has been recognized for more than 100 years as a very significant aspect that impacts wound healing. The most apparent thing is that malnutrition or specific nutritional shortages following trauma and surgery can have a profound impact on the wound healing. Special nutrients are also needed in patients with chronic or non-healing wounds and with nutritional deficiencies. The metabolism of energy, carbohydrates, proteins, fats, vitamins, and minerals will all affect the healing process[2].

TRADITIONAL USE OF MEDICINAL PLANTS IN WOUND HEALING

Medicinal plants are good source of compounds which could serve as leads for drug discovery for wound healing[17]. The wound healing activities displayed by medicinal plants are attributed to the presence of bioactive chemicals such as phenols, alkaloids, triterpenes and flavonoids. In wound healing, these bioactive compounds have been reported to have antioxidant and antimicrobial activities, improve collagen deposition and increase the proliferation of both fibroblasts and keratinocytes[18,19].

Curcumin

One of the most extensively studied phytochemicals for wound healing is curcumin, which isa chemical compound present in the Asian spice turmeric or *curcuma longa*. Apart from usage in Indian and Chinese cuisine, turmeric has been used topically for cutaneous wounds including ulcers, traditionally in the Indian subcontinent[20]. The main mechanism by which curcumin impacts wound healing is through its anti-inflammatory properties. Invitro studies have been demonstrated the suppression of TNF-α and IL-1 production by human macrophages[21]. Moreover, curcumin is also a potent inhibitor of phosphorylase kinase (PhK)and NF-κB activation[22,23]. This make curcumin a great phytochemical candidate for the treatment of hyper-inflammatory wounds such as chronic diabetic wounds and burns.

Since curcumin is a hydrophobic compound, its dermal delivery is minimal[24]. Consequently, different formulations has been created to enhance topical usage of curcumin such as gels[25], polymetric bandages[26], collagen films[27], alginate foams[28]. Moreover, lipid-core nano capsule (LCN) significantly enhances the dermal delivery of curcumin[29]. Thus, LCN-based delivery systems of curcumin show significant promise for topical applications of curcumin.

Curcumin and chronic wounds

Chronic wounds are hyper-inflammatory and highly proteolytic environments. Thus, controlling this dysregulated inflammation is crucial to ensure adequate wound healing. Topical curcumin shows promise in the management of chronic non-healing wounds. Topical curcumin treatment of wounds of streptozotocin-induced diabetic rats showed faster re-epithelialization, increased migration of fibroblasts to the wound bed, improved vascularization and significantly higher collagen content than control animals[30]. Diabetic wounds have diminished angiogenic potential, thus prolonging wound healing[31]. It is interesting to note that topical curcumin treatment on the wounds of diabetic rats also showed enhanced angiogenesis demonstrated by significant upregulation in VEGF[32].

Curcumin and hypertrophic scarring

In hypertrophic scarring and keloids, there is an abundance of TGF-β1 expression, fibroblast proliferation, and excess

collagen and extracellular matrix (ECM) synthesis[33]. Apart from being a potent inhibitor of NF-κB, curcumin inhibits TGF-β1 signaling in keloid fibroblasts and also diminishes ECM production[34]. Therefore, topical curcumin may show promise in hypertrophic scar prevention.

Honey

Honey has been a component of traditional medicine in diverse parts around the globe. Oneof its most common usages has been topical treatment for chronic wounds and burns[35].

Since the primary components of honey are plant-based, honey has been extensively studied for its phytochemical properties[36,37]. Studies have found that types of honey may differ in their wound healing properties depending on their phytochemical profile, which depends on their floral sources[35]. Honey has some antibacterial effects[38]. This is particularly important for burns and chronic wounds. Apart from its antimicrobial effects, honey also have immunomodulatory effects that are useful for the management of chronic wounds. Honey is also shown to promote angiogenesis and fibroblast proliferation in human clinical trials[39].

