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Medicinal Plants in Wound Healing

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Abstract

Wound healing process is known as interdependent cellular and biochemical stages which are in trying to improve the wound. Wound healing can be defined as stages which is done by body and delayed in wound healing increases chance of microbial infection. Improved wound healing process can be performed by shortening the time needed for healing or lowering the inappropriate happens. The drugs were locally or systemically administrated in order to help wound healing. Antibiotics, antiseptics, desloughing agents, extracts, etc. have been used in order to wound healing. Some synthetic drugs are faced with limitations because of their side effects. Plants or combinations derived from plants are needed to investigate identify and formulate for treatment and management of wound healing. There is increasing interest to use the medicinal plants in wound healing because of lower side effects and management of wounds over the years. Studies have shown that medicinal plants improve wound healing in diabetic, infected and opened wounds. The different mechanisms have been reported to improve the wound healing by medicinal plants. In this chapter, some medicinal plants and the reported mechanisms will be discussed.

Keywords: antibacterial, animal studies, inflammatory phase, medicinal plants, wound healing

1. Introduction

Wound healing is defined as a collection of complex process which comprises different compounds including soluble mediators, blood cells, extracellular matrix, and parenchymal cells [1, 2]. Wound healing is divided into stages including inflammation process, tissue formation, and tissue remodeling. The inflammatory phase involves different stages such as platelet accumulation, coagulation, and leukocyte migration. Re-epithelialization, angiogenesis, fibroplasia, and wound contraction are stages for tissue formation. Remodeling phase may be

lasted for 1 month, and the dermis may respond to injury with the production of collagen and matrix proteins and then returns to its pre-injury phenotype [3, 4].

The different treatments are used in order to treat the wound healing. The different treatments have locally and systemically been used in order to help wound healing. The different agents are used in order to wound healing including antibiotics and antiseptics, desloughing agents (chemical debridement, e.g., hydrogen peroxide, eusol and collagenase ointment, wound healing promoters, some substances such as tissue extracts, vitamins, and minerals and a number of plant products [5]. Medicinal plants heal wound healing process by promoting blood clotting, fighting against infection and accelerating wound healing. It can be stated plants and chemical agents obtained from plants improve treatment and manage wound healing [5]. Medicinal plants show wound healing effects by the different mechanisms, such as modulation in wound healing, decreasing bacterial count, improving collagen deposition, increasing fibroblasts and fibrocytes, etc. In this chapter, we will describe different mechanisms in medicinal plants.

2. Medicinal plants

2.1. Cinnamon

Cinnamomum verum, cinnamon, belongs to the *Lauraceae* family. Cinnamon has been traditionally used in traditional systems of medicine. Cinnamon bark is used as spice, condiment and flavoring agent. It has some properties such as antioxidant, antiulcer, antimicrobial, antidiabetic, hypoglycemic, hypolipidemic and anti-inflammatory activity [6], which can be beneficial in types of wound such as diabetic and infected wounds. In addition to mentioned properties, cinnamon is known to have significant levels of polyphenols that may enhance glucose uptake in animals [7]. It increases glucose transporters-1 (GLUT-1) mRNA levels in mice adipocytes [8]. Studies have shown that cinnamon alcoholic and aqueous extracts accelerating the wound healing by their antioxidant properties [9, 10]. In this association, other studies have shown that faulted antioxidant system causes to increase oxidative stress which damages proteins, nucleotides, lipid levels and delays wound healing [11, 12]. On the other hand, anti-inflammatory effects of cinnamon components including cinnamaldehyde [13], 2-hydroxycinnamaldehyde [14] and quercetin [15] can help to accelerating wound healing.

