

## WOUNDHEALING POTENTIAL OF INDIAN MEDICINAL PLANTS

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#### ABSTRACT

Wound is delineated as disruption of structural and physiological continuity of a living tissue. It may be produced by physical, chemical, thermal, microbial, or immunological damage to the tissue. Healing of wounds is one of the important areas of clinical medicines explained in many Ayurvedic texts. The Indian traditional system of medicine, Ayurveda is based on empirical knowledge of the observations and the experience over millennia. In different classical ayurvedic texts, more than 1200 diseases are mentioned. More than 1000 medicinal plants (89.93%); 58 minerals, metals or ores (5.24%); and 54 animal and marine products (4.86%) to heal wounds. Plants have the immense potential for the management and treatment of wounds. In most of the countries, a large number of plants are used by tribal and folklore for the treatment of wounds and burns. These natural agents induce healing and regeneration of the lost tissue by various mechanisms. These phytomedicine are not only cheap and affordable but are also safe. The presence of wide range of life-sustaining constituents in plants has urged scientists to examine these plants with a view to determine potential wound healing properties. Numerous pharmacological reports are available on number of plants employing different wound healing models and its underlying molecular mechanism for the validation of their traditional claims and development of potent, safe and effective and globally accepted herbal drugs for wounds.

Key words: Indian Medicinal Plants, Wound healing, Proliferative phase, Ayurvedic remedies.

#### INTRODUCTION

#### Wound

Wound is delineated as disruption of structural and physiological continuity of a living tissue. It may be produced by physical, chemical, thermal, microbial, or immunological damage to the tissue. When skin is torn, cut, or punctured it is termed as an open wound and when force trauma causes a contusion, it is called closed wound, whereas the burn wounds are caused by fire, heat, radiation, chemicals, electricity, or sunlight [1, 2].

#### Pathology of wounds

Wounds are physical injuries that results in an opening or breaking of the skin. Proper healing of wounds is very essential for the restoration of disrupted anatomical continuity and disturbed functional status of the skin. Healing is a complex process initiated in response to an injury that restores integrity and function of damaged tissues of skin. Wound healing involves continuous interactions between cell–cell and cell–matrix that allow the process to proceed in three overlapping phases viz. inflammatory phase(0-3days), cellular proliferation or proliferative phase (3-12 days) and remodeling phase (3-6 months) [3-5]. Healing requires the collaborative efforts of various tissues and cell lineages [6]. It involves aggregation of platelets, clotting of blood, fibrin formation, an inflammatory response to injury, alteration in the ground substances, angiogenesis and reepithelialization. Healing process is not complete until the disrupted surfaces are firmly knit by collagen[7] The basic principle behind optimal wound healing is to minimize tissue damage and provide adequate tissue perfusion and oxygenation, proper nutrition to tissue and moist wound healing environment to restore the anatomical continuity and function of the wound[8]. Cutaneous wound healing is accompanied by sequence of biological events starting with wound closure and progressing to the repair and remodeling of damaged tissue [9] in an order. In spite of tremendous advances in the pharmaceutical industry, the availability of drugs capable of stimulating wound repair

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processes is still limited [10]. Moreover, due to high cost therapy and presence of unwanted side effects, management of chronic wounds is another major problem [11-12]. It is agreed that reactive oxygen species (ROS) are deleterious to wound healing process, as they show harmful effects on cells and tissues. Absorbable synthetic biomaterials are considered to be degraded via ROS [13]. Cytoprotective enzymatic group of enzymes called Freeradical-scavenging enzymes (FRSE) plays an essential role in the reduction, de-activation and removal of ROS as well as in regulation of wound healing process. Inflammation, which is a part of acute response, results in a coordinated influx of neutrophils at the site of wound. These cells produce free radicals through their characteristic "respiratory burst" activity. [14]. Free radicals are also generated by wound related non-phagocytic cells by nonphagocytic NAD (P)H oxidase mechanism [15]. Thus, the wound site has rich concentration of both oxygen and nitrogen centered reactive species along with their derivatives. These radicals results in oxidative stress leading to lipid peroxidation, breakage of DNA, and enzyme inactivation, including free-radical scavenger enzymes. Evidence for the role of oxidants in the pathogenesis of many diseases suggests that antioxidants may be of therapeutic use in these conditions. Application of compounds topically with free-radical-scavenging properties in patients has shown to improve wound healing processes significantly and protect tissues from oxidative damage [16].

#### Classification

Based on underlying cause of wound creation, Wounds are classified as open and closed wounds and on the basis of physiology of wound healing, acute and chronic wounds.

#### **Open wounds**

In this class, bleeding is clearly visible as blood escapes from the body. It is further classified as: Incised wounds, Laceration wounds, Abrasions or superficial wounds, Puncture wounds, gunshot wounds and penetration wounds [17].

#### **Closed wounds**

In closed wounds, blood escapes from circulatory system but remains in the body. It involves Contusion or bruises, hematomas or blood tumor, Crush injury etc.

