Wound healing and antioxidant properties: do they coexist in plants?

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ABSTRACT

Introduction: It is known that the wound-healing process can be aided by the presence of antioxidants. Many plants have been reported to possess wound-healing and antioxidant properties. This review aims to appraise published literature and evaluate whether wound-healing and antioxidant properties co-exist in plants. **Methods:** Web of knowledge, Google Scholar and PubMed were primarily used to search for published reports on wound-healing and antioxidant properties of plants. Other relevant publications, e.g., books and journal articles, were also consulted. **Results:** Literature search has revealed that several wound-healing plants also possess considerable antioxidant properties as evident from the results of various *in vitro* and *in vivo* assays. It has appeared that the wound-healing properties of plants, in most cases, are associated with their antioxidant activities. **Conclusions:** The wound-healing property and antioxidant activity co-exist in many plant species from a variety of families.

Keywords: wound, wound-healing, oxidative stress, antioxidant, plants.

INTRODUCTION

Wounds are physical injuries that result in an opening or breaking of the skin. Wound-healing is a process that comprises three phases, e.g., inflammation, proliferation and remodeling, and proceeds with complicated and well-organized interaction between various tissues and cells by overlapping between successive stages.[1–3] Alterations in any of these steps can lead to delay or inability in dermal wound-healing. Therefore, wound-healing is not a linear process. It is rather a 'to and fro' process that depends on various factors. There are many points at which the normal wound-healing process can be disturbed.[4,5]

Two important pathological manifestations in wounds are fibrotic wounds, and keloid scar formation and ulcers. While in fibrotic wounds excess deposition of the matrix and lack of remodeling lead to hypertrophy, in keloid scar formation and ulcers, the wound is stuck in a state of chronic inflammation.[6,7] Proper healing of wounds is essential for the restoration of disrupted anatomical continuity and disturbed functional status of the skin. In order to establish proper treatment regime, a number of important local wound factors have to be considered, e.g., appraisal of location, depth, size, neighboring tissues, organs, necrosis, secretion, coloring and sensibility.[1,3]

When wound occurs, it is generally accompanied by classical symptoms of inflammation, i.e., pain, reddening and edema. The inflammation stage begins immediately after injury; first with vasoconstriction, and platelet aggregation at the injury site, and then the infiltration of leukocytes and

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T-lymphocytes into the wound area. The cicatrisation process proceeds naturally, since the damaged tissue attempts to re-establish hemostasis. In the inflammatory stage, the main aim is the removal of debris, damaged tissue, and bacteria by neutrophils and macrophages which have a role in anti-microbial defense and debridement of devitalized tissue by production of proteolytic enzymes and reactive oxygen species (ROS).[1] ROS is produced in high amounts at the site of wound as a defense mechanism against invading bacteria.[8] However, the presence of increased numbers of neutrophils and ROS overwhelm the antiprotease substances that normally protect the tissue cells and the extracellular matrix.[9] At high concentrations, ROS can induce severe tissue damage and even lead to neoplastic transformation decreasing the healing process by damages in cellular membranes, DNA, proteins and lipids.[1] Fibroblasts may be killed and skin lipids will be made less flexible by excess ROS. Because of these, the overall role of antioxidants appears to be significant in the successful treatment and management of wounds. Antioxidants reduce these adverse effects of wounds by removing products of inflammation. They counter the excess proteases and ROS often formed by neutrophil accumulation in the injured site and protect protease inhibitors from oxidative damage.[10] The most likely mechanism of antioxidant protection is direct interaction of the extracts (or compounds) and the hydrogen peroxide rather than altering the cell membranes and limiting damage.[11] Compounds with high radical-scavenging capacity have been shown to facilitate wound-healing.

The proliferative phase is characterized by the proliferation of the granulation tissue to cover the wound area for the complete tissue repair and the angiogenesis process.[1] This phase ends up with the contraction of the wound in which the wound edges come together. The process of angiogenesis is pushed forward by the late inflammatory stage. In angiogenesis, endothelial cells migrate towards the injured area and form new blood vessels and capillaries, bringing oxygen and nutrients to the wound area. The process of fibroplasia is also based on migration and is also stimulated by hypoxia and action of cytokines.[6]

The remodeling stage is characterized by improvement in the components of the collagen fiber that increases the tensile strength.[1] The collagen III is replaced by collagen I, which is able to bond and form cross-linkages, creating an organized network of collagen and a stronger tissue.[6] Collagen synthesis may be affected by decrease of iron, O_2, vitamin C and alpha-ketoglutarate. These deficiency impair the proline and lysine hydroxylation which result in a synthesis of low resistance collagen and consequently in cicatrization deficiency.[12]

Research into the role of antioxidants from plants in wound-healing has been widely published.[10,13,14] This review aims to appraise published literature and evaluate whether wound-healing and antioxidant properties coexist in plants.