2.2. *Aloe vera*

Aloe vera is a native plant in Africa and is so called lily of the desert or the plant of immortality. The *Aloe vera* extract has some beneficial properties which can decrease inflammation; enhance mature granulation tissue and resulting in help to accelerate wound healing [16]. It also decreases the blood glucose which can be beneficial in diabetic wounds [17]. Topical administration of *Aloe vera* gel is beneficial tool in healing minor burns and application of the *Aloe vera* gel is harmless as hypersensitive reactions to it are rare. However, *Aloe vera* gel may have harmful effects on severe burns and may actually prevent healing [18]. Gels have been traditionally found which contain 96% of water and essential oil, amino acids, minerals, vitamins, enzymes and glycoproteins. In addition, *Aloe vera* extract promotes the wound healing process because of its anti-inflammatory property. Because *Aloe vera* extract contains tannic

acid and a type of polysaccharide [19] that help wound healing process. *Aloe vera* extract shows beneficial effects on wound healing by decreasing the inflammatory phase and supplying more mature granulation tissue which finally promotes healing and may be caused to produce a sound well-remodeled scar [16]. The *Aloe vera* leaf gel has beneficial effects on wound healing by antioxidant properties which can be attributed to some compounds including indoles, and alkaloids [20]. The spectrophotometric analyses show that *Aloe vera* contains non-flavonoid polyphenols compounds phytosterols, and indoles that may encourage the symptoms related with diabetes [20]. These compounds also shows antibacterial properties which may help to alleviate the wound healing in infected wounds. Chitra et al. [21] have reported the different mechanisms for wound healing of *Aloe vera* which mainly attributed to enhancing collages turnover rate and level of lysyl oxidase.

2.3. *Anethum graveolens*

Anethum graveolens L. (dill) (Apiaceae) is known as one of the most popular medicinal plants in all over world. *Anethum graveolens* is known to have some properties such as antimicrobial, antidiabetic and anti-inflammatory that can improve wound healing [22]. Some compounds including cis-carvone, limonene, α -phellandrene, and anethofuran are major compounds in dill essential oil [23]. Alpha-phellandrene is other major compounds in dill essential oil which may decrease bacterial growth and colonization and is to be beneficial in infected wounds [24, 25].

2.4. *Eucalyptus*

Eucalyptus is also known as Dinkum oil and is belonging to family *Myrtaceae*. Eucalyptus contains some compounds such as cineole which is also known as eucalyptol. It not only contains cineole but contains other compounds such as pinene, camphene, and phellandrene, citronellal, geranyl acetate. It is traditionally used for skin care including burns, blisters, herpes, cuts, wounds, skin infections and insect bites [26].

2.5. *Securigera securidaca*

Securigera securidaca, a native plant of Iran, has traditionally been used in the southern part of Iran in order to treatment the diabetes. It is commonly used in order to treat the wound healing. Flavonoids and coumarins are broadly used as major constituents in aerial parts, of *Securigera securidaca* that act as strong antioxidants [27]. It is also known to have antibacterial properties that improve wound healing in infected wounds [28].

2.6. *Trigonella foenum*

Trigonella foenum-graecum, is so called fenugreek, is extensively used in preparations the Ayurveda and also known to have effects antiulcer action and hypocholesterolaemic effects. Fenugreek (*Trigonella foenum-graecum*) has commonly been used as a condiment and in food preparations. Fenugreek is known to have hypoglycemic effects [29]. Fenugreek seeds have some polysaccharides such as diosgenin, yamogenin, gitogenin, tigogenin, and neotigogens. Saponins can produce steroidal effects which can decrease inflammation in the body. Other bioactive constituents of fenugreek are including mucilage, volatile oils, flavonoids and

amino acid, alkaloids. The other active ingredient found in fenugreek is 4-hydroxyisoleucine [30]. It has been reported that fenugreek releases anti-inflammatory substance into wound region and decreases inflammation [31]. In addition, antimicrobial properties of fenugreek may increase its anti-inflammatory responses. A study has shown that flavonoids and triterpenoids may promote the wound healing process because of its antimicrobial properties [32]. Fenugreek is known to have antioxidant properties which can accelerate wound healing [33]. The kinetics of wound contraction and epithelialization were improved in a significant level from topical administration of the fenugreek seed [34].

