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Plant-Derived Compounds for Wound Healing- A Review

Rex Jeya Rajkumar S[1], MSA Muthukumar Nadar[1] and Paulraj Mosae Selvakumar[2]*

[1]*Department of Biosciences and Technology, Karunya University, India*

[2]*Department of Chemistry, Karunya University, India*

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***Corresponding author:** Paulraj Mosae Selvakumar, Department of Chemistry, Karunya University, Tamil Nadu, India, Email: pmosae@gmail.com

Abstract

Wounds are the result of damages or injuries that disturb the normal structure of the skin tissue. Wound healing is a natural but a protracted and complex process of tissue repairing, regenerating, and remodelling in response to wounding injury. Various plant products have been used in the treatment of wounds over the years. Compounds that are derived from medicinal plants need to be identified, screened and analyzed for its antimicrobial, anti-oxidant, and wound healing activity. Wound healing phytochemical compounds fights infection, promotes blood clotting, and accelerate the healing process. Numerous phytochemical compounds have been identified and synthesized from medicinal plants that have unique properties associated with the mechanism of wound healing. This review focus on the plant-derived phytochemical compounds that promote wound healing process.

Keywords: Phytochemicals; Compounds; Wound; Wound Healing; Medicinal Plants

Abbreviations: CAM: Chick Chorioallantoic Membrane; JNK: Jun N-Terminal Kinases; FAK: Focal Adhesion Kinases; Erk: Extracellular Signal-Regulated Kinases

Introduction

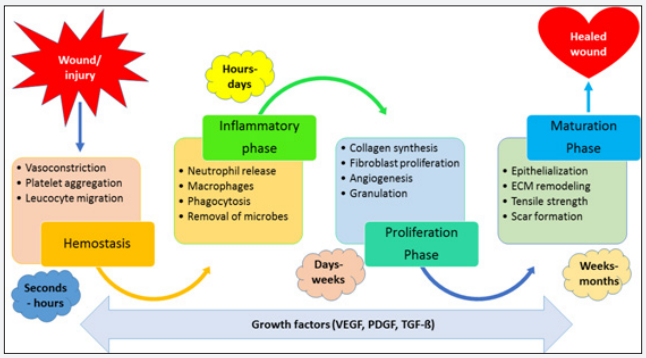

Figure 1: Phases of wound healing.

Wound healing is a natural but a systematic and complex process which involves three different phases i.e. inflammatory phase, proliferative phase and maturation phase [1,2]. Wounds affect the patients quality of life by high cost for the treatment [3]. Medicinal plants have been used worldwide, as traditional treatments for wound healing. The plant-derived compounds from medicinal plants have proven to have wound healing properties, of which many have been used to start the development of new inputs for the pharmaceutical industry. Traditional medicinal plants have a strong perspective on the treatment and management of wounds. The therapeutic value of these plant-derived compounds that produce certain physiological action on the human body [4]. These compounds belong to the families like alkaloids, essential oils, flavonoids, tannins, terpenoids, saponins, and phenolics (Figure 1) [5]. Numerous studies in the literature detailed the activities and effects of plant-derived compounds with anti-microbial, antioxidant properties that promote faster-wound healing and skin regeneration [6-12]. In this chapter, we review the various types of plant-derived phytochemical compound that promotes wound healing process (Table 1).

Table 1: Plant-derived phytochemical compounds with wound healing properties.

S. No	Phytochemical Class	Compounds
1	Alkaloid	Berberine
2	Cardenolides	Calotropin
3	Coumarin	Cleomiscosin A, B, C and D
4	Cyanogenic glucoside	Acalyphin

5	Flavonoid	Kaempferol, Quercetin
6	Glycoside	Morindin, Rutin
7	Polyphenol	Curcumin, Chlorogenic acid, Ferulic acid, Caffeic acid
8	Sterol	ampesterol, ß-sitosterol and Stigmasterol
9	Tannins	Gallic acid, Tannic acid
10	Terpenes	Asiaticoside, Lupeol, Asiatic acid , Jasminol, Madecassic acid, Cleomeolide, Scabertopin, Salograviolide A, Ursolic acid

Plant-derived wound healing compounds

Asiaticoside: A triterpene glycoside compound Asiaticoside, isolated from Centella asiatica, is commonly known for its significant wound healing properties that have been studied in normal as well as diabetic wound healing. A topical application of 0.4% solution of asiaticoside over the wound of streptozotocin-induced diabetic rats increased the tensile strength, hydroxyproline content, protein content and epithelialization thereby facilitating the wound healing [13]. In guinea pig, 0.2% solution of asiaticoside was applied topically which produced an increase in hydroxyproline, tensile strength and quick healing. Asiaticoside promoted angiogenesis in the CAM (chick chorioallantoic membrane) model at 40 µg/disk concentration. Enhanced wound healing activity was achieved by Asiaticoside has been attributed to Angiogenesis, collagen formation increased remodelling of the collagen matrix and stimulation of glycosaminoglycan synthesis in a rat wound chamber model [14,15]. Since antioxidants play an important role in the wound healing process, the effects of asiaticoside on the levels of antioxidants in the wound were reported in many researchers to explore the possible mechanism of asiaticoside in wound healing (Figure 2).

