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Role of Herbal Extracts in Wound Healing Process – A Review

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Abstract : In developed countries, herbs are widely used for treating a spectrum of conditions. Wound healing process involves the activation of extracellular matrix components, remodeling enzymes, cellular adhesion molecules, growth factors, cytokines, and chemokines genes. However, the molecular pattern underlying in the woundhealing process is still remain unclear. Herbs are frequently being used due to their availability and lower costs. It is therefore important to scientifically characterize mechanisms by which each herbal act. Plants have medicinal properties due to the presence of phytochemicals. The bioactivity of phytochemicals is rooted in the diversity of their molecular structures, which gives them specific properties. Curcumin, Aloe-vera and Ginger are popular natural medications for treating wounds. Fibroblasts, the most common connective tissue cell, play a critical role in wound healing. Most wounds will heal without complications. In addition, many herbs are available that will potentially heal the wound without damaging healthy tissue, reduce infection, and improve the rate of wound healing. Thus, this review focuses on the role of herbal extracts in the wound healing process.
Keywords : Cytokines, Growth factors, Herbal extracts, Phytochemicals,Wound healing.

Introduction

A wound is defined as a physical, chemical, immunological, or microbial condition of a tissue associated with loss of function. Chronic wound may become infected with micro-organisms and this may result in delay in the wound healing. Wound healing is an intricate complex process through which an organ, tissue or skin starts to restore the cellular structures and tissue layers in damaged tissue together to its normal state. The process commences in the fibroblastic stage where cell to cell and cell to matrix signaling, and shrinkage of wound occurs. It consists of four phases: hemostatis, inflammation, proliferation and remodeling[1,2]. The inflammatory phase is characterized by vasoconstriction and platelet aggregation to induce blood clotting, haemostasis and phagocytosis causing inflammation[3]. Proliferative phase is followed by epithelialization, angiogenesis and collagen deposition where fibroblasts produce a variety of substances

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necessary for wound repair, including glycosaminoglycans and collagen[4]. In the maturation phase, the wound undergoes contraction resulting in a smaller amount of apparent scar tissue. Granulation tissue formed in the final part of proliferative phase is made up of fibroblasts, collagen, oedema and new small blood vessels. Increase in the hydroxyproline content of the granulation tissue increases collagen turnover, which ultimately contributes to wound strength.

The reason for the use of medicinal plants as anti-infective, antioxidant, anti-coagulative, anticancer and wound healing activities is because they are rich in phytochemicals[5]. The word "phytochemical" is derived from the Greek "phyto" meaning plant. They can be divided into three main classes: terpenoids, phenolic compounds, and alkaloids. Plants synthesize them for protection, against organisms that would eat them, and against environmental stress; this helps the plant to survive under harsh biotic and abiotic conditions[6, 7]. Considering the side effects and higher costs of synthetic chemicals in wound therapies, the interest to administrating herbal agents in this field of therapy is increased.

A large number of plants are used by folklore traditions in India for treatment of cuts, wounds and burns. Various research data revealed that plants may worked as healing and regeneration of the tissue by multiple mechanisms. There are several reports stating that the extracts of several plants, used for wound healing properties. The leaf part is most medicinally important in traditional system of medicine and it has hypoglycemic, oral contraceptive, cardiovascular, and antimicrobial activities. It is also used for weight loss, digestive and skin problems. Traditional uses and earlier reports have revealed, enhanced healing with less scarring of cuts, wounds, burns, acne, seborrhea, dermatitis, and psoriasis after topical application of aqueous stevia extracts.