Honey and chronic wounds

The antibacterial effects of honey, which include both bacteriostatic and bactericidal activities, make it of use to eliminate pathogens whilst having a moist environment favorable to wound healing[40]. In order to achieve wound healing in diabetic ulcers, debridement of old cells and tissues is crucial. Honey contains protease enzymes that facilitate debridement of wounds[40]. However, since chronic wounds have a hyper- inflammatory microenvironment, without controlling inflammation there is little chance of achieving wound repair. Honey exerts its anti-inflammatory effects by the inhibition of cyclooxygenase-2 (cox-2), inducible nitric oxide synthase (iNOS), TNF-α and IL-6 expression[41]. Honey is also shown to inhibit MMP9, which may help reduce the degradation of ECM in chronic wounds[42]. Furthermore, honey contains various compounds including flavonoids, phenolic acids, catalase, peroxidase, carotenoids, and ascorbic acid, which possess antioxidant properties that can counteract the abundance of free-radicals found in chronic wounds[43,44].

Honey and burns

Honey has been used for burns in various ancient societies. Greek and roman physicians, for instance, used honey for the treatment of burn wounds[45]. In rat models of partial-thickness burn injuries, honey formulations shortened the period of epithelialization and increased wound contraction compared to vehicle controls[46]. In humans a systemic review of randomized controlled trials of eight studies comparing the efficacy of honey to silver sulphadiazine-impregnated gauze showed that honey had a superior healing effect[47]. However, this was limited to superficial and partial thickness burns only.

Terminalia chebula

T. chebula is reported to enhance extracellular matrix deposition in granulation tissuesin rat excision wound models[48]. *T. chebula* extracts have been shown to enhance keratinocytes and fibroblasts growth invitro[49]. Furthermore, rat wounds treated with *T. chebula* had significantly reduced lipid peroxide levels, suggesting the antioxidant role of *T. chebula* topical treatment[48], which was confirmed by electronic spin resonance (ESR)-2,2-diphenyl-1-picrylhydrazyl (DPPH) assays[48,49]. Tannins extracted from *T. chebula* alsopromote angiogenesis in wounds of rat models shown by the upregulation of vascular endothelial growth factor (VEGF) A expression and increased new vessel formation in the inflammatory phase[50]. It is also possible that the wound healing effects of *T. chebula* are also due to its anti-inflammatory effects.

Chebulagic acid (CA), an antioxidant compound extracted from *T. chebula*, when cultured with macrophages in vitro, significantly suppressed NF-κB activation as well as TNF-α and cox-2 expression[51]. It is possible that topical application of *T. chebula* would be beneficial in hyper-inflammatory wounds such as chronic diabetic wounds or burns. Supporting this concept, increased wound healing in streptozotocin-induced diabetic rats with the topical application of *T. chebula* extract has been shown[52]. Moreover, *T. chebula* extract accelerates wound healing in burn wounds in comparison to 1% silver sulfadiazine in rat models[53].

Aloe vera

Aloe vera, applied to wounds for over 5000 years by Egyptians, romans, indigenous peoples of Africa Asia, and the Americans, *Aloe vera* continues to be a first-line treatment for burns, ulcers, and surgical wounds[54]. *Aloe vera* contains many natural bioactive compounds, including pyrocatechol, saponins, acemannan, anthraquinones, glycosides, oleic acid, phytol, as well as simple and complex water-soluble polysaccharides[55]. Acetone extracts from the leaves of *Aloe vera* exhibit stronger antimicrobial activity than alcohol and aqueous extracts. Gram-positive bacterial species appear to be more sensitive than gram-negative species to *Aloe vera*[56]. Compounds with known antimicrobial activity are saponins, acemannan, and anthraquinone derivatives[57].

Acemannan, a major mucopolysaccharide (mesoglycan) from *Aloe vera*, is a potent stimulator of macrophage and T-cell activity and induces the transcription of proinflammatory mRNAs (including IL-1α, IL-1β, IL-6, TNF-α, PGE2, and nitrous oxide)[58]. Mesoglycan moieties bind and captureendogenous mitogen inhibitors and reactive oxygen species and promote phagocytosis. Coincidentally, glycans stabilize secreted cytokines, growth factors, and other bioactives, prolonging their activity. Topically applied acemannan has been reported to significantly reduce the time to wound closure in a rat wound healing model, acting via cyclin D1 and AKT/mTOR signal pathways[59]. *Aloe vera* glycans are also reported to

significantly improve denovo formation of granulation tissue by an unknown mechanism[60].