2.7. *Nelumbo nucifera*

Nelumbo nucifera is belonging to family Nymphaeaceae which is so called Kamal in Hindi and Lotus in English. It has mud with large flower and is extensively used as natural and traditional healers. Its leaves are known to have wound healer effects [35]. It is reported that methanolic extract of *Nelumbo nucifera* rhizomes in the formulation of ointment could improve types of wound model in rats. This effect was studied in excision wound model, incision wound model and dead space wound model in the different concentrations of 5 and 10% w/w ointment. The both concentrations could significantly improve wound models. The both concentrations could improve contracting activity, wound close time, tensile strength, regeneration of tissue at the wound site and lysyl oxidase activity. The observed effects were similar to standard drugs [36].

2.8. Neem

Neem leaf extracts and essential oil from seeds are known to have antimicrobial effect which may be beneficial in the infected wounds. In addition, it can be stated that neem maintains wound and lesion free from secondary infections through reducing bacterial population. Clinical studies have shown that neem extract prevents inflammation and subsequently increases wound healing [5]. Neem leaf extracts and oil from seeds show antimicrobial effect which is mainly attributed to its compounds including margosic acid, glycerides of fatty acids, butyric acid and trace valeric acid [35].

2.9. Chamomile

Chamomilla recutita is so called as chamomile and is belonging to the *Asteraceae* family. It contains some substances such as chamazulene, alpha bisabolol, bisabolol oxides, spiroethers, and flavonoids which induce therapeutic effects [37]. It is also known to have anti-inflammatory which decreases inflammation during infected wounds [37]. Gholami Dogoury et al. [38] have shown that topical administration of *Chamomilla recutita* could decrease inflammatory phase and increase the proliferative stage. They have also advised to consider *Chamomilla recutita* as safe alternative chemicals for nitrofurazone ointment in wound healing process.

2.10. Bael

Bael which is so called *Aegle marmelos* which is belonging to family *Rutaceae*. It contains carbohydrates, protein, volatile oil, tanines, vitamin C and vitamin A. two alkaloids Omethylhalfordional and isopentylhalfordinol. It is traditionally used to treat wound healing properties [39].

2.11. *Linumu sitatissimum*

Flaxseed (*Linumu sitatissimum*) is one of oldest cultivated plant and is often cultivated for its fiber and oil. Flaxseed and its derivatives are known as rich sources of the essential fatty acid and alpha-linolenic acid, which are biological precursor for omega-3 and fatty acids such as eicosa-pentaenoic which may improve wound healing. Dogoury et al. [38] reported that topical administration of *Chamomilla recutita* and *Linumu sitatissimum* could decrease inflammatory phase and enhance the proliferative stage. They have also advised to consider *Chamomilla recutita* and *Linumu sitatissimum* as alternative agents for nitrofurazone ointment in wound healing process.

2.12. *Moltkia coerulea*

Moltkia coerulea is considered as one of most important plants in *Boraginaceae* that is belonging to *Lithospermeae* subfamily [40]. It is known to have some properties such as antioxidant and antibacterial effects, because of large amounts of flavonoids and phenols [41] which may accelerate wound healing. Farahpour et al. [42] have shown that topical administration of *Moltkia coerulea* improved well-formed clot in wound area, down-regulated the inflammation by exerting antioxidant properties, increased vascularization, promoted the collagen synthesis by up-regulating the fibroblasts and fibrocytes cells proliferation.

2.13. Ribwort plantain

Ribwort plantain (*Plantaginaceae*) is a perennial plant species with a worldwide distribution and large ecological amplitude. It is also known to have antibacterial properties [43, 44]. Studies have shown that *Ribwort plantain* accelerates epithelialization and wound contraction [45, 46]. Farahpour and Heydari [47] have shown that antioxidant properties reduce inflammation and increase wound contraction in rabbits.