Plants possessing both wound-healing and antioxidant properties

For centuries, plants have been used to treat several diseases worldwide, and are still playing a major role in healthcare systems in many developing countries. The use of plant extracts or plant-derived compounds in the treatment and management of wounds has been well documented. Similarly, the presence of effective antioxidants in various plant extracts is well known. It has also been noted that many plants or plant-derived compounds possessing high levels of antioxidant properties also show wound-healing activities. In recent years, the search for "natural remedies" for the treatment of wounds and for novel antioxidants has gained momentum, and a significant body of literature is now available in this area of research. A list of plants that possess both wound-healing and antioxidant properties is presented in Table 1.

The effectiveness of *Centella asiatica* in promoting wound-healing of skin was studied extensively both *in vitro* and *in vivo*, and the application of *C. asiatica* extract had been shown to promote wound-healing in incision type and open wounds as represented by a greater collagen content and thickness of epithelium.[15] Asiaticoside derived from *Centella asiatica* (common names: gotu kola, Indian Pennywort and Mandookaparni) showed good wound-healing activity in both normal as well as delayed type healing models.[16] It was also shown to possess fibroblast proliferating activity.[17] Shukla et al.[18] observed that in asiaticoside treated wounds, the decreased levels of all antioxidants (enzymatic and nonenzymatic) were restored and increased significantly. These increased *in situ* levels of antioxidant can bring about enhanced healing. One of the mechanisms of the augmented healing by asiaticoside isolated from *C. asiatica* might be due to its capacity to increase tissue antioxidant levels. It was also reported that the application of asiaticoside could be helpful in wound repair only if applied during the active phase of healing. Idrus et al.[15] have recently shown in an *in vitro* study that supplementation of *C. asiatica* aqueous extract at low concentrations can be useful to promote corneal epithelium wound healing. It can be noted that *C. asiatica* has traditionally been used for centuries as a medicinal herb for the treatment of wounds, and was listed as a wound-healing plant in the French pharmacopoeia in

Table 1 Examples of some plants possessing both wound-healing and antioxidant properties

Name of plant	Family	References
Acacia Senegal (L.) Willd.	Fabaceae (*alt*. Leguminosae)	[41]
Acalypha indica L.	Euphorbiaceae	[41]
Allophylus rubifolius (Hochst. Ex A. Rich.) Engl.	Sapindaceae	[41]
Anagallis arvensis L.	Primulaceae	[43]
Anagallis foemina Mill.		
Anogeissus dhofarica A. J. Scott	Combretaceae	[41]
Aristolochia bracteolate L.	Aristolochiaceae	[42]
Becium dhofarense Sebald	Lamiaceae (*alt*. Labiatae)	[41]
Bridelia ferruginea Benth.	Phyllanthaceae	[39]
Buddleja globosa Hope	Scrophulariaceae	[20]
Centella asiatica (L.) Urb.	Araliaceae	[15-18]
Chromolaena odorata (L.) R. M. King & H. Rob.	Asteraceae (*alt*. Compositae)	[21]
Clerodendrum infortunatum L.	Lamiaceae (*alt*. Labiatae)	[40]
Combretum smeathmanii G. Don	Combretaceae	[25]
Cordia perrottettii L.	Boraginaceae	[41]
Curcuma longa L.	Zingiberaceae	[22,23]
Dendrophthoe falcata (L. f.) Ettingsh.	Loranthaceae	[35]
Ficus asperifolia Miq.	Moraceae	[34]
Ficus lutea Vahl		[41]
Gossypium arboreum L.	Malvaceae	[34]
Gunnera perpensa L.	Gunneraceae	[24]
Hippophae rhamnoides L.	Elaeagnaceae	[38]
Holoptelea integrifolia (Roxb.) Planch.	Ulmaceae	[36]
Memecylon edule Roxb.	Melastomataceae	[37]
Moringa peregrina (Forssk.) Fiori	Moringaceae	[41]
Olea europaea L.	Oleaceae	[41]
Phyllanthus muellerianus (Kuntze) Exell.	Phyllanthaceae	[25]
Plagiochasma appendiculatum Lehm. & Lindenb.	Aytoniaceae	[31]
Pluchea Arabica (Boiss.) Qaiser & Lack	Asteraceae (*alt*. Compositae)	[41]
Pulicaria crispa Sch. Bip.		
Rhizophora mangle L.	Rhizophoraceae	[32]\
Secamone afzelii (Schult.) K. Schum.	Apocynaceae	[28]
Spathodea campanulata P. Beauv.	Bigoniaceae	[28]
Stryphnodendron obovatum Benth.	Fabaceae (*alt*. Leguminosae)	[27]
Stryphnodendron polyphyllum Mart.		
Terminalia sericea Burch. Ex DC.	Combretaceae	[24]