Centella asiatica

Centella asiatica, also known as Asiatic pennywort, has been used to promote wound healing for eons[61]. Extracts from the aerial parts of *Centella asiatica* are reported to improvethe healing of chronic ulcers in sprague-Dawley rats in terms of width, depth, and length[61]. Wounds associated with acute radiation dermatitis in rats were observed to heal earlier when treated with extracts from *Centella asiatica* compared to the no-treatment control group[62].

A triterpene glycoside compound Asiaticoside, isolated from *Centella asiatica*, is commonly known for its significant wound healing properties that have been studied in normal as well as diabetic wound healing. A topical application of 0.4% solution of asiaticoside over the wound of streptazotocin-induced diabetic rats increased the tensile strength, hydroxyproline content, protein content and epithelialization thereby facilitating the wound healing[63]. In guinea pig, 0.2% solution of asiaticoside was applied topically which produced an increase in hydroxyproline, tensile strength and quick healing. Asiaticoside promoted angiogenesis in the CAM (chick chorioallantoic membrane) model at 40 µg/disk concentration. Enhanced wound healing activity was achieved by asiaticoside has been attributed to angiogenesis, collagen formation increased remodelling of the collagen matrix and stimulation of glycosaminoglycan synthesis in a rat wound chamber model[64,65]. Since antioxidants play an important role in the wound healing process, the effects of asiaticoside on the levels of antioxidants in the wound were reported in many researchers to explore the possible mechanism of asiaticoside in wound healing.

Topical application of asiaticoside (0.2%) in cutaneous wounds in rats led to increased enzymatic and non-enzymatic antioxidants such as glutathione peroxidase, superoxide dismutase, catalase, vitamin E and vitamin C (ascorbic acid) in newly formed tissues and decrease in lipid peroxide levels. Studies revealed that asiaticoside enhanced induction of antioxidant levels at an initial phase of wound healing. All these reports indicate that asiaticoside exhibits significant wound healing activity in normal as well as delayed healing models[66].

Citrullus lanatus

Watermelon (*Citrullus lanatus*) is an important horticultural crop which belongs to the Cucurbitaceae family. Watermelon has been used to treat various ailments, such as cardio- vascular diseases, aging related ailments, obesity, diabetes, ulcers, and various types of cancers. The medicinal properties of watermelon are attributed by the presence of important phytochemicals with pharmaceutical values such as lycopene, citrulline, and other polyphenolic compounds. Watermelon acts as vital source of L-citrulline, a neutral- alpha amino acid which is the precursor of L-arginine, an essential aminoacid necessary for protein synthesis. Supplementation of L-citrulline and lycopene displayed numerous health benefits in invitro and *in vivo* studies.

In particular, watermelon can be considered as an excellent functional food due to its rich lycopene, vitamin A, vitamin C contents and antioxidant potentials[67,68]. Bioactive compounds present in watermelon render numerous health benefits, such as decreasing therisk of cardio-vascular disease, aging related ailments, obesity, diabetes, and various cancer alleviating effects have been reported[69-74]. In 1930, Wada[75] determined and isolated citrulline, a non-essential amino acid from watermelon which is involved in the synthesis of arginine. The amino acid arginine is vital for the endogenous synthesis of nitric oxide, a crucial signaling molecule involved in various neurological and immune responses in animals and humans[76].

However, direct intake of L-citrulline and L-arginine could lead to gastro-intestinal discomforts such as nausea and diarrhea[77,78]. Therefore, the consumption of fruits rich in L-citrulline (precursor of L-arginine, an essential amino acid for protein synthesis)-such as watermelon is important to obtain the necessary nutrition. Supplementation of whole watermelon in powder form improved the lipid profiles, antioxidant status, and anti- inflammatory properties of high fat fed rats[79]. Moreover, the ingestion of watermelon regulated the expression of genes associated with lipid metabolism[79]. In detail, the augmentation of watermelon and L-arginine enhanced the regulation of hepatic gene expression of endothelial nitric oxide synthase. Nitric oxide (NO) is a ubiquitous signaling molecule vital for the relaxation of blood vessels and it also reduces the atherosclerosis by influencing the lipid metabolism[79-81]. On the other hand, watermelon supplementation down-regulated the genes involved in lipid metabolism such as fatty acid synthase (FAS), 3- hydroxy-3-methyl glutaryl-coA reductase (HMGCR), sterol regulatory element binding protein (SERB) 1, SERB 2, cyclooxygenase-2 (COX2), and nuclear factor -κB (NF-κB) in rats[79].

