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Mini Review

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Wound healing potentials of plant products

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Abstract

Wounds are perhaps, inescapable events in the life of an organism and at times they are dangerous or even life threatening. In the management of wound , control of pain, bleeding and infection have received due attention and have been successfully dealt with. These achievements, together with astounding advances in the surgical skill, and techniques, have greatly improved the asthetics of wound scar. Yet there is a ring of truth in what has been recently emphasized "the scope of surgery over the centuries has been directly proportional to the degree to which we have been able to depend upon repair and resistance to infection. Extensive screening of plants for wound healing profile has shown some good results. These plant products affect various phases (coagulation,inflammation,fibroplasia, collagenation, epithelization and wound contraction) of healing alike or differently. This is possible because various phases of wound healing are apparently independent , but interlinked and run concurrently. Some plant products are already in use. Isolation of active principles of these plants may provide the basic nucleus upon which synthetic drugs can be produced. The selected and careful use of these plant products may definitely help in better wound management. Hence it is possible that, herbal remedies definitely hold hope for the discovery of potent prohealers.

Key words: Wound healing, plant products, *Aloe vera*, *Lantana camara*, *Hypericum* spp.

1. Introduction

Wound is defined simply as the disruption of the cellular and anatomic continuity of a tissue [1].Wound may be produced by physical, chemical, thermal, microbial or immunological insult to the tissue. The process of wound healing consists of integrated cellular and biochemical events leading to reestablishment of structural and functional integrity with regain of strength of injured tissue. The events include coagulation, inflammation, formation of granulation tissue and tissue remodeling [2,3]. Many a time, it is difficult to say whether healing will take a normal course or not. Clinically, one often encounters non-healing, under-healing or over healing.

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Therefore, the aim of treating a wound is to either shorten the time required for healing or to minimize the undesired consequences [4]. Attention is directed towards discovering an agent, which will accelerate wound healing either when it is progressing normally [5,6], or when it is suppressed by various agents like corticosteroids [7], antineoplastics [8], non steroidal anti-inflammatory agents [9] etc.

Medical treatment of wound includes administration of drugs either locally (topical) or systemically (oral or parenteral) in an attempt to aid wound repair [10,11,12]. The topical agents used include antibiotics and antiseptics [13] (e.g chlorhexidine, povidone iodine, aminoglycosides, metronidazole, mupiromycin; they should be carefully used in chronic ulcers for the fear of contact sensitization), desloughing agents (chemical debridement , eg. Hydrogen peroxide, eusol and collagenase ointment) [14], wound healing promoters (eg.tretinoin, *aloe vera* extract, honey, comfrey, benzoyl peroxide, *chamomilia* extract, dexpanthenol, tetrachlordecaoxide solution, clostebol acetate and the experimental cytokines.

Various growth factors like platelet derived growth factor, macrophage derived growth factor, monocyte derived growth factor [5,6] etc. are necessary for the initiation and promotion of wound healing. Many substances like tissue extracts [15,16], vitamins [17], minerals [18] and a number of plant products [19,20,21], have been reported by various workers, to possess prohealing effects. These approaches are being advocated in wound management as body's repair kit [22].

In this modern age, the incidence of accidents has steeply risen, which is mostly responsible for different types of wounds. Consequently there exists a need for new agents which may be useful in proper wound management. In this direction a number of herbal products are being investigated.

2. Herbal products for wound management

Holistic approach to healing, popularly phrased as holistic medicine, has a bright future despite many dramatic discovery likely to take place in the new millennium. Over the past 20 years, there has been an ever increasing demand for an alternative system of healing.

Herbal products have been used in wound management for many years. Major medical institutions of India, Australia and United States of America realizing the importance of the alternative medicine, particularly the herbal products, are integrating this to their course work and practical experience [23]. A few plants/ plant products with promising outcome are discussed here.

2.1 Aloe vera

Aloe, native to Africa, is also known as "lily of the desert", the plant of immortality; and the medicinal plant. The name was derived from the alloeh meaning "bitter" because of the bitter liquid found in the leaves. In 1500 B.C Egyptians recorded use of this herbal plant in treating burns, infections and parasites.

Extensive research since 1930's has shown that the clear gel has a dramatic ability to heal wounds, ulcers, burns by putting a protective coating on the affected areas and speeding up the healing process. The plant contains 96% of water and rest is essential oil, aminoacids, minerals, vitamins, enzymes and glycoproteins. Various constituents of *Aloe vera* have been shown to have anti-inflammatory activity as well as to stimulate wound healing [24]. There are reports that *Aloe vera* gel applied topically could help heal radiation burns [25].