Evidence shows that necrotic tissue interference with the blood supply, lymphatic blockage, diabetes mellitus and bacterial infection delay the wound healing process [8,9]. It is known that the inflammatory phase starts immediately after the injury, and it pulls the trigger of hemostatic mechanisms which prevent blood loss from the wound site. Bioflavonoids such as quercetin, which is derived from several medicinal plants, such as Evodia rutaecarpa, Croton gratissimus and Eucomis species can considerably support this phase[10-12]. Shenoy and colleagues[13] reported that alcoholic and aqueous extracts of Hyptis suaveolens significantly increased the collagen turnover in the proliferative phase compared to controls. New collagen is formed in the third phase (remodeling), and the tensile strength of the tissue will be increased through the cross linking of collagen by vitamin C-dependent hydroxylation. Upadhyay and colleagues[14] claimed that leaf extracts of Hippophae rhamnoides increased endogenous antioxidants, and that these extracts play an important role in angiogenesis, deposition of extracellular matrix and the remodeling phase of wound healing. Approximately 450 plantspecies have been identified with promising wound healing properties.

The plant material as an active ingredient in herbal products may also be related to health risks, because italso contains some toxic constituents or constituents that are known to affect the bioavailability and pharmacokineticor pharmacodynamic interaction of other compounds or drugs. Plants promote wound healing by multiple mechanisms, usually by promoting angiogenesis. Clear evidence illustrates that phytochemicals derived from plants are affordable, safe, and have significant potential for treating infections and wounds[15-17]. A few important medicinal plants has been described below

Aloe Vera L.

This thickened and fleshy plant (succulent) originates from northern Africa, and belongs to the family Xanthorrhoeaceae. Evidence shows that A. vera contains phytochemicals such as pyrocatechol, saponin, acemannan, β-mannan, anthraquinone, C-glycosides, diethylhexylphthalate, bradykininase, oleic acid, phytol, and magnesium lactate along with water-soluble polysaccharides like glucomannan[18]. Reports indicate that Aloe has been used successfully to treat burns and skin irritations, canker sores (aphthous stomatitis), gastric and duodenal ulcers caused by Helicobacter pylori[19]. Mannose-6-phosphate is the main sugar in A.vera, which improved wound healing process at a dosage of 300 mg/kg. Evidence indicates that the use of A. vera extracts for four days at a concentration range of 300 mg/kg reduced the action of wound healing inhibitors, such as sterols and certain amino acids[20].The influence of A. vera on the process of wound healing is comparable to that of mast cell stabilizer drugs such as lodoxamide, and lipid peroxidation inhibitors such as lazaroids, with 82% to 85% tissue survival compared to the control[21].

Blumea Balsamifera (L)

Blumea Balsamifera (L.), leaves have been used for healing eczema, dermatitis, skin injury, skin bruises, beriberi, lumbago, menorrhagia, rheumatism, and some other diseases. The extracts of the leaves are plasmin-inhibitory, anti-fungal, free radical scavenging and anti-obesity functions. The content, l-borneol, induces resuscitation, relieves pain, has an anti-inflammatory effect, activates blood, and inhibits sympathetic nerve conduction. Its oil improves wound contraction and closure. It improved the formation of collagen and fibroblasts, and reduced the number of inflammatory cells that were required to accelerate effective wound healing and granulation of wound. The granulation tissue is comprised of fibroblasts, collagen, edematous fluids, and small neovascularized blood vessels. It promoted wound healing by influencing the proliferative and remodeling phases of wound healing, and via the pathways of angiogenesis, collagen deposition, granular tissue formation, epithelial deposition, and wound contraction. It can improve blood circulation and eliminate extravagated blood. In promotes capillary regeneration, blood circulation, collagen deposition, granular tissue formation, epithelial deposition, and wound contraction[22].

Camellia Sinensis (L.) Kuntze (Green Tea)

C. sinensis contains chemicals such as epigallocatechin- 3-gallate, acetamide, 5-N-ethyl-glutamine, cetophenone, actinidiolide dihydroactinidiolide, afzelechin, amyrin, aniline, apigenin, benzothiazole, arbutin, assamicain, camellianin, caffeine, catechin, carvacrol, catechol, limonene, menthol, vitamin C, tannins and thymol[23]. Epigallocatechin-3-gallate (EGCG), the major catechin found in green tea, has been shown to have anti-carcinogenic and antimicrobial properties against a number of bacterial pathogens, including an inhibitory influence on Stenotrophomonas maltophilia, which is recognized as an important nosocomial pathogen. Theophylline is a colorless crystalline alkaloid, and an isomer of theobromine, which has been extracted from C. sinensis leaves and used to treat asthma, emphysema, brachycardia, acute bronchitis and bronchial spasm[24]. It is reported that extracts of C. sinensis accelerate keratinocyte cell differentiation and improve the wound healing process.