1884, the ancient traditional Chinese Shennong Herbal some 2,000 years ago, and in the Ayurvedic medicine about 3,000 years ago.

The leaves of *Buddleja globosa* (common name: Orange Ball Buddleja) are used traditionally in Chile for wound-healing. The infusion of the leaves is used topically for the treatment of wounds, burns and external and internal ulcers. To reaffirm its traditional medicinal use as a wound-healing agent, this species was tested for its ability to stimulate growth of fibroblasts and for antioxidant activity *in vitro*, as the effect of the aqueous extract of the leaves of *B. globosa* on two of these processes are considered to be extremely important in the initial stages of tissue repair and wound-healing.[19,20] It was reported that the damage caused by oxygen free radicals, which were produced during the inflammatory stage of the wound-healing process delayed wound-healing.[18] Therefore, strong antioxidant activity of the extract, because of the presence of flavonoids and caffeic acid derivatives, could be attributed as one of the mechanisms of *B. globosa* extract in the wound-healing process.[19] It is worth mentioning that the leaves of several other species of *Buddleja* are also applied topically as a poultice or lotion for healing of wounds.

The wound-healing property of the extracts of the leaves of *Chromolaena odorata* (common names: Jack in the bush, Fragrant boneset, Fragrant mistflower, Crucita and Blue mistflower), which has traditionally been used to treat skin wounds in Indonesia, was investigated.[21] It was revealed that the extracts played an important role in a biological free-radical-scavenging system and made a positive contribution to promote wound-healing. Extracts from the leaves of *C. odorata* displayed enhanced proliferation of

fibroblasts, endothelial cells and keratinocytes, stimulation of keratinocyte migration in an *in vitro* wound assay, up-regulation of production by keratinocytes of extracellular matrix proteins and basement membrane components, and inhibition of collagen lattice contraction by fibroblasts.[21] This plant is also rich in antioxidant flavonoids.

Curcumin, a naturally occurring *o*-methoxyphenol derivative from *Curcuma longa* (common name: Turmeric and Haldi), has been shown to possess several biological properties including antioxidant, induction of detoxification of enzymes and protection against degenerative diseases.[22,23] Topical applications of compounds with free-radical-scavenging properties in patients have shown to improve significantly wound-healing and to protect tissues from oxidative damage.[23]

Aqueous and methanol extracts of *Terminalia sericea* (common names: Mususu, Silver cluster-leaf or Silver terminalia and Vaalboom) and *Gunnera perpensa* (common name: River pumpkin) are well documented for their use for topical wound-healing and treating inflammation.[24] Steenkamp et al.[24] demonstrated that the methanol and the water extracts of these plants could display significant free-radical-scavenging activity in a concentration dependant manner in *in vitro* assays.

According to an *in vitro* study conducted by Agyare et al.[25] strong antioxidative potential was observed with the wound-healing active extracts of *Phyllanthus muellerianus* (common name: Mbolongo), which has traditionally been used for the treatment of wounds in Western Africa, and *Combretum smeathmanii* (common name: Honey plant). The activity was attributed to the high polyphenol content in form of tannins. Their study demonstrated that hydrophilic extracts from *P. muellerianus* and the lead compound geraniin, an ellagitannin with significant antioxidant property, could stimulate activity on dermal fibroblasts and keratinocytes, leading to increased cell proliferation, barrier formation and formation of extracellular matrix proteins, and thus could justify the traditional clinical uses of such extracts for wound-healing.