However, a large modern, placebo controlled study did not find aloe effective in this regard [26]. Some clinical reports suggest topical *Aloe vera* gel for healing minor burns [27]. Except in a rare person who is allergic to *Aloe vera*, topical application of the gel is harmless. In some severe burns, aloe gel may actually impede healing [28].

2.2 Lantana camara Linn

Lantana camara Linn (Fam-Verbenaceae) a shurb, native of tropical America and completely naturalised in many parts of India as an ornamental plant. The plant has wound healing, abortificient, antimalarial and anti-inflammatory properties [29,30,31].

The leaves of the plant are reported to be useful in the treatment of wounds, ulcers, bruises, sores etc. [32]. In a recent study by Dash *et al* both hydroalcoholic extract and fresh juice of leaves have favoured wound contraction [33].

The toxicities of the plant include nephrotoxicity, hepatotoxicity, photosensitization, dermatitis, intestinal haemorrhages [34,35]. In view of the alarming reports of its toxicity, the use of this plant in whole or any part thereof needs to be carefully regulated until the alarming toxic principles of the plant are properly identified and removed.

2.3 St.John's Wort

St.John's wort is a bushy perennial plant with numerous yellow flowers. It is native to many parts of the world including Europe and the United States. The plant has been used as an herbal remedy since the middle ages. It has a 2400 years history of safe and effective usage in many folk and herbal remedies. It is claimed to be useful in mental depression, anxiety, sleep disorders, menstrual cramping, sciatica and arthritis. The blossoms have been used in folk medicine to relieve ulcers, gastritis, diarrohea and nausea. Externally it is used on cuts as disinfectant and to relieve inflammation and promote healing. Fayazuddin has claimed that the tincture of *Hypericum* spp. given orally has a remarkable effect in lacerated and suppurated wounds, and play an important role in restoring tissue vitality [36].

Further studies on *Hypericum* spp. confirmed that Tincture of *Hypericum* spp. has prohealing action [37], as evidenced by the increase in wound contraction rate and granulation tissue breaking strengths. In addition, epithelization phase was also enhanced, as indicated by less time taken for the eschar to fall off.

2.4 Tridax procumbens

The common name of *Tridax procumbens* (TP) is Mexican Daisy Coatbuttons. It is genus of hardy perennial herb, native of tropical America and naturalized in tropical Africa, Asia and Australia. TP has grown wild after being introduced to India. Leaves of TP mainly consists of crude protein 26%, crude fibre 17% soluble carbohydrate 39% calcium oxide 5% [38].

The juice of the leaves of TP is used by villagers to arrest bleeding from cuts and bruises. It has been shown that TP juice accelerates two phases of healing namely epithelization and collagenation; and retards scar formation and granulation [39]. From these observations it was postulated that TP perhaps certain components with prohealing and some with antihealing properties. During the course of their work, Diwan *et al* observed that TP increased adrenal weight. So it was thought that TP may have corticotropic action.

From their study they suggested the possible use of the plant in suppressing wound contraction and preventing keloids and

hypertropic scars. With the results obtained from the above study they extended the work with TP on steroid depressed wound healing.

They reported that TP antagonized anti-epithelization and tensile strength depressing effect of dexamethasone (a known healing suppressant agent) without affecting anticontraction and antigranulation action of dexamethasone [40]. Udupa *et al* studied the effects of various extracts (whole plant extract, aqueous extract, butanol extract and ether fraction) of TP in dead space wound model [41].

The authors reported that whole plant extract has the greatest prohealing activity with increase in tensile strength and lysyl oxidase activity among the various extracts. Aqueous extract was also effective in increasing lysyl oxidase but to a lesser degree than whole plant extract.

Further it has been shown that extract of leaves of TP promotes wound healing in both normal and immunocompromised (steroid treated) rats in dead space wound model. The plant increased not only lysyl oxidase but also, protein and nucleic acid content in the granulation tissue, probably as a result of increase in glycosamino glycan content [42].

2.5 Chromolaena odorata

Chromolaena odorata was first identified in central America and Vietnam. The aqueous extract and the decoction from leaves of this plant have been used throughout Vietnam for the treatment of soft tissue wounds and burn wounds.

In clinical use it has been noted that aqueous extract of *Chromolaena odorata* enhances hemostatis [43] and stimulates granulation tissue and reepithelization [44]. Tang *et al* observed that Eupolin extract inhibits wound contraction and the inhibition of contraction is reversible. This supports the suggestion that it might be of therapeutic value in minimizing post burn scar contracture and deformities [45].

