Chapter

Anti-Inflammatory Potential of Ginseng for Wound Healing

Dimple Sethi Chopra, Abhishek Gupta, Dhandeep Singh and Nirmal Singh

Abstract

The recovery of skin wounds is a complex biological process involving three basic mechanisms: inflammatory phase, re-epithelialization followed by granulation and tissue remodeling. The interactions between inflammatory cells, fibroblasts, and keratinocytes induce microenvironmental changes at the wound site. Tissue remodeling is initiated by matrix-producing proteins and protease enzymes and collagen fibers in the dermis. A saponin extracted from ginseng, known as ginsenoside, has been shown to accelerate neovascularization in burn wounds in mice. It also increases levels of vascular endothelial growth factor and interleukin (IL-β). IL-β accelerate wound healing by promoting accumulation of macrophages at skin wound sites. Saponins are major active constituents of ginseng. They contain many ginsenosides. The purified ginsenosides or the extracts of ginseng root have been reported to have beneficial effects on damaged skin. For instance, red ginseng root extract protected skin from acute UVB-irradiation. Ginsenoside F_1, an enzymatically modified derivative of the ginsenoside Rg_1, protected HaCaT against UVB-induced apoptosis. *Panax ginseng* root extract promotes type I collagen synthesis in human dermal fibroblasts (HDF) via the Smad activation pathway and exhibits antioxidant activity against free radicles including diphenyl-p-picrylhydrazyl treatment. In addition, ginsenoside Rb_1 promotes healing process of burn wound by enhancing angiogenesis. Among the various ginsenosides, ginsenoside Rb_1 has been found to most potent agent for wound healing.

Keywords: *Panax ginseng*, skin wound healing, total ginseng saponin, mice, ginsenoside Rd., wound-healing, cyclic AMP-dependent protein kinase, keratinocyte progenitor cells, human dermal fibroblasts

1. Introduction

A wound is disruption of barrier function of the skin which may result from a physical or chemical injury. Depending on time taken for healing process, it can be categorized as simple, acute wound and chronic wound. The human body has the potential to initiate wound healing process in order to replace the damaged cellular structures and tissue layers. This complex process is comprises of sequence of events starting from homeostasis, inflammation, proliferation/granulation leading to remodeling/maturation [1].

Acute wounds are characterized by minimal localized microbial infection and scab formation. Infiltration of immune cells leads to re-epithelialization,

angiogenesis and fibroblast migration. If the immune system is unable to control the infection, microbial biofilm is formed leading to impaired wound healing. Chronic wounds are characterized by increased inflammatory process, lower oxygenation of the deep tissues due to fibrin cuffs formation, fibroblast senescence, impaired angiogenesis and re-epithelialization. Most chronic wounds are ulcers that are associated with ischemia, diabetes mellitus, venous stasis disease, or pressure [2, 3].

Wound care is a million-dollar global industry which determines the appropriate treatment to promote wound healing with minimal infections [4]. Several aspects of wound healing are encompassed in the management including, but not limiting to maintaining optimum moist environment at the wound site, infection control, treatments for deep seated tissue regeneration using stem cell therapy [4, 5]. Despite medical advancements in wound care, there is a mounting demand for alternative treatments from the clinical and economic perspective. It has been reported that chronic wounds affect 6.5 million people in the USA, and costs over US $25 billion each year. Alarmingly, the burden of chronic wounds is expected to rise due to global increases in vascular diseases, diabetes, obesity, metabolic syndrome, and the general aging of the population [6]. In ancient times, tribal people used plants to cure wounds. Even now, plants are considered as huge source of novel bioactive agents. It has been found that at present there are more than 450 plant species being extensively used for their wound healing ability, yet the search for novel wound healing agents from natural resources with minimal scaring is never ending [7].