Proanthocyanidins or condensed tannins are a group of biologically active polyphenolic bioflavonoids which are known to facilitate wound-healing. Herbal extracts such as the grape seed extract are highly rich in antioxidants. Grape seed proanthocyanidin extract has been reported to have various clinically relevant redox-active properties. It was observed that grape-seed-derived natural extracts facilitate oxidant-induced VEGF expression in keratinocytes which suggested that they may have beneficial effects in promoting dermal wound healing and other related skin pathologies.[26] It was also reported that tannins promote the cicatrisation of wounds through several cellular mechanisms: chelation of free radicals and ROS, promoting contraction of the wound and increasing the formation of capillary vessels and fibroblasts and inducing keratinocyte proliferation.[27]

Stem barks of the two species *Stryphnodendron polyphyllum* and *S. obovatum,* from the family Leguminosae, are widely used in traditional medicine in Brazil for wound-healing. Lopes et al.[27] investigated the wound-healing and antioxidant properties of these species. The healing effect of the ointments containing crude extracts of the stem bark of *S. polyphyllum* and *S. obovatum* was studied in cutaneous wounds of Wistar rats. An increase in epidermal growth was observed with the extracts of these plants. The antioxidant activity through scavenging of the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical in thin layer chromatography (TLC), confirmed the anti-radical properties of these extracts in both species which probably favored cicatrisation. The extract from *S. polyphyllum* showed more effective wound-healing ability than that of *S. obovatum*, despite the fact that the former had a lower tannin content.

Similarly, the DPPH assay was used to investigate the two Ghanaian species *Secamone afzelii* shoots and *Spathodea campanulata* stem bark, both well known for their wound-healing properties.[28] Both extracts showed strong ROS scavenging effects and in *Secamone afzelii, in vitro* bioassay-guided fractionation led to the isolation of vitamin E as the major antioxidant compound.

α-Lipoic acid (LA) and its reduced form, dihydrolipoic acid, are known for their antioxidant activity. LA has been shown to be beneficial in various forms of oxidative stress and is of interest as a therapeutic agent in ischemia reperfusion injury, diabetic complications, cataract formation, HIV activation, neurodegenerative disorders, and radiation injury.[29] The effect of LA supplementation in patients undergoing hyperbaric oxygen therapy (HBO) was investigate.[30] It was shown that LA exerts its antioxidant activity either by directly interacting with free radicals, thereby counteracting lipid and DNA oxidation induced by oxygen exposure, or by recycling vitamin E, thus enhancing the total antioxidant status of the plasma. An inhibitory effect of LA on pro-inflammatory cytokine was also reported. It was demonstrated that an adjuvant effect of LA in HBO therapy on impaired wound-healing by eliminating the undesired secondary effects of oxygen exposure, which accelerates the healing process.

Singh et al.[31] reported potent wound-healing properties of the extract of one of the Indian liverworts, *Plagiochasma appendiculatum,* which was evident from the wound contraction and increased tensile strength *in vitro*. It was also shown that the same extract had potent antioxidant activity, evident from its lipid peroxidation inhibiting and the superoxide dismutase and catalase increasing activity. Thus the wound-healing activity could be attributed to its potent radical-scavenging activity.

The bark of *Rhizophora mangle* (common name: Red mangrove) has been used traditionally in folk medicine in Caribbean countries. Aqueous extracts are rich in tannins and have been proven experimentally to possess antibacterial, wound-healing and antiulcerogenic effects.[32] The gastroprotective effect of *R. mangle* in a model of diclofenac-induced ulcers in rats was studied.[32] Pretreatment with the extract resulted in a significant decrease of the ulcerated area. The highest dose of the extract reported to induce glutathione peroxidase and superoxide dismutase activity. Moreover, lipid peroxidation levels were inhibited in a dose-dependent manner. These results suggested that the gastroprotective effect of *R. mangle* might have been mediated through an antioxidant dependent way. The wound-healing properties of this plant was also studied on human volunteers.[33] Thirty-seven patients with open wounds from surgical intervention of pilonidal cyst or pilonidal fistula were enrolled on a voluntary basis in a comparative blinded clinical trial and randomly assigned to a topical treatment with an aqueous extract of *R. mangle* once a day or twice a day or mercurochrome twice a day. A thin dark red coloured film covering the wound was observed in all the cases treated with the extract. The wound areas of the groups treated with the extract exhibited a greater reduction compared to the group treated with mercurochrome. No subject showed any sign of adverse effects and no secondary infections were observed.