2.6 Hydnocarpus wightiana

The oil of *Hydnocarpus* spp. has been recognized for several years as anti-leprosy drug and as an anti-parasitic drug in the treatment of guinea worm infestation. There are reports that wounds in leprosy patients and in patients with diabetic ulcers and gangrene healed faster when the oil of *Hydnocarpus* spp. was given orally or administered topically [46].

Recently the wound healing effect of oil of *Hydnocarpus* spp. was studied with reference to collagenation and the strength of scar tissue [47]. The drug treated group showed a significant increase in strength of scar tissue in the incision wound model and also increased the strength of collagen tissue and hydroxyproline content in the dead space wound model.

In another study Oommen *et al* reported that *Hydnocarpus oil* administered orally promoted epithelization, but not wound contraction [48]. External application of oil of *Hydnocarpus* spp. and its paste significantly shortened the epithelization period when compared to control group. Further it was suggested that this finding is useful clinically because the oil may act as adjuvant in healing of wounds and ulcer in leprosy patients.

2.7 Helianthus annus Linn.

An ornamental annual herb, with erect, rough and hairy stem, common in Indian Gardens in swampy areas. In traditional medicine the plant is used by tribals for inflammation of eyes, sores, dysuria, colic, bite of tigers and bone fractures [49]. The seed oil contains high levels of lysine , arginine, aspartic and glutamic acids and tannins [50,51]. The alcoholic extract of whole plant of *H.annus* applied in the form of

an ointment on the excised wound of rat led to a significant reduction in total healing period.

This has been confirmed by histology where early appearance of fibroblasts are seen. Further it is stated that *H.annus* has hastened repair process which is indicated by a high degree of accumulation and an early appearance of the mucopolysaccharide [52].

2.8 Jasminum auriculatum

A small herb found in South India and the Western Peninsula. The alcohol free defatted extract of *J.auriculatum* leaves has been reported to contain lupeol and jasminol [53]. *J.auriculatum* has been shown to be beneficial in wound healing. The juice of the leaves in the form of jelly, on local application to a linear uniform excised wound in rats was found to promote wound healing, as assessed by histological, biochemical and contraction rate studies [54]

Further, it has been reported that the fresh juice of the leaves showed an increased and early gain of the tensile strength in the treated linear wounds in rats. The study indicated that collagenation contributed to improved tensile strength in the early phase of healing [55].

Further studies on musculoperitoneal wounds on the abdomen of rats, with 2.5% *J.auriculatum* leaves extract injected intramuscularly confirmed the prohealing property of leaves. The effect was more marked in case of skin wounds than in the musculoperitoneal wounds [56].

Ghee medicated with *J.auriculatum,* on topical application was found to accelerate the healing time of second degree burn wounds in rats by six days. The mucopolysaccharide accumulation was found to be significantly higher in groups treated with medicated ghee. The acceleration of the healing time was approximately 20% with unmedicated ghee and 30% in medicated ghee [57].

2.9 Ginkgo biloba

Ginkgo biloba (Salisburia aduantifolia) is also known as maiden hair tree. The genus ginkgo originated 200 million years ago and is considered as a living fossil [58,59]. Every part of the tree has been used. Extracts of leaves have been used therapeutically for centuries [60].

The main constituents are flavonoids and terpene trilactones. *Ginkgo biloba* exhibits a variety of interesting pharmacological activities such as increase in blood fluidity, antioxidant, prohealing, membrane stabilizing and improvement in cognition [61,62,63]. *Ginkgo biloba* has promoted epithelization without altering wound contraction. In case of dead space wounds *Ginkgo biloba* has increased granulation tissue breaking strength without altering granulation tissue mass weight.

However, it did significantly enhance the content of hydroxyproline of granulation tissue. Further it is reported that the prohealing action of the *Ginkgo biloba* is due to the presence of flavonoids [63].

2.10 Septilin

A proprietary herbal preperation claimed to be helpful in Gram negative and Gram positive infections [64,65]. It consists of *Balsamodendron mukul* (guggul), extracts *Maharasanadi kwath,* extract *Phyllanthus emblica,* extract *Tinospora cordifolia, Rubia cordifolia,* extract *Glycyrrhiza glabra* and shanka bhasma which are claimed to have wound healing promoting action. Septilin has promoted gain in tensile strength in incision wound model, but at the same time, did not modify the granulation phase of healing [66].

In case of excision wound Septilin promoted epithelization and wound contraction [67]. This may be due its effect on migration and mitosis of epithelial cells and promotion of contraction of myofibroblasts, the later being now recognized as responsible for wound contraction [68].