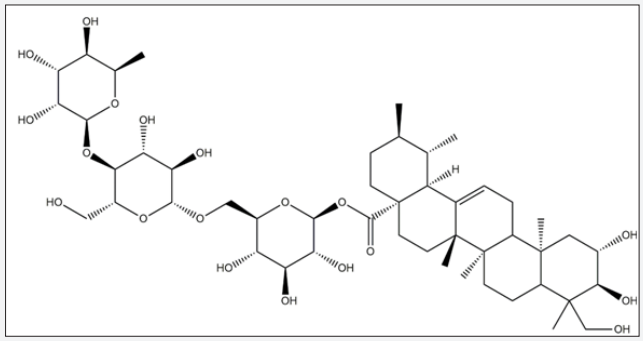

Figure 2 : Structure of Asiaticoside.

Topical application of Asiaticoside (0.2%) in cutaneous wounds in rats led to increased enzymatic and non-enzymatic antioxidants such as glutathione peroxidase, superoxide dismutase, catalase, vitamin E and Vitamin C (ascorbic acid) in newly formed tissues and decrease in lipid peroxide levels. Studies revealed that asiaticoside enhanced induction of antioxidant levels at an initial phase of wound healing. All these reports indicate that asiaticoside exhibits significant wound healing activity in normal as well as delayed healing models [16].

Curcumin: A phenolic compound, Curcumin, isolated from Curcuma longa Linn [17,18] known for its various biological and therapeutic properties reported possessing significant wound healing, antioxidant, anti-inflammatory, antimutagenic, anticarcinogenic, anti-infective and anticoagulant effects [17,19]. The wound-healing potential of curcumin is attributed to its anti-inflammatory, anti-oxidant and anti-infectious properties and also due to the inhibition of STAT, TNF-α, cyclin D1, COX-2, NFkB, IL (-1b, -6, -8) expressions, and down-regulation of MMP-8 expression [20]. Numerous studies demonstrated its diabetic wound healing of Curcumin (Figure 3) [21]. Curcumin is involved in collagen deposition, tissue remodelling, increased in fibroblast proliferation, granulation tissue formation and vascular density [17]. Curcumin is reported to have a strong antibacterial activity of curcumin is due to its action against the bacterial membrane [22]. Curcumin inhibited the growth of dangerous pathogens like methicillin-resistant Staphylococcus aureus (MRSA) [23], P. gingivalis, P. intermedia, F. nucleatum, T. denticola [24], B. cereus, E. coli [25], S. mutants, E. faecalis, P. aeruginosa and B. subtilis [22].

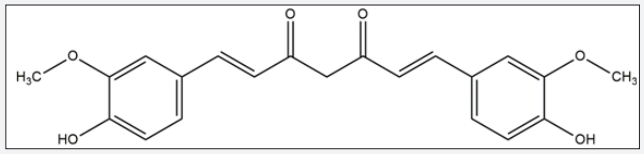

Figure 3 : Structure of Curcumin.

Chlorogenic acid: A polyphenolic compound, Chlorogenic acid is one of the most abundant polyphenols in the human diet [26]. Most of the heat-clearing Chinese medicines contain chlorogenic acid, which is also commonly used as the characteristic marker of quality control for traditional Chinese medicines because of its antibacterial activities [27]. As for other polyphenols, data obtained from in vivo and in vitro experiments showed that chlorogenic acid mostly presents antioxidant and anti-carcinogenic activities [28]. Rats treated with chlorogenic acid showed a significant increase in the activity of SOD, CAT, and GSH with a decrease in the TBARS level in granulation tissue compared with controls. Therefore, the antioxidant activity of chlorogenic acid may contribute to wound healing efficacy. Its wound healing promoting activity in excision wounds could also be attributed to its antioxidative effect (Figure 4).

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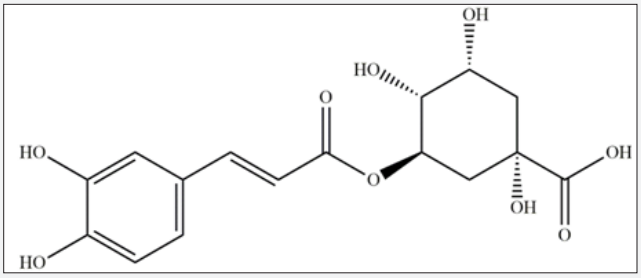

Figure 4 : Structure of Chlorogenic acid.