Gossypium arboreum (common name: Tree cotton) and *Ficus asperifolia* (common name: Fig) extracts, which are used in wound-healing in Ghana, were shown to possess both significant dose-dependent effects on the growth of human dermal fibroblast and antioxidant properties *in vitro*.[34] The effects of the extracts on hydrogen peroxide induced damage on the fibroblast cells were assessed and it was observed that fibroblast cells were protected against hydrogen peroxide damage by various degrees by the extracts. Both extracts displayed protection against oxidative damage to the fibroblast cells and it was concluded that antioxidant effect could contribute the wound-healing activity.

To confirm the ethnotherapeutic claims of *Dendrophthoe falcata* (common name: Indian common mistletoe) for its use in the treatment of skin diseases, and wounds, the wound-healing activity of this plant was studied *in vitro* in rat models.[35] Anti-microbial and antioxidant activities were also assessed to try to understand the mechanism of wound-healing by this plant. The results showed that *D. falcata* extract had potent wound-healing capacity. Hydroxyproline and hexosamine expressions were correlated well with the observed healing pattern. The results also exhibited that *D. falcata* extract was able to inhibit lipid peroxidation, reduce glutathione, superoxide dismutase levels and increase the catalase activity *in vivo* in rats – all of which are indicative of its potent antioxidant property.[35]

Reddy et al.[36] evaluated the antioxidant and antimicrobial activity of the methanolic extract of *Holoptelea integrifolia* (common names: Chirhol or Tapasi) in addition to wound-healing activity in rats. The results confirmed the wound-healing activity of *H. integrifolia*, which also showed significant antimicrobial and antioxidant activity. The anti-inflammatory, analgesic and antioxidant activities of the leaves of *Memecylon edule* (common names: Kaayam, Delek bangas, Delek air, Miat and Nemaaru), used traditionally in Thailand, were studied.[37] The results of the study provided evidence for the topical use of the leaves of this plant as an anti-inflammatory, analgesic agent and as an antioxidant, in the traditional management of pain and inflammatory diseases and for wound-healing. The efficacy of *Hippophae rhamnoides* (common name: Sea buckthorn) (SBT) seed oil on burn wound model was investigated.[38] The SBT seed oil augmented the wound-healing process as indicated by significant increase in wound contraction, hydroxyproline, hexosamine, DNA and total protein contents in comparison to control and reference control groups. It was observed that SBT seed oil also had significant antioxidant properties as evident from considerable increase in reduced glutathione (GSH) level and reduced production of ROS in wound granulation tissue.

Crude ethanolic extract of *Bridelia ferruginea* leaf demonstrated significant *in vitro* antioxidant activity which was relevant to wound treatment.[39] The DPPH assay revealed a concentration-dependant antioxidant activity of the crude ethanolic extract of *B. ferruginea* leaves. The aqueous and ethanolic extracts were shown to be effective in protecting the fibroblast cells from the damage by hydrogen peroxide. The antioxidant data, as measured by the DPPH assay, was shown to be well comparable with the antioxidant effects of crude extracts from plant species used to treat wounds in Vietnam, Ghana and

Nigeria. It was concluded that the ethanolic extract of *B. ferruginea* could stimulate fibroblast growth and protect the cells from hydrogen peroxide-induced injury, both of which might play a vital role in its effect on tissue repair. Gouthamchandra et al.[40] studied the natural antioxidants from chloroform, petroleum ether and ethanol extracts of *Clerodendrum infortunatum* (common name: Hill glory bower) leaves. Free-radical-scavenging and wound-healing activities of these extracts were also assessed, and the polyphenols present in the extract were thought to be partly responsible for the wound-healing effect.