2.11 Centella asiatica

Centella asiatica (Brahmi) also known as "gotu kola", is the main herb in Ayurveda for nervous system, it is used in the repair of nervous tissue from crushing trauma, such as spinal injury, neuromuscular disorders, and to increase general brain function and memory concentration. Used extensively in Asia for the treatment of leprosy, gotu kola heals a host of corrupt skin conditions, including wounds, cellulitis, varicose vein.

Only the aqueous extract suspension in 5% propylene glycol of *Centella asiatica* as compared to other extracts (viz. alcoholic, petroleum ether, chloroform, glycosidal extract) promoted wound healing in experimentally induced open wounds on topical administration in rats as evidenced by the increase in collagen content and thickness of epithelium [69].

However, Suguna *et al* demonstrated that alcoholic extract (oral and topical) of *Centella asiatica* improved the rate of wound healing in rats [70]. Sunil Kumar *et al* showed that topical administration of the aqueous extract increased cellular proliferation, promoted the collagen synthesis at the wound site as evidenced by the increase in DNA, protein, collagen content of granulation tissue and in tensile strength. The treated wound epithelised faster and the rate of wound contraction was higher as compared to control.

Among the various formulations (ointment, cream and gel) of aqueous extract, the process of healing was better with the gel formulation [71]. Recently Maquart *et al* [72] and Sukla *et al* [73] demonstrated that active principles (Triterpens and asiaticoside) promote rapid wound healing.

2.12 Cissus quandrangularis

Cissus quandrangularis (Asthishankala) found in hotter parts of India. It is also wide spread in the drier parts of Africa and Arabia. Powdered roots are used for fracture of bone. Juice of the stem is dropped in to the ear in otorrhoea and in to the nose in epistaxis. The effect of the total extract of the plant on the healing of cortisone treated fracture has been compared with that of anabolic steroid nandrolone. Total extract of the plant, on parenteral administration, was found to neutralize anti-anabolic effect of cortisone in healing fracture.

The stimulatory effect of the total extract was found to be greater than that of anabolic steroid probably due to its vitamin content [74]. The total extract was found to hasten fracture healing by reducing the total convalescence period by 33% in experimental rats and dogs. The drug produced a quick recovery in animals. The Ca^{2+} 45 up-take study indicated early completion of calcification process and earlier remodeling phenomenon.

The tensile strength studies showed an early gain, leading to a 90% gain of its normal strength at the end of six weeks in comparison to 60% gain in strength noted in controls [75]. The plant extract has been found to influence fracture healing indirectly. Its effect on organic and inorganic phase of bone repair in normal and some pathological condition like alloxan diabetes and in cortisone treated animals, and its effect on endocrine response during fracture healing suggested that parenteral administration of drug acted directly on the testes and through pituitary to release the androgenic hormone in to blood.

The other evidence of its androgenic property was its ability to produce a positive nitrogen balance, increase in body weight and total weight of testis of animals. A potent anabolic steroid isolated from the plant showed a marked influence on the rate of fracture healing by influencing early regeneration process of all the connective tissue involved in the healing and quicker mineralization of the callus [76].

Recently it has been reported that methanolic extract of *Cissus quadrangularis* promoted the healing process of experimentally fractured radius-ulna of dogs as evidenced by radiological and histopathological examinations. The treated group also exhibited a reduction in serum calcium levels as compared to saline control animals [77].

2.13 Miscellaneous prohealers from plants

Thaker and Anjaria have reported on effects of *Azadirachta indica, Ocimum sanctum,* and *Begia odorata* on infected experimental wounds in laboratory animals. They have found that all these plants, notably *Ocimum sanctum* to promote healing [78]. *Euphorbia nerrifolia* (aqueous extract) when applied topically facilitated the healing of surgically produced cuteneous wounds in guinea pigs. It has increased the gain in tensile strength, DNA content and promoted epithelization [79].

Both crude betel nut extract and its polyphenols promoted healing of incision and dead space wounds[80]. Alcoholic extract of *Indigofera aspalathoids* has anti-inflammatory, wound healing and analgesic effect [81].

In a preliminary clinical trial in ten patients, fresh leaves of *Kalanchoea integra* showed encouraging results in inflammatory wound healing [82]. Mango butter which is extracted from the seeds of *Mangifera indica* has a wound healing property. It is used as application for ulcerations, fissures of lips, hands and chapped skin. Anecdotal evidence, some clinical observations, some animal model studies and few randomized clinical trials support the efficacy of honey in managing wounds [83,84].

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