There are numerous medicaments available to augment skin wound healing, disinfectants like ethyl alcohol, iodine, ether, ointments containing antibiotics and steroid hormones. Iodine based preparations and silver releasing agents have been used as antimicrobial agents to treat infected wounds. They target bacteria at cell membrane, cytoplasmic organelle, and nucleic acid level, thus minimizing bacterial resistance [8]. They can be used either alone or in conjunction with systemic antibiotics. Advanced silver dressings, aim to deliver sustained doses of silver to the wound [9, 10]. In addition to the microbicidal effect of silver on common wound contaminants, silver may also be effective against resistant strains like methicillin resistant *Staphylococcus aureus* (MRSA). Zinc, an antioxidant, used in a paste bandage is useful in treating infected leg ulcers. Phenytoin, applied topically, promotes wound healing by inhibiting the enzyme collagenase. It is effective in some low grade pressure ulcers and trophic ulcers due to leprosy. The possibility of systemic absorption and toxicity has limited its use. Analgesics are in great demand for treatment of ulcers. They may comprise of simple analgesics like NSAIDs or strong analgesics like opiates in case of severe pain. Tricyclic antidepressants (such as amitriptyline) or antiepileptic drugs (such as gabapentin) are drugs of choice for ulcers associated with neuropathic pain [11]. These agents provide preliminary relief but interfere with the normal healing process. They injure not only invading foreign organisms but also normal body cells. They can lead to emergence of resistant bacterial infection and hypersensitivity reactions. From ancient times, various natural substances have been widely used for wound healing [12].

The polyphenols in plant extracts are capable of neutralizing free radicals by combining with active oxygen [13]. A stable phenoxyl radical is formed when a polyphenolic compound combines with free radicals formed during the metabolic process. Superoxide, hydroxyl, lipid peroxyl, nitric oxide radicals, and peroxynitrites are the most common free radicals with which polyphenolic compounds usually combine. In wounds there is a high oxidative stress due to the activation of platelets, neutrophils, macrophages, lymphocytes and fibroblasts. The concentration of reactive oxygen species varies at different time points of the healing

process [3]. This is further enhanced by infection from microbes. In such conditions, plant based polyphenol may assist in the healing process by modulating the concentrations of reactive oxygen species [14].

In case of burn wounds, coagulative necrosis is quite predominant resulting in scar formation after repair. Macrophages migrate to the injured area to kill invading organisms and produce cytokines that recruit other inflammatory cells that are responsible for cascade of inflammatory reactions. Angiogenesis at the injured area is vital in wound healing process. Moreover, growth factors and cytokines play crucial role in wound-healing process [15, 16]. Hypoxia induces cytokine and growth factor production from macrophages, keratinocytes, and fibroblasts. These include platelet-derived growth factor (PDGF), transforming growth factor (TGF-β), vascular endothelial growth factor (VEGF), tumor necrosis factor-α (TNF-α), and endothelin-1. They in turn promote cell proliferation, migration, chemotaxis and angiogenesis in wound healing [17]. Although, hypoxia stimulates wound healing such as the release of growth factors and angiogenesis, still oxygen is needed to sustain the healing process [18].

Hence, burn wound healing is a multiple step process, involving inflammatory phases such as monocyte migration, cytokine production, growth factors and angiogenesis during re-epithelialization. Preliminary experiments, reveal that total ginseng saponins isolated from Red Ginseng roots accelerated burn wound healing in mice. There are significant number of indications on wound healing effects of ginsenosides with diverse associated mechanisms, one such report is on skin regeneration by the ginsenoside Rd (discussed later in the chapter) isolated from ginseng leaves. GinsenosideRb$_1$ promotes burn wound healing process by enhancing angiogenesis [19].

2. Anatomical and physiological changes in wound bed

In mammals, wound healing is a rapid process involving cessation of bleeding from the wound, restoration of damaged tissues, moisture deposition around the wound to develop functional defense membrane which prevents microbial invasion. Thus, wound healing can be categorized into four stages which comprises of initial inflammatory phase, re-epithelialization, granulation tissue formation, and finally tissue remodeling [20]. This categorization is based upon histological examination or functional activities which are considerably overlapping. A deep interaction between cells and tissues involved in these phases finally results in wound healing [21].

Activated blood coagulation factors, complement components and damaged cells secrete growth factors and platelets which trigger chemotactic stimulus. Blood coagulation factors in conjunction with platelets initiate blood coagulation and activate fibrin. Fibronectin and vitronectin present in blood plasma form the substrate for cell migration involving keratinocytes. This is eventually followed by proteinases which result in scab formation around the wound [22].