Marwah et al.[41] investigated the antioxidant activities of the some edible and wound-healing herbs in Oman. The DPPH and the phosphomolybdenum assay methods were used. Of the 19 plants investigated, the aqueous ethanol extracts of *Acacia senegal, Acalypha indica, Allophylus rubifolius, Anogeissus dhofarica, Becium dhofarense, Cordia perrottettii, Ficus lutea, Moringa peregrina, Olea europaea, Pluchea arabica* and *Pulicaria crispa* showed the highest levels of inhibition of DPPH radical. The highest total antioxidant capacity of the ethanol extracts was obtained for *Caralluma quadrangular, M. peregrine, O. europaea* and *P. crispa* in the phosphomolybdenum assay. The traditional uses of the plants in wound-healing were rationalized on the basis of their antioxidant capacity. The leaves of *Aristolochia bracteolata* (common name: Worm killer) are used in India for the rapid healing of cuts and wounds. The ethanol extract of this plant showed a considerable effect on wound-healing, with a significant increase of the level of two powerful antioxidant enzymes, super oxide dismutase and catalase, in the granuloma tissue.[42] The wound-healing potential of *Anagallis arvensis* (common names: Red pimpernel, Red chickweed and Poorman's barometer) and *Anagallis foemina* (common name: Poorman's weatherglass), which are traditionally used for dermatological purposes, were evaluated by measuring the antimicrobial, anti-inflammatory and antioxidant properties using *in vitro* assays.[43] Both species exerted antimicrobial and anti-inflammatory effects. The aqueous extracts were found to be better free-radical-scavengers. The study revealed that both species had antimicrobial, anti-inflammatory and antioxidant activities related to their ethnomedicinal uses as wound-healing agents.

CONCLUSION

Many plants that have traditionally been used in the treatment of wounds, or have been shown to have a wound-healing property, also possess high level of antioxidant property. This review finds that the wound-healing property and antioxidant activity co-exist in many plant species from a variety of families. It appears that the wound-healing properties of plants, in most cases, are associated with their significant antioxidant activities.

REFERENCES

1. Jorge M P, Madjarof C, Ruiz A L T G, Fernandes A T, Rodrigues R A F, Sousa I M O, Foglio M A, Carvalho J E. Evaluation of wound healing properties of *Arrabidaea chica* Verlot extract. Journal of Ethnopharmacology. 2008; 118:361–6.
2. Judith R, Nithya M, Rose C, Mandal A B. Application of a PDGF-containing novel gel for cutaneous wound healing. Life Sciences. 2010; 87:1–8.
3. Singh M, Govindarajan R, Nath V, Rawat A K S, Mehrotra S. Antimicrobial, wound healing and antioxidant activity of *Plagiochasma appendiculatum* Lehm. et Lind. Journal of Ethnopharmacology. 2006; 107:67–72.
4. Agyare C, Asase A, Lechtenberg M, Niehues M, Deters A, Hensel A. An ethnopharmacological survey and *in vitro* confirmation of ethnopharmacological use of medicinal plants used for wound healing in Bosomtwi-Atwima-Kwanwoma area, Ghana. Journal of Ethnopharmacology. 2009; 125:393–403.