Cichorium intybus L

Cichorium L. from the family Asteraceae, has antidiabetic activities while the aerial parts has antioxidant, antimicrobial and anthelmintic effects. The roots of the plant has antimalarial, anti-ulcerogenic, analgesic, anti-inflammatory and anticarcinogenic activities. The aerial parts of Cichorium species revealed the presence of polyamines, sterols, flavonoids, phenolicacids, anthocyanins, hydroxyl cinnamic acid derivatives, sesquiterpene lactones, triterpenoids, norisoprenoids and besides these compounds, several polysaccharides including homogalacturonan, rhamnogalacturonan-I, cellulose, xyloglucan, heteroxylan and glucomannan have been determined in the leaves of C. intybus whereas,the roots were found to be rich in sesquiterpene lactones, coumarinsandinulins. Collagen is an important structural protein of the connective tissue which has a big importance in wound healing. C. intybus were rich in phenolic constituents. Significantant inflammatory and antioxidant effects of these active extracts and fractions and β-Sitosterol demonstrated a possible contribution of such activities in wound healing process. The C. intybus roots exerted a prominent wound healing activity and β -sitosterol was isolated as, atleast, one of the active component responsible from this effect. The wound healing effect of this compound might be due to its significant anti-inflammatory and antioxidant effects, as well as hyaluronidase and collagenase enzyme inhibitory activities. The ethyl acetate extract of C. intybus roots exerted anti-inflammatory activity through the inhibition of prostaglandinE2 (PGE2) production in human colon carcinoma HT29cells. Moreover, characteristic bitter Sesquiterpene lactonesin C. intybus leaves and roots, lactucin and its derivatives lactucopicrin and13-dihydrolactucin,were found to possess analgesic and sedative properties in mice. L actucopicrin appeared to be the most potent analgesic among these compounds. Free radicals are known to induce cell damage due to lipid peroxidation and therefore antioxidant activity is known to contribute in the healing process[25].

Curcumin

The turmeric plant is an herb belonging to the ginger family. The rhizome (root) part of the plant has also been used for centuries in Indian and Chinese traditional medicines and is the most valuable part of the plant for medicinal purposes. The wound healing potential of curcumin is attributed to its biochemical effects such as its anti–inflammatory, anti-infectious, and antioxidant activities. Curcumin has also been found to enhance cutaneous wound healing through involvement in tissue remodeling, granulation, tissue formation, and

collagen deposition.In the inflammatory stage, curcumin inhibits the activity of NF-(κ)B transcription factor, reducing the production of TNF-α and IL-1 cytokines, and thereby reducing inflammation. It plays a scavenger action against ROS (at lower dose) and increases the ROS formation (at higher dose) by increasing or decreasing the production of anti-oxidant enzymes. It enhances the fibroblast migration, granulation tissue formation, collagen deposition, and in general re-epithelization, thereby eliminating unwanted inflammatory cells from the wound site in the proliferating stage. Improving wound contraction by increasing the production of TGF-β and therefore increasing fibroblast proliferation in the remodeling stage. Various studies have shown that curcumin's application on wound also enhances epithelial regeneration and increases fibroblast proliferation and vascular density[26-28].