Moreover, watermelon also down regulated the expression of Cox-2 enzyme responsible for the synthesis of pro-inflammatory prostaglandins. Furthermore, Hong *et al.*[82], illustrated that the watermelon supplementation exhibited similar mechanism to non- steroidal anti-inflammatory drugs that inhibits the activity of Cox-2 and reduces the inflammatory response. Previous studies suggest that the direct influence of NO and L- arginine on the up-regulation of PPAR-γ whereas ulcerative colitis leads to the reduction in the levels of PPAR-γ[83,84]. The important enzymes such as Cox-2, iNOS, and NF-κB involved in the generation of reactive oxygen species are inhibited by PPAR-γ; on the other hand, the activities of antioxidant enzymes are enhanced by PPAR-γ[85].

Similarly, pigments such as lycopene and β-carotene present in watermelon also displayed antioxidant properties. Among the carotenoids, lycopene consists of

strong antioxidants, for instance, the free radical scavenging rate of lycopene is higher in comparison with carotenoids such as β-carotene and tocopherol. According to previous reports, the capability of lycopene to quench the singlet oxygen is ten times higher than tocopherol and two-fold higher than β-carotene[86,87]. Polyphenolic compounds are vital antioxidants classified into phenolic acids, flavonoids, lignans and stilbenes. According toTilili *et al*.[71], in watermelon the occurrence of polyphenols is responsible for the hydrophilic antioxidant activity, and the fresh juice of watermelon is reported to have 16.94-20.23 mg Gallic acid equivalent (GAE)/100 mL of polyphenols. Therefore, the intake of watermelon as dietary snack or in beverage form can induce the antioxidant potentials in the human body and helps in the improvement of cell signaling, adhesion, and other biological activities. In addition, the watermelon rind powder consisted of different polyphenolic substances such as 4-hydroxybenzoic acid, vanillin, and coumaric acid[88]. The presence of polyphenolic compounds in watermelon rind powder significantly increased the efficiency of 1,1- diphenyl-2-picrylhydrazyl (DPPH) radical scavenging[88].

Arctium lappa

Arctium lappa, commonly known as burdock, is a widely cultivated perennial herb[89]. Scientific analyses demonstrate *Arctium lappa* has antioxidant[90], anti-inflammatory[91], antidiabetic[92], antimicrobial[93], antiviral[94], anticancer[95], and hepatoprotective[96] properties. The root extract of *Arctium lappa* has been shown to significantly improve dermal ECM metabolism, affecting glycosaminoglycan turnover and reducing visible wrinkles in human skin in vivo[97]. *Arctium lappa* is also reported to regulate cell adhesion and gene expression in canine dermal fibroblasts, affecting the Wnt/β-catenin signalling pathway, known to be a key regulator of wound healing[98]. In a pilot study of one commercial preparation including *Arctium lappa*, Burns and Wounds™ topical ointment (B&W), pain and healing of first and second-degree burns in humans was demonstrated to be managed more effectively thanthe control treatment[99].

Commiphora myrrha

Myrrh, the resinous exudate produced by commiphora myrrha[100], has well-documented antioxidant[101], anti-inflammatory[102], antibacterial[103], and analgesic[104] activities. Medicinal applications of myrrh include the treatment of gastrointestinal diseases, fractures, arthritis, obesity, parasitic infections, and as an anticoagulant[105-107]. Myrrh has been used topically to clean wounds, reduce edema, and provide pain relief (analgesia)[108]. Myrrh is commonly used in combination with other ingredients. Galehdari et al. showed that the combination of myrrh, adiantum capillus-veneris, *Aloe vera*, and Lawsonia inermis, significantly improved wound healing in diabetic mice[109]. The short-term application of myrrh effectively reduces pain and controls the recurrence of mouth ulcers in humans[110]. In common with several other herbal preparations described here, myrrh is found to modify the expression of TGF- β1 and VEGF in mouse dermal fibroblasts in vitro, suggesting a common mechanism of action[111].