2.14. *Rosemary officinalis*

Rosemary is belonging to the mint family which is known to have antioxidant properties because of its compounds including carnosic acid, carnosol, rosmarinic acid, diterpene, triterpenoid, phenolic acid and flavonoids [48]. It is also known to have anti-inflammatory [49] and anti-microbial properties [50] which may promote wound healing. In addition, its essential oil contains major levels of terpenoids, limonene, 1, 8-cineol, carnosic acid, rosmarinic acid and α -pinene, that can reduce inflammatory phase and can accelerate the healing process by promoting the proliferation stage [51]. Abu-Al-Basal [52] reported that rosmarinus aqueous extract accelerates wound healing by closure of the wound area and full-thickness epidermal regeneration and organization in diabetic BALB/c mice. Nejati et al. [53] have reported that topical application of rosemary ointment significantly decreased inflammatory cells, increased fibroblast migration and also increased wound contraction in wound healing in infected rat model.

2.15. *Allium sativum*

Allium sativum L. (*Amaryllidaceae*) is a member of the lily family which contains high levels of alliin, allyl cysteine, allyl disulfide, and allicin and has powerful antioxidant agents [54].

Farahpour et al. [55] have shown that topical administration of *Allium sativum* accelerated wound healing because of its preliminary impact on mast-cell distribution and increased collagen synthesis and up-regulated angiogenesis, and improved the healing process by increasing the intra-cytoplasmic carbohydrate ratio.

2.16. *Vitis vinifera*

Grape *Vitis vinifera* is belonging to *Vitaceae* family and contains vitamin E, linoleic acid, oligomer pro-anthocyanidins compounds and phenolic compounds such as flavonoids, phenolic acids and antioxidants [56] stilbenes and anthocyanins [57]. Active compounds present have beneficial effects including anti-inflammatory and wound healing [58], antimicrobial and diabetes properties [59]. Nejati and Farahpour [60] have shown that *Vitis vinifera* accelerated wound healing process by increasing neovascularization, fibroblast migration and epithelialization and can stimulate the enclosure of burn wounds.

2.17. *Calendula officinalis*

Calendula officinalis L. is so called pot marigold and is one of the medicinal plants in the *Asteraceae* family. Phytochemical evaluations of *Calendula officinalis* showed the presence of the flavonoids, flavonol glycosides, coumarins, saponins, triterpenes, alcohol triterpenes, fatty acid esters, carotenoids, essential oils, hydrocarbons, and fatty acids [61, 62]. Some studies have reported biological activities in *Calendula officinalis* including wound healing and anti-inflammatory effects [61, 62]. Farahpour [63] showed that *Calendula officinalis* aerial part hydroalcoholic extracts, have antinociceptive and anti-inflammatory activities in chemical pain and anti-inflammatory tests.

2.18. *Curcuma longa*

Turmeric (*Curcuma longa* L.) is known as turmeric and is belonging to *Zingiberaceae* family [64]. Turmeric extract contain major amounts of mineral dyes, curcumin, curcuminoids, phenolic compounds and volatile oils including turmerone, atlantone and zingiberene [65]. Farahpour et al. [66] showed that topical application of differential levels of hydroethanolic extract of turmeric rhizome remarkably accelerated wound healing activity by increasing in the rate of wound contraction and re-epithelialization, tensile strength value and collagen deposition in rat as an *in vivo* experimental wound models, and suggested to use various types of wounds in animal and human beings.

2.19. *Pistacia atlantica*

The *Pistacia atlantica* is belonging to *Anacardiaceae* family and is known to have anti-inflammatory, antibacterial, antimicrobial properties [67, 68]. Haghdoust et al. [69] have shown that *Pistacia atlantica* has beneficial effect on burn wound healing. Farahpour et al. [70] shown that the different levels of *Pistacia atlantica* decreased the healing time, improved the wound contraction, up-regulated hydroxyproline content and increased the neovascularization. They have also reported that *Pistacia atlantica* increased collagen deposition simultaneously by up-regulating the mast cells and fibroblast distribution. Finally, obtaining better results

from high dose administration of *Pistacia atlantica* suggests that dosing higher concentration contains more constituents that plays major role in shortening healing time. In other study, Farahpour and Fathollahpour [71] have shown that ointment prepared from flaxseed and pistachio oil decreased polymorphonuclear and mononuclear cell distribution, improved new vessel formation and fibroblast distribution in injured rabbits.