As the blood coagulation process advances, within few hours neutrophils reach at the site of damaged tissue. They eliminate infective agents by phagocytizing them and promote blood coagulation and healing by secreting various factors [23]. Monocytes arrive at the wound within two days and differentiate into macrophages, to perform phagocytosis and antigen presenting functions. These macrophages regulate wound healing process by secreting, transforming growth factors-α and β, basic fibroblast growth factor, and platelet-derived growth factor [24]. Within few hours of inflammatory reaction, both re-epithelialization and granulation tissue formation takes place simultaneously. Keratinocytes present around the edges of the

wound and in residues of skin appendages migrate into the wound and form a scab [25]. These keratinocytes are typically hyper-proliferative facilitating them to fill the damaged epithelial layer and reform the basement membrane within two days, restoring cellular contacts. This process leads to differentiation of keratinocytes into epidermal skin layer [26]. At almost the same time fibroblasts located around the undamaged dermis begin to proliferate and migrate as a result of the stimulus caused by the aforementioned growth factors, granulation tissue formation [27]. The extracellular around the wound is formed by proteoglycans, collagen type I and III, and collagen secreted by fibroblasts [22]. A portion of fibroblasts differentiate into myofibroblasts, which secrete actin, which builds up mechanical tension brings the edges of the wound closer resulting in wound contraction and finally wound closure [26]. The migration and proliferation of endothelial cells result in appearance of new blood vessels in granulation tissue [24]. The dermis remodeling phase of skin wound healing involves reduction of fibroblasts by apoptosis and removal of damaged blood vessels. The residual fibroblasts rearrange the collagen fiber, repeating collagen deposition and degradation for several months in order to recover the original tension of the skin [27].

Radicals produced by wounds are largely superoxide radical anions produced by neutrophils and macrophages, and also play an important role in removal of microorganisms and pathogens [28]. Superoxide radical anions are quickly transformed into hydrogen peroxide (H_2O_2) which is able to permeate microorganisms or pathogenic cell membranes by superoxide dismutase, promoting the formation of hypochlorous acid, chloramines, and aldehyde which are all maintained in more stable forms than H_2O_2, and are characterized by long half-lives. Thus, if H_2O_2 remain in the wound for extended period of time, acute inflammatory reactions can damage even normal cells [29].

Saponins present in various plant extracts possess extensive biological activities. They augment anti-oxidants and anti-inflammatory reactions. Saponins are one of several kinds of glycosides present in plants of high order [30]. Saponin types are named based upon their internal structure. A saponin referred to as fruticesaponin B is known to have a very high anti-inflammatory activity [31]. Navarro et al. [32] reported that anti-inflammatory activity of saponins is highly dependent on their chemical structure. In fact, both types of saponins tested in the study, prevented neutrophil access to wounds thereby decreasing chronic skin inflammatory reactions. On day 5, the wound healing rate was much faster in saponin-treated group than the control leading to complete joining of both sides of the incisional wounds on day 7. Except for day 1, during all time periods of evaluation, the wound area contracted more in the saponin-treated group than the control group. However, except day 1, the rate of keratin cell migration in the saponin-treated group was found to be higher than the control group during all periods. Another study reported that the burn wound area in a saponin-treated group was found to gradually increase up to day 4 then gradually decrease until day 20. In control group, the burn wound area gradually increased up to day 8 and then diminished in size [33]. The long lead time in healing the burn wound was due to inflammatory reaction around the burn wound which persisted longer [34]. Saponins were found to stimulate overexpression of factors, leading to proliferation of epidermal cells [35]. It was also found that rate of keratinocytes migration involved in re-epithelialization was faster in the saponin-treated group than in the control group. Hence, it was concluded that saponin not only enhances epidermal cell proliferation but also promotes migration of keratinocytes. The influx of inflammatory cells was measured in an animal wound model. On day 1 and day 3 it was found that the number of inflammatory cells in the saponin-treated group were much less in comparison to the control group. But were found to increase from day 5.

On day 7, the number of inflammatory cells were greater in the treated group than the control group. In burn wound number of leukocytes and macrophages increased up to day 9 [19]. Accumulation of macrophages was induced by IL-1β expression by hypoxia-inducible factor-1α. Hence, it is quite obvious that saponins are involved in inhibition of the inflammatory reaction at an early stage. Moreover, wound shrinkage increased sharply from day 3 onwards as compared to control group. Matrix remodeling analysis confirmed that matrix synthesis was promoted in the saponin-treated group compared to the control group. A recent study revealed that when saponin are used to treat skin tissue exposed to ultraviolet rays, collagen synthesis of fibroblasts was increased and expression of matrix metalloproteinases was inhibited [36]. It was also found that saponins increased collagen synthesis through phosphorylation of Smad 2 protein. Hence, saponins promote the regeneration of matrix at the wound site [37].