Equisetum Arvense L. (Bottlebrush, Cat's Tail)

This perennial plant with underground rhizomes belongs to the family of Equisetaceae and is found in the northern hemisphere. Chemical screening of E. arvense indicates that it is rich in calcium, potassium and silicon. It has been used medicinally by ancient and modern cultures to cure wounds and tissue injuries. Currently, compounds such as petrosins, onitin, onitin-9-O-glucoside, apigenin, luteolin, kaempferol-3-O-glucoside, quercetin-3-O-glucoside, luteolin-7-O-D-glucoside, apigenol 7-O-glucoside, rosmarinic acid, chlorogenic acid, caffeic acid, rutin and apigenol have been isolated from extracts of E. arvense[29]. Extracts from this plant have considerable ability to stimulate collagen synthesis and glycosaminoglycan metabolism, and accelerate the wound healing process[30]. The presence of silicon in the tissue of E. arvense makes this plant a valuable natural source of silicon, a necessary element for the synthesis and integrity of connective tissue[31].

Moltkia coerulea

It is one of the important plants of Boraginaceae which belongs to Lithospermeae subfamily. A range of biological activities, including antioxidant, antibacterial and antiviral effects have been reported for Moltkia petraea. M. coerulea contains a large amount of flavonoids and phenols. Flavnoids and phenols are known potent anti-oxidant agents, which are involved in promoting the anti-oxidant capacity of different tissues. Administrating anti-oxidant chemicals result in significant inhibition of inflammation during the wound healing process. Considering high anti-oxidant potential of Moltkia petraea, it was suggested that Moltkia petraea down-regulates the inflammation by exerting anti-oxidant properties. It promoted the collagen synthesis by up-regulating the fibroblasts and fibrocyte cells proliferation. The extract of Moltkia coerulea has beneficial impact, partly by its anti-oxidant properties. Moreover, in the wound healing activity, the extract shortens the inflammatory phase and provokes the fibroblasts, fibrocytes proliferation and enhances the angiogenesis[32,33].

Napoleona vogelii

Lecythidaceae family, it is used in the treatment of ulcers, stomach aches, and diarrhoea. The extract from this plant has antimicrobial activity against bacterial agents. The bark of N. vogelii has been used in the management of cancer. Topical preparation from the stem bark has been used and found beneficial in the treatment of dermatosis, ingested to treat sexual asthenia, and extract from the leaves has been used in the treatment of external wounds. The toxicity test showed that the leaf extract was relatively less toxic with an LD50 exceeding 5 000mg/kg bw. This indicates that the plant extract is well tolerated at high concentrations and therefore has a very high margin of safety. The methanol extract of N. vogelii leaves demonstrated wound healing activity and caused a significantly reduction in the wound area. Comparatively, the extract relatively accelerated wound healing significantly in the treated animals than the natural healing process. The wound healing potential of the plant extract was reinforced by the phytochemical analysis of the leaf extract which revealed the presence of several bioactive and therapeutic metabolites including glycosides, alkaloids, saponins, tannins, terpenoids, steroids, flavonoids, resins, protein and carbohydrates. The anti-microbial and astringent properties of the tannins, flavonoids, saponins, glycosides and terpenoids were suggested to play critical role in the wound healing process by increasing the rate of wound contraction, epitheliazation and prevention of secondary bacterial infection that would have complicated and delayed wound healing[34]. Being anti-oxidants, saponins, sterols, flavonoids, and tannins reduced lipid peroxidation thereby preventing cell necrosis, promoting tissue vascularity and local microcirculation, increasing strength and viability of collagen fibrils in the wound area[35]. These bio-active components are potent effectors of one or several stages in the healing process that include disinfection, anti-inflammation, cell proliferation, synthesis of tissue ground substances and environment that promote normal healing process[36]. Conclusively, the N. vogelii leaf extract contains bio-active

compounds that are active as wound healing agents. Further studies are suggested to determine the LD50 of the methanol leaf extract of this shrub, and to use different solvent of varying polarities in the extraction process[37].