5. Hu X, Sun H, Han C, Wang X, Yu W. Topically applied rhGM-CSF for the wound healing: A systematic review. Burns. 2011; 37:729–41.
6. Tabatabai M A, Eby W M, Singh K P. Hyperbolastic modeling of wound healing. Mathematical and Computer Modelling. 2011; 53:755–68.
7. Menke N, Ward K, Witten T, Bonchev D, Diegelmann R. Impaired wound healing. Clinical Dermatology. 2007; 25:19–25.
8. Reddy B S, Reddy R K K, Naidu V G M, Madhusudhana K, Agwane S B, Ramakrishna S, et al. Evaluation of antimicrobial, antioxidant and wound-healing potentials of *Holoptelea integrifolia*. Journal of Ethnopharmacology. 2008; 115:249–56.
9. Mensah A Y, Sampson J, Houghton P J, Hylands P J, Westbrook J, Dunn C M, et al. Effects of *Buddleja globosa* leaf and its constituents relevant to wound healing. Journal of Ethnopharmacology. 2001; 77:219–26.
10 Houghton P J, Hylands P J, Mensah A Y, Hensel A, Deters A M. *In vitro* tests and ethnopharmacological investigations: wound healing as an example. Journal of Ethnopharmacology. 2005; 100:100–7.
11. Annan K, Houghton P J. Antibacterial, antioxidant and fibroblast growth stimulation of aqueous extracts of *Ficus asperifolia* Miq. and *Gossypium arboreum* L., wound-healing plants of Ghana. Journal of Ethnopharmacology. 2008; 119:141–4.
12. Maehata Y, Takamizawa S, Ozawa S, Izukuri K, Kato Y, Sato S, et al. Type III collagen is essential for growth acceleration of human osteoblastic cells by ascorbic acid 2-phosphate, a long-acting vitamin C derivative Matrix Biology. 2007; 26(5):371–81.
13. Thang P T, Patrick S, Teik L S, Yung C S. Anti-oxidant effects of the extracts from the leaves of *Chromolaena odorata* on human dermal fibroblasts and epidermal keratinocytes against hydrogen peroxide and hypoxanthine–xanthine oxidase induced damage. Burns. 2011; 27:319–27.
14. Adetutu A, Morgan W A, Corcoran O. Antibacterial, antioxidant and fibroblast growth stimulation activity of crude extracts of *Bridelia ferruginea* leaf, a wound-healing plant of Nigeria. Journal of Ethnopharmacology. 2011; 133:116–19.
15. Idrus R B H, Chowdhury S R, Manan N A B A, Fong O S, Adenan M I, Saim A B. Aqueous extract of *Centella asiatica* promotes corneal epithelium wound healing *in vitro*. Journal of Ethnopharmacology. 2012; 140:333–8.
16. Shukla A, Rasik A M, Jain G K, Shanker R, Kulsreshtha D K, Dhawan B N. *In vitro* and *in vivo* wound healing activity of asiaticoside isolated from *Centella asiatica*. Journal of Ethnopharmacology. 1999; 65:1–11.
17. Maquart F X, Bellon G, Wegrowski Y, Barel J P. Stimulation of collagen synthesis in fibroblast culture by a triterpene extracted from *Centella asiatica*. Connective Tissue Research. 1990; 24:107–20.
18. Shukla A, Rasik A M, Dhawan B N. Asiaticoside-induced elevation of antioxidant Levels in healing wounds. Phytotherapy Research. 1999; 13:50–4.
19 Yamasaki T, Li L, Lau B H S. Garlic compounds protect vascular epithelial cells from hydrogen peroxide-induced oxidant injury. Phytotherapy Research. 1994; 8:408–12.
20. Mensah A Y, Sampson J, Houghton P J, Hylands P J, Westbrook J, Dunn C M, et al. Effects of *Buddleja globosa* leaf and its constituents relevant to wound healing. Journal of Ethnopharmacology. 2001; 77:219–26.