2.20. *Astragalus membranaceus*

Astragalus is known as Huang Qi in China and contains polysaccharides, saponins, flavonoids, amino acids and trace elements. *Astragalus* had high potential in wound healing and its mechanism was by preventing inflammation, accelerating cell cycle and promoting the secretion of repair factors in wound healing model [72].

2.21. *Morinda citrifolia* Linn

Morinda citrifolia Linn (Rubiaceae) is so called noni or Indian mulberry. A significant enhance in the wound-healing activity has reported in the animals treated with the *Morinda citrifolia* extract in comparison to animals receiving the placebo control treatments. *Morinda citrifolia* extract improves wound healing by decreasing wound size and time to epithelialization [14].

2.22. Lucidone

Lucidone is a natural compound in *Lindera erythrocarpa* Makino which is known to have some properties such as antioxidant, anti-inflammatory, neuroprotective and anti-vital efficacies [73]. It has reported that Lucidone prevents free radical-induced oxidative stress and inflammation in human skin HaCaT cells [74]. Lucidone maintains human skin keratinocytes against UVA-induced DNA damage and mitochondrial dysfunction. Lucidone promoted wound healing by cooperation of keratinocyte/fibroblast/endothelial cell growth and migration and macrophage inflammation by PI3K/AKT, Wnt/ β -catenin and NF- κ B signaling cascade activation [75].

2.23. Genistein

Genistein is one of the most important isoflavones in legumes and has estrogen-like effects [76] antioxidative effects by regulating antioxidant enzyme activities such as super oxide dismutase, heme oxygenase-1 and glutathione peroxidase [77]. Studies have reported that dietary supplementation of genistein improved the regular wound healing process by regulating the antioxidant defense system and pro-inflammatory cytokines [78]. Treatment with genistein improved NLRP3 inflammasome in the basal level and alleviated inflammation and antioxidant defense system at early stage of wound healing in diabetic mice [79]. Eo et al. [79] have also reported that genistein improved wound healing by modulating in inflammation and oxidative stress during inflammatory stage.

2.24. Asiaticoside

Asiaticoside is a glycoside compound which is commonly used in order to wound healing. A study has shown that topical application of 0.4% solution of asiaticoside on the wound of

streptozotocin-induced diabetic rats could improve the tensile strength, hydroxyproline content, protein content and epithelialization and accelerate facilitating the wound healing [80]. Another study has shown that 0.2% solution of asiaticoside increased hydroxyproline, tensile strength and quick healing. It also promoted angiogenesis collagen formation, remodeling of the collagen matrix and stimulated of glycosaminoglycan synthesis in a rat wound chamber model [81]. Antioxidants have major important role in the wound healing process that may improve wound healing by antioxidant property.

2.25. Curcumin

Curcumin is a phenolic compound which is isolated from *Curcuma longa* Linn [82] and used for its various biological and therapeutic properties. It also has antioxidant, anti-inflammatory, antimutagenic, anticarcinogenic, anti-infective and anticoagulant effects [82]. Curcumin can improve wound healing by its anti-inflammatory, anti-oxidant and anti-infectious properties and also because of the prevention of STAT, TNF- α , cyclin D1, COX-2, NF- κ B, IL (1 β , 6, 8) expressions, and down-regulation of MMP- 8 expression [83]. Curcumin also increases collagen deposition, tissue remodeling, fibroblast proliferation, granulation tissue formation and vascular density [82]. It also prevented the growth of dangerous pathogens like methicillin-resistant *Staphylococcus aureus* (MRSA) [84], *P. gingivalis*, *P. intermedia*, *F. nucleatum*, and *T. denticola* [85].

3. Conclusion

In this chapter, the possible mechanisms were described. We only mentioned some medicinal plants. The most medicinal plants act through antioxidant and antibacterial properties. However, some medicinal herbs and especially active compounds act by gene expression. It cannot certainly be stated efficiency medicinal plants in improving wound healing, but they have major potential for improving wound healing. The use of active compounds is a new strategy to improve the wound healing. Medicinal plants and active compounds help to decrease the inflammation. Future studies will be needed to determine the more mechanisms.

Conflict of interest

None.

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