Rubus ellipticus

R. ellipticus is a weedy raspberry reported as an in vitro antioxidant, its traditional uses and pharmacological properties, such as anti-inflammatory, analgesic, and antipyretic activities. the leaf methanol extract of Rubus ulmifolius to evaluate the antioxidant potential and confirmed that the activity is related to the nature of phenolics; thus contributing to their electron transfer/hydrogen donating ability. The R. ellipticus fruit extracts exhibited a significant antidiabetic effect in experimental models of diabetes mellitus. The plant products may have the property to counteract the effect of NO formation and in turn may be of considerable interest in preventing the ill effects of excessive NO generation in the human body. Further, the scavenging activity may also help to arrest the chain of reaction initiated by the excess generation of NO that is detrimental to human health. Because R. ellipticus showed good NO scavenging activity, it is clear that it can be used for scavenging reactive nitrogen species in human body. The human body has several mechanisms to counteract the damage by free radicals; these act on different oxidants as well as in different cellular compartments. One important line of defense is a system of antioxidant enzymes such as SOD, catalase, and GPX. SOD is a metalloprotein, which converts superoxide radicals into H2O2. To eliminate H2O2, organisms use catalaseda homo tetrameric ferri heme containing enzyme and/or GPX, a selenium-dependent enzyme[38]. Flavonoids and their derivatives are known to decrease lipid peroxidation by improving vascularity and by preventing or slowing down the progress of cell necrosis. Hence, any drug that inhibits lipid peroxidation is supposed to increase the viability of collagen fibrils by increasing the circulation and strength of collagen fibers, by encouraging DNA synthesis, and preventing cell damage; these factors enhance wound healing. Therefore, the wound healing potential of R. ellipticus may be attributed to the phytoconstituents in leaves, which may be either due to their individual or additive effect[39].

Stevia rebaudiana

Stevia rebaudiana Bertoni is a weak perennial shrub belonging to Asteraceae (Compositae) family, native to subtropical regions of Brazil and Paraguay. Root extracts of stevia have also shown to possess good anti-oxidant potential. Scientists showed that anti-diabetic compounds with anti-oxidant properties would be more beneficial in treatment of diabetes.Traditional uses and earlier reports have revealed, topical application of aqueous stevia extracts enhanced healing of cuts and wounds with less scarring[40].Kuntal Das,[41] demonstrated the wound healing activity of the leaf, Stevia rebaudiana and found that the wound healing activity is by dose dependent manner. The individual or cumulative effect of wound healing is attributed due to the phytoconstituents present in Stevia rebaudiana. This provides a rationale for the use of stevia preparations in the traditional system of medicine to promote wound healing. The preliminary phytochemical analysis revealed the presence of tannins, carbohydrate, saponins, diterpenes, flavonoids and polyphenolic compounds. The presence of flavonoids, tannins and saponins in the leaf extracts are known to promote the wound-healing process. Flavonoids reduce lipid peroxidation not only by preventing or slowing the onset of cell necrosis but also by improving vascularity. The plant extracts has an astringent and antimicrobial property which is responsible for wound contraction and increased rate of epithelialisation. Stevia overcomes the impaired wound healing in type 2 diabetes mellitus by several mechanisms such as coating the wound, forming complexes with proteins of microorganism cell wall, chelating free radicals and reactive oxygen species, stimulating the contraction of the wound and increasing the formation of new capillaries and fibroblasts[42].

Conclusion

Most people in the developing countries depend on herbal remedies for effective treatment of wounds. Despite the availability of a wide range of modern medicines, wound healing, especially chronic wounds, remains a challenging field of research, and debilitating diseases such as diabetes and burns delays wound healing. Herbs showing antioxidant properties therefore enhance wound healing activity by reducing the damage caused by radicals. In addition to individual plant extracts or isolated compounds, poly-herbal formulations have also been determined to be effective in wound healing. Recently it has been found that certain plants also promote angiogenesis through the activation of the mitogen-activated protein kinases pathway. Naturally, wound healing is slow and sometimes may become chronic with a long clinical course thereby resulting in a constant release of inflammatory modulators that cause pain and swelling. It has been

observed that the wound healing potential of medicinal plants and their products is often linked with angiogenesis-promoting potential, which is a critical step of wound healing. Moreover, plants are the oldest known medicines for wound care and management, and they are still promising materials for novel drugs discovery.

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