Hence, the literature findings very well indicate that saponins stimulates re-epithelialization of the wound and effectively inhibit early phase inflammatory reactions during and promotes matrix synthesis throughout the wound healing process. On the basis of the evidence existing in literature saponins are beneficial in healing incisional skin wounds. Ginseng leaves can be easily acquired and much cost effective compared to ginseng roots, hence there are several reports on isolation of active compounds from the Chinese ginseng leaves. These novel compounds were also tested for wound-healing activity [15].

3. Role of ginsenosides in wound healing

The principal active constituent of ginseng is a saponin called ginsenosides. Ginsenosides are found exclusively in the *Panax* species (ginseng); thus, they are also known as panaxosides. Nearly, 150 naturally occurring ginsenosides have been isolated from the roots, leaves, stems, fruits and flower heads of ginseng plant [38]. Ginsenosides are often divided into the Rb_1 group (characterized by the presence of protopanaxadiols: Rb_1, Rb_2, Rc and Rd) and the Rg_1 group (protopanaxatriols: Rg_1, Re, Rf and Rg_2). The remaining non-saponin components of ginseng are polysaccharides, polyacetylenes, peptides and amino acids. *P. ginseng* component, Rb_1 (G-Rb_1) has been studied extensively. It has been found to possess anti-inflammatory, antioxidant and antimicrobial activity. G-Rb_1 has also been found to enhance protein synthesis, neovascularization or angiogenesis and immunostimulation [39]. There have been inconsistent reports on effects of G-Rb_1 on dermal cell activities. This might be due to substantial variances in responses to G-Rb_1 in numerous cell lines being tested. An *in vitro* study revealed that G-Rb_1 had no cytotoxic effect on human keratinocyte (HaCaT) multiplication [19]. However, another study confirmed that G-Rb_1 improved the viability of human retinal pigment epithelial cells [40, 41]. An *in vivo* study showed that G-Rb_1 inhibits the chemoinvasion of endothelial cells during neovascularization [31]. However, another study showed that G-Rb_1 increases the number of blood vessels in burn wound areas of mice [42]. Schwann cell proliferation is significantly inhibited at 1 mg/ml, whereas 10 μg/ml of G-Rb_1 induces proliferation [40]. The effect of G-Rb1 on collagen synthesis is also uncertain. One study revealed that G-Rb_1 enhances collagen production in HaCaT cells [42]; however, G-Rb_1 reduced collagen levels in normal rat renal tubular epithelial cells (NRK-52E) [43]. Similarly, the effects of G-Rb_1 on cell function have been varied. Hence, the efficacy of G-Rb_1 on human dermal fibroblasts has not been confirmed. Lee et al. [44] treated cultured human dermal fibroblasts with one of six concentrations of *P. ginseng*: 0, 1, 10, 100 ng/ml and 1 and 10 μg/ml. Cell proliferation was determined 3 days post-treatment using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide

assay. The collagen type I carboxy-terminal propeptide method was used to evaluate collagen synthesis. It was found that *P. ginseng* stimulated human dermal fibroblast proliferation and collagen synthesis at an optimal concentration of 10 ng/ml. This study, reported that G-Rb1 had significant positive effects on dermal fibroblast proliferation and collagen synthesis, which are essential factors during wound healing. *P. ginseng* generally is well tolerated. Although mild and reversible adverse effects of *P. ginseng* have been reported in cases where it was administered orally, including capsules, liquids or powders [45–49].

4. Summary and conclusion

Recently, the prime focus of wound specialists has been stimulation of wound healing. That is only possible when there is precise interplay of biological and molecular events, including cell migration, proliferation, extracellular matrix deposition and remodeling. The environment that favors the activities of key cell types need to be facilitated, clinically, for successful wound healing. These factors play a major role in regulating wound healing process by releasing various growth factors and cytokines. One such important cell type are fibroblasts. They perform numerous functions, including production of collagen, growth factors, antioxidants, initiating tissue remodeling, maintaining balanced levels of matrix-producing proteins and protease enzymes. A large number of clinical and experimental studies have confirmed that *P. ginseng* has multi-faceted effects in wound healing in humans, including angiogenesis, immunostimulation, and antimicrobial and anti-inflammatory actions. These activities contribute to wound healing potential of *P. ginseng* even in elderly population with greater predisposition to chronic wounds due to poor blood circulation, weak immune system, deficient nutritional factors and decreased cell activities. Hence ginseng is a potential candidate for incorporation in future dressings for wound management.

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