Camellia sinensis

Green tea, an aqueous extract made from the leaves of *camellia sinensis*, is revered throughout Asia for its reputed health benefits[112]. Centuries of anecdotal evidence has been experimentally validated by demonstrating that *camellia sinensis* has antioxidant[113], anti- inflammatory[114], antimicrobial[115], anticarcinogenic[116], antiaging[117], antiobesity[118,119], cardioprotective[120], and neuroprotective[121] activities. Catechins, the polyphenolic compounds from *camellia sinensis*, are primarily responsible for these pharmacological activities[122]. The major catechin, (-)-epigallocatechin-3-gallate (EGCG)[112], stimulates the proliferation and differentiation of keratinocytes[123]. Klass et al. found that EGCG suppresses TGF-β signaling, reducing MMP-1 and MMP-2 expression, and attenuating synthesis of collagen type 1 in human dermal fibroblasts. These properties suggest that EGCG is a potential anti-scarring agent[124]. In addition, EGCG was demonstrated to induce keloid shrinkage[125] and inhibit growth and pathological features of keloids by suppressing STAT3 signaling[126]. Methanol extracts from *camellia sinensis* reportedly increase fibroblast proliferation and collagen synthesis[115]. Furthermore, invivo studies have been demonstrated that *camellia sinensis* significantly improves wound healing by increasing angiogenesis in rats[122,127]. Extracts from camellia sinensis are also reported to improvewound healing in a diabetic mouse model[128].

Cinnamomum cassia

Cinnamomum cassia is a commonly used spice and flavouring agent, and the bark of *Cinnamomum cassia* is also used to increase blood circulation and as analgesic[129]. *Cinnamomum cassia* is frequently formulated with other herbs; it is one of the seven botanical components of shexiang baoxan pill (SBP), a well known traditional chinese medicine (TCM) prescribed for chest pain and discomfort associated with coronary artery disease[130]. SBP is currently the subject of a randomized double-blinded clinical trial for the treatment of coronary artery disease not amenable to revascularization[131]. Attention is also focussed on SBP anti-inflammatory[132] and anticancer activities[133,134], as well as its impact on hypertension, insulin resistance, and noninsulin-dependent diabetes mellitus[135]. In vitro and In vivo studies indicate that cinnamaldehyde, a bioactive component from *Cinnamomum cassia*, is a natural insecticide, is an antimicrobial, antidiabetic, antilipidemic, anti-inflammatory, and neuroprotective agent[136], and activates PI3K/AKT and MAPK signaling pathways, increasing VEGF expression, and stimulating angiogenesis in human umbilical veinendothelial cells[129]. Cinnamaldehyde is also reported to improve wound healing in zebrafish[129].

Hibiscus rosa-sinensis

Hibiscus rosa-sinensis or shoeblack plant, is an evergreen shrub native to tropical south eastern Asia[137]. The flowers of *Hibiscus rosa-sinensis* are edible. Traditional texts describe preparations of the leaves of flowers promote hair growth and prevent greying[138]. Alcoholic extracts of *Hibiscus rosa-sinensis* flowers are claimed to provide women with control of their fertility[139]. Extracts from *Hibiscus rosa-sinensis* have also been found to have antibacterial[140] and wound healing properties[141]. They attenuate inflammation, enhance fibroblast proliferation, and collagen deposition, as well as upregulate VEGF and TGF-β1 expression in rat excisional wounds[142].