21. Thang P T, Patrick S, Teik L S, Yung C S. Anti-oxidant effects of the extracts from the leaves of *Chromolaena odorata* on human dermal fibroblasts and epidermal keratinocytes against hydrogen peroxide and hypoxanthine–xanthine oxidase induced damage. Burns. 2001; 27:319–27.
22. Sarker S D, Nahar L. In "Turmeric: The Genus *Curcuma*" (editors: P. N. Ravindran, K. N. Babu and K. Sivaraman), Bioactivity of turmeric, CRC Press, USA, 2007.
23. Gopinath D, Ahmed M R, Gomathi K, Chitra K, Sehgal P K, Jayakumar R. Dermal wound healing processes with curcumin incorporated collagen films. Biomaterials. 2004; 25:1911–17.
24. Steenkamp V, Mathivha E, Gouws M C, Rensburg C E J. Studies on antibacterial, antioxidawnt and fibroblast growth stimulation of wound healing remedies from South Africa. Journal of Ethnopharmacology. 2004; 95:353–7.
25. Agyare C, Asase A, Lechtenberg M, Niehues M, Deters A, Hensel A. An ethnopharmacological survey and *in vitro* confirmation of ethnopharmacological use of medicinal plants used for wound healing in Bosomtwi-Atwima-Kwanwoma area, Ghana. Journal of Ethnopharmacology. 2009; 125:393–403.
26. Sen C K, Khanna S, Gordillo G, Bagchi D, Bagchi M, Roy S. Oxygen, oxidants, and antioxidants in wound healing: an emerging paradigm. Annals of the New York Academy of Science. 2002; 957:239–49.
27. Lopes G C, Sanches A C C, Nakamura C V, Filho B P D, Hernandes L, Mello J C P. Influence of extracts of *Stryphnodendron polyphyllum* Mart. and *Stryphnodendron obovatum* Benth. on the cicatrisation of cutaneous wounds in rats. Journal of Ethnopharmacology. 2005; 99:265–72.
28. Houghton P J, Hylands P J, Mensah A Y, Hensel A, Deters A M. *In vitro* tests and ethnopharmacological investigations: Wound healing as an example. Journal of Ethnopharmacology. 2005; 100:100–7.
29. Packer L, Witt E H, Tritschler H J. α-Lipoic acid as a biological antioxidant, Free Radical Biology and Medicine. 1995; 19:227–50.
30. Alleva R, Nasole E, Donato F D, Borghi B, Neuzil J, Tomasetti M. α-Lipoic acid supplementation inhibits oxidative damage, accelerating chronic wound healing in patients undergoing hyperbaric oxygen therapy. Biochemical and Biophysical Research Communications. 2005; 333:404–10.
31. Singh M, Govindarajan R, Nath V, Rawat A K S, Mehrotra S. Antimicrobial, wound healing and antioxidant activity of *Plagiochasma appendiculatum* Lehm. et Lind. Journal of Ethnopharmacology. 2006; 107 67–72.
32. Berenguer B, Sanchez L M, Quilez A, Lopez-Barreiro M, deHaro O, Galvez J, et al. Protective and antioxidant effects of *Rhizophora mangle* L. against NSAID-induced gastric ulcers. Journal of Ethnopharmacology. 2006; 103:194–200.
33. Fernandez O, Capdevila J Z, Dalla G, Melchor G. Efficacy of *Rhizophora mangle* aqueous bark extract in the healing of open surgical wounds. Fitoterapia. 2002; 73:564–8.
34. Annan K, Houghton P J. Antibacterial, antioxidant and fibroblast growth stimulation of aqueous extracts of *Ficus asperifolia* Miq. and *Gossypium arboreum* L., wound-healing plants of Ghana. Journal of Ethnopharmacology. 2008; 119:141–4.
35. Pattanayak S P, Sunita P. Wound healing, anti-microbial and antioxidant potential of *Dendrophthoe falcata* (L.f) Ettingsh. Journal of Ethnopharmacology. 2008; 120:241–7.
36. Reddy B S, Reddy R K K, Naidu V G M, Madhusudhana K, Agwane S B, Ramakrishna S, et al. Evaluation of antimicrobial, antioxidant and wound-healing potentials of *Holoptelea integrifolia*. Journal of Ethnopharmacology. 2008; 115:249–56.
37. Nualkaew S, Rattanamanee K, Thongpraditchote S, Wongkrajang Y, Nahrstedt A. Anti-inflammatory, analgesic and wound healing activities of the leaves of *Memecylon edule* Roxb. Journal of Ethnopharmacology. 2009; 121:278–81.
38. Upadhyay N K, Kumar R, Mandotra S K, Meena R N, Siddiqui M S, Sawhney R C, et al. Safety and healing efficacy of Sea buckthorn (*Hippophae rhamnoides* L.) seed oil on burn wounds in rats. Food and Chemical Toxicology. 2009; 47:1146–53.
39. Adetutu A, Morgan W A, Corcoran O. Antibacterial, antioxidant and fibroblast growth stimulation activity of crude extracts of *Bridelia ferruginea* leaf, a wound-healing plant of Nigeria. Journal of Ethnopharmacology. 2011; 133:116–19.
40. Gouthamchandra K, Mahmood R, Manjunatha H. Free radical scavenging, antioxidant enzymes and wound healing activities of leaves extracts from *Clerodendrum infortunatum* L. Environmental Toxicology and Pharmacology. 2010; 30:11–18.
41. Marwah R G, Fatope M O, Mahrooqi R A, Varma G B, Abadi H A, Al-Burtamani S K S. Antioxidant capacity of some edible and wound healing plants in Oman. Food Chemistry. 2007; 101:465–70.
42. Shirwaikar A, Somashekar A P, Udupa A L, Udupa S L, Somashekar S. Wound healing studies of *Aristolochia bracteolata* Lam. with supportive action of antioxidant enzymes. Phytomedicine. 2003; 10:558–62.
43. López V, Jäger A K, Akerreta S, Cavero R Y, Calvo M. Pharmacological properties of A*nagallis arvensis* L. "scarletpimpernel" and *Anagallis foemina* Mill. "bluepimpernel" traditionally used as wound healing remedies in Navarra (Spain) Journal of Ethnopharmacology. 2011; 134:1014–17.