Since chlorogenic acid is abundant in common plants, it could be a fairly economical therapeutic agent for wound management as a healer, as well as to control abnormal healing [29]. Chlorogenic acid may present an example of an antioxidant therapeutic strategy for wound repair. Studies clarified the healing effects of chlorogenic acid supplementation on wound healing [30]. The improving wound healing activity of chlorogenic acid may be explained by the following mechanisms: enhanced capillary density and collagen production effect, antioxidant and free radical scavenger effects on oxidative parameters, and anti-inflammatory effects on MMPs in wound tissues. Based on the literature, chronically excess chlorogenic acid intake may cause pro-oxidative effects on the liver, kidney, and bone marrow as side effects during long-term therapy [30].

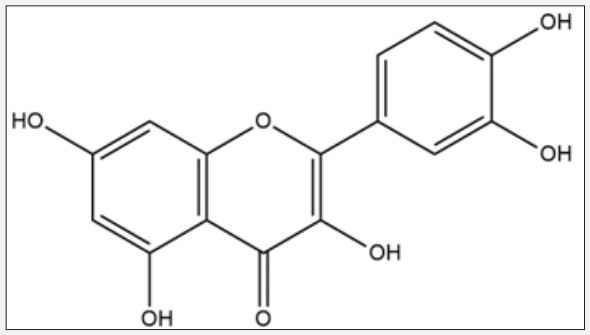

Figure 5 : Structure of Quercetin.

Quercetin: A flavonoid compound, Quercetin which is found in most of the herbs, vegetables and fruits Quercetin is reported to have the powerful anti-inflammatory, anticancer, and antioxidant supplements. Quercetin is also effective in wound healing by increasing the production of collagen and fibronectin. Quercetin may also help speed wound healing; studies have also shown that quercetin helps repair damage to nerve tissues in skin wounds. Quercetin incorporated collagenous matrix treated animal showed a better healing with an increase in proliferation of cells and wound contraction than the control group. Studies also suggested that quercetin incorporated collagen matrix could be a novel dressing material for dermal wound healing (Figure 5) [31]. It was reported that quercetin, a naturally-occurring antifibrotic agent, diminishes scar formation. Quercetin was examined using both mice and fibroblast cells on fibrosis and the wound healing rate and it was found to be decreased fibrosis, on wound healing, and relates quercetin's effects to changes in integrin expression on the surface of fibroblast cells.

The wound healing was occurred in about 14 days in the quercetin-treated group. Histopathology results revealed diminished fibrosis at the wound site in quercetin-treated animals suggest that quercetin could alter the cells' interactions with the extracellular matrix through the regulation of integrin expression to promote a decrease in fibrosis [32]. In another study, it was reported that a topical application of quercetin promotes wound healing by effectively modulating the growth factors cytokines, and cells involved in phases of wound healing. A significant time-dependent increase in wound closure was observed and also VEGF and TGF-β1 expressions were significantly up regulated whereas TNF-α level was markedly reduced. IL- 10 levels and CD31 stained vessels were markedly higher and in histopathology analysis, it was found to have less inflammatory cells, increased microvessel density, more fibroblast proliferation, more regular collagen deposition and epithelialization in quercetin-treated male Wistar groups [33].

Gallic acid: Gallic acid, a plant-derived polyphenolic compound which has a wide range of therapeutic and biological activities, including anti-oxidant, anti-inflammatory, anti-oxidant, anti-microbial, anti-cancer and wound healing activities (Figure 6) [34]. It is also used as an astringent in internal haemorrhage treatment. Studies revealed that Gallic acid possesses strong antioxidant that directly upregulates the expression of antioxidant genes and also accelerated cell migration of keratinocytes and fibroblasts in both normal and hyperglycemic conditions leads to the activation of growth factors that are responsible for wound healing, such as c-Jun N-terminal kinases (JNK), focal adhesion kinases (FAK), and extracellular signal-regulated kinases (Erk) [35]. Numerous studies reported that Gallic acid is a viable wound healing agent and a possible intervention to treat wounds ensuing from metabolic complications [35-37].

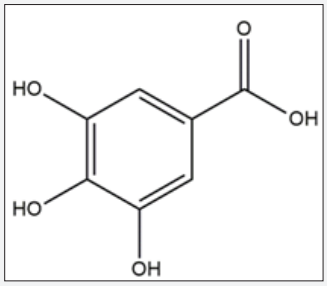

Figure 6 : Structure of Gallic acid.

Conclusion

Many plant-derived compounds with high levels of wound healing properties, being used for the design of topical formulations and wound dressings. However, there is a lack of reports regarding the dosage level, toxicological and adverse effects of these compounds. Henceforth, a standardized protocol and clinical trials are to be followed to give more solid evidence supporting the use of pharmacologically active plant-derived compounds in treatment and management of wounds.

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