Paeonia suffruticosa

Paeonia suffruticosa, also known as moutan peony, has been bred for millennia[143]; over 1000 distinct cultivars are now available. The root bark of *Paeonia suffruticosa* is the source for bioactive ingredients used for TCM preparations. Pharmacological investigation of *Paeonia suffruticosa* has demonstrated it has antioxidant[144], neuroprotective[145], antitumour[146], anti-inflammatory[147], and antidiabetic[148] properties. The dried root of *Paeonia suffruticosa* is commonly applied to cracked skin to assist healing and relieve pain[149]. When tested invitro at low concentrations (≤10 µg/mL), *Paeonia suffruticosa* is found to stimulate the viability and proliferation of human primary dermal fibroblasts and HaCaT keratinocytes, suggesting its potential use as a wound healing therapy[150].

In this review, we show that there is anti-inflammatory and antioxidant phytochemicals are involved in wound healing. The main mechanism by which curcumin impacts wound healing is through its anti-inflammatory properties and it is also a potent inhibitor of phosphorylase kinase (Phk) and NF-κB activation. It also involves in the suppression of TNF-α and IL-1 production by human macrophages. This makes the curcumin effective in hypertrophicscarring and chronic diabetic wounds. Honey involves in wound healing activity as it exerts anti-inflammatory effects by the inhibition of cyclooxygenase-2 (Cox-2), inducible nitric oxide synthase (iNOS), TNF-α and IL-6 expression. Honey has greater wound healing potential in chronic wounds by its antioxidant properties that can counteract the abundance of free-radicals and also by inhibiting MMP9, which may help reduce the degradation of ECM in chronic wounds. Chebulagic acid derived from *T. chebula* has potent anti-inflammatory effects such as the inhibition of Cox-2 and NF-κB. Also, tannic acid strengthenscollagen scaffolds and inhibits the MMP-mediated destruction of ECM which is useful in chronic wounds and hypertrophic scarring. *Aloe vera* exhibits its wound healing activity by its antimicrobial activity and also by the stimulation of macrophage and T-cell activity and induces the transcription of pro-inflammatory mRNAs (including IL-1α, IL-1β, IL-6, TNF-α, PGE2 and nitrous oxide). Asiaticoside enhances induction of antioxidant levels at an initial phase of wound healing this indicates that asiaticoside exhibits significant wound healing activity in normal as well as delayed healing models. It also increases hydroxy proline content, tensile strength and promote angiogenesis, collagen formation, epithelialization thereby facilitating wound healing. *Arctium lappa* has been shown to improve dermal ECM metabolism and also regulate cell adhesion and gene expression, affecting the Wnt/β-catenin signaling pathway which is a key regulator of wound healing. *Commiphora myrrha* exhibit a common mechanism of action in wound healing by modifying the expression of TGF-β1 and VEGF. Watermelon inhibits the activity of Cox-2 and reduces the inflammatory response similar to the mechanism of non-steroidal anti-inflammatory drugs. Polyphenolic compounds and pigments such as lycopene and β-carotene present in watermelon induce antioxidant potentials and helps in the improvement of cell signaling, adhesion, and other biological activities.

Epigallocatechin-3-gallate (EGCG) found in *camellia sinensis* stimulates the proliferation and differentiation of keratinocytes and suppresses TGF-β receptors by modifying TGF-β signaling, reducing MMP-1 and MMP-2 expression and attenuating synthesis of collagen type 1 in human dermal fibroblasts. These properties suggest that EGCG is a potential anti scarring agent. *Cinnamomum cassia* enhances wound healing by its antimicrobial anti-inflammatory properties and also by activating PI3K/AKT and MAPK signaling, increasing VEGF expression and stimulating angiogenesis. *Hibiscus rosa-sinensis* involves in woundhealing through its antibacterial properties and also it attenuate inflammation, enhance fibroblast proliferation and collagen deposition as well as upregulate VEGF and TGF-β1 expression. Along with antioxidant and anti-inflammatory properties, *Paeonia suffruticosa* found to stimulate the viability and proliferation of human primary dermal fibroblasts and HaCaT keratinocytes, suggesting its potential use in wound healing.

Wound healing is a biological process that starts with trauma and ends with scar formation. The present review clearly revealed that provides huge number of plants that show significant wound healing activities. These natural substances are rich for the development of alternatives to synthetic drugs. However, there is a need for scientific validation, standardization and safety evaluation of plants of the traditional medicine before these could be recommended for healing of the wounds.

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