#### Acute wounds

Acute wound is an injury to tissue that normally proceeds through an orderly and timely reparative process that results in sustained restoration of anatomic and functional integrity. Acute wounds are generally caused by cuts or surgical incisions and complete the wound healing process within the expected time frame [18].

#### Chronic wounds

Wounds that are failed to progress through the normal stages of healing and therefore enter in to a state of pathologic inflammation. These wounds either require a prolonged time to heal or recur frequently. Most common frequent causes of chronic wounds are Local infection, hypoxia, trauma, foreign bodies and systemic problems such as diabetes mellitus, malnutrition, immunodeficiency or medications [19, 20].

#### MECHANISM OF WOUND HEALING

The response to injury caused either surgically or traumatically, is immediate and the damaged tissue or wound then passes through four phases in order to affect a final repair.

# The Four Phases of Wound Healing First phase

It involves a brief and transient period of vasoconstriction and hemostasis. A 5-10 minute period of intense vasoconstriction is followed by active vasodilation accompanied by an increase in capillary permeability. Aggregated platelets within a fibrin clot secrete a variety of growth factors and cytokines that set the stage for an orderly series of events leading to tissue repair [21]

#### Inflammatory phase

The second phase of wound healing, the inflammatory phase, usually lasts between 24 and 48 hrs and in some cases persists for about 2 weeks [22] presents itself as erythema, swelling, and warmth, and is often associated with pain. The response increases vascular permeability, resulting in migration of neutrophils and monocytes into the surrounding tissue. First line of defence against infection is provided by neutrophils, engulfs cell debris and microorganisms. Migration of neutrophils ceases after the first few days of post-injury if the wound is not contaminated. Acute Inflammatory Phase persists due to wound hypoxia, infection, nutritional deficiencies, medication use, or other factors related to the patient's immune response, it can interfere with the late inflammatory phase [23]. In the late inflammatory phase, monocytes converted to macrophages in the tissues, which digest and kill bacterial pathogens, scavenge tissue debris and destroy remaining neutrophils. Transition from wound inflammation to wound repair is the function of macrophages that secretes a variety of chemotactic and growth factors that stimulate cell migration, proliferation, and formation of the tissue matrix.

#### **Proliferative phase**

The subsequent proliferative phase lasts for about 2 days to 3 weeks after the inflammatory phase, dominated by the formation of granulation tissue and epithelialization [24]. Its duration also depends up on the size of the wound. Chemotactic and growth factors released from macrophages and platelets stimulate the migration and activation of wound fibroblasts that produce a variety of substances essential to wound repair, including glycosaminoglycans (hyaluronic acid, chondroitin- 4sulfate, dermatan sulfate, and heparin sulfate) and collagen [25]. These form an amorphous, gel-like connective tissue matrix necessary for migration of cells. This phase also includes contraction of wound edges pull together to

reduce the defects in the third step epithelial tissues are formed over the wound site [26].

#### The Remodeling phase

This phase lasts for 3 weeks to 2 years. It involves formation of new collagen. The amount of collagen secreted determines the tensile strength of the wound. Tissue tensile strength is increased due to intermolecular cross-linking of collagen via vitamin-C dependent hydroxylation. Improper cross-linkage of collagen fibers has been responsible for nonspecific postoperative bleeding in patients with normal coagulation parameters [27].The scar flattens and scar tissues become 80% as strong as the original [28, 29].

#### Complications associated with wounds

Complications associated with wounds may include infection, cellulitis, deformity, overgrowth of scar tissue (keloid formation), gangrene that may require bleeding (wound hemorrhage), overwhelming systemic infection (sepsis), and tetanus, fatal infection of the nervous system. Open wounds involves decreased circulation (ischemia) and tissue death (necrosis) that require amputation of affected parts. Wounds involving nerve injury may be complicated by temporary or permanent loss of sensation or function of the affected body part. Trauma not involving direct nerve injury may lead to delayed involvement of the nervous system (reflex sympathetic dystrophy).

### Medications for wounds

• Antimicrobial ointments such as silver sulfadiazine, mafenide, silver nitrate, and povidone-iodine are used to reduce risk of infection.

• Nitrofurazone used for open wounds.

• Antibiotics such as oxacillin, mezlocillin, and gentamicin are used to treat infection.

• Prescription pain medications such as acetaminophen with codeine, morphine, or meperidine and anabolic steroids such as oxandrolone, may be used for severe burns to help decrease time of wound healing.

#### SIDE EFFECTS

Leukopenia has been reported as well following prolonged silver sulfadiazine application and could be secondary to medullar toxicity [30] silver sulfadiazine remains the main topical product used in burn units [31, 32] various observed toxic effects confirm that topical application of this cream should not be used for long periods on extensive wounds [30]. Impaired reepithelialization has been described. Bone marrow toxicity with silver sulfadiazine is observed [33]. 0.5% Silver nitrate is the standard and most popular silver salt solution widely used for topical burn wound therapy. Concentrations exceeding 1% silver nitrate are toxic to the tissues. Bacterial resistance to silver nitrate has been described [33]. The same is observed in case of antibiotics.

#### Ayurvedic remedies for healing of wounds

The Indian traditional system of medicine, Ayurveda is based on empirical knowledge of the observations and the experience over millennia. In different classical ayurvedic texts, more than 1200 diseases are mentioned. More than 1000 medicinal plants (89.93%); 58 minerals, metals or ores (5.24%); and 54 animal and marine products (4.86%) [34] are involved in management of different forms of these diseases. Healing of wounds is one of the important areas of clinical medicines explained in many Ayurvedic texts under the heading "Vranaropaka". Maharshi Agnibesha was first discussed the wound as a medical problem in Agnibesha Samhita (later known as Charaka Samhita) as the "Vrana". Maharshi Sushruta in Sushruta Samhita elaborated on wounds and also gave some more details about wound and its healing. According to the Ayurveda, Vrana (wounds or ulcers) is the discontinuation of lining membrane that after healing leaves a scar for life closely resembling the modern definition oe wounds. Similarly, inflammation is considered to be an early phase in the wound pathogenesis termed Vranashotha. Various types of wounds as mentioned in Ayurveda may be endogenous in origin due to a defect in human functional units, such as Vata (nerve impulses), Pitta (enzymes and hormones), and Kapha (body fluids), or exogenous because of trauma, such as Viddha (punctured wound), Chinna (cut wound), Bhinna (perforated wound), Picchita (contusion), Kshata (lacerated wound), and Ghrista (abrasion wound) [34]. According to Sushruta samhita, Classical management of wounds follow 60 therapeuic steps, starting with an aseptic dressing of the affected part of body and ending with the rehabilitation of the normal structure and function. These therapeutic measures were concentrated not only to accelerate the healing process but also to maintain the quality and aesthetics of the healing. As described in different Ayurvedic classics like Charaka Samhita (ca. 5000 b.c.), Sushruta Samhita (ca. 1000 b.c.), Astamga Hridaya (ca. a.d. 600), Dhanwantari Nighantu (ca. a.d. 1800), Bhavaprakash Nighantu (ca. a.d. 1500), and Ayurveda Siksha (a.d. 20th century), it has been estimated that 70% of the wound healing Ayurvedic drugs are of plant origin, 20% of mineral origin, and remaining 10% arise from animal products. These drugs are stated to be effective in various conditions such as Vrana (wounds or ulcers), Nadivrana (sinuses), Vranajakrimi (maggots in Vidradhi (abscess), Visarpa (erysipelas), wounds), Upadamsha (syphilitic ulcers), Netravrana (hordeolum), Dustavrana (septic wounds), Vranashotha (inflammatory changes of wounds), Vranavisha (cellulitis), Ugravrana (purulative ulcer), Pramehapidaka (diabetic carbuncle), and Bhagandara (fistula-in-ano) [34]. Scientific investigations have also been carried out to assess the wound healing properties of some these drugs.

Many Ayurvedic herbal plants have a very important role in the process of wound healing. Plants are more potent wound healers because they promote and enhance the repair mechanisms in the natural way. Extensive research has been carried out in the area of wound healing management through medicinal plants. Herbal medicines in wound management involve disinfection, debridement and providing a moist environment to encourage the establishment of the suitable environment for natural healing processes [35].

#### **Role of Plants**

Plants have the immense potential for the management and treatment of wounds. In most of the countries, a large number of plants are used by tribal and folklore for the treatment of wounds and burns. These natural agents induce healing and regeneration of the lost tissue by various mechanisms. These phytomedicine are not only cheap and affordable but are also safe. The presence of wide range of life-sustaining constituents in plants has urged scientists to examine these plants with a view to determine potential wound healing properties [36]. phytopharmaceutical laboratories Manv are now concentrating their efforts mainly to identify the active constituents and modes of action of various medicinal plants [37]. The medicinal property of these plants lies in bioactive constituents that produce definite physiological action on the human body [38]. These constituents include various chemical classes like alkaloids, essential oils, flavonoids, tannins, terpenoids, saponins, and phenolic compounds [39]. For the discovery of new potent drugs, the screening of herbal extracts has been of great interest to the scientists [40]. A number of reports concerning the antibacterial, antiinflammatory, and wound healing activity of various plants have appeared in the literature, but the vast majority has yet to be explored. Numerous pharmacological reports are available on number of plants employing different wound healing models and its underlying molecular mechanism for the validation of their traditional claims and development of potent, safe and effective and globally accepted herbal drugs for wounds.

# MEDICINAL PLANTS WITH SIGNIFICANT WOUND HEALING ACTIVITY

Recent studies with significant findings for wound healing characteristic of some medicinal plants are emphasized here

#### Rafflesia Hasseltii

*Rafflesia hasseltii* is one of the world's largest parasitic flowering plants belongs to the family *Rafflesiaeae*. The buds and flowers have a high content of tannins and phenols, toxic in huge quantities [41, 42]. The plant has been reported to pocesses anti-microbial activity [43] and tannins inflicted with antioxidant activity [42]. Wound healing acceleration of *R.hasseltii* is due to its antioxidant and antimicrobial properties. Enhancement in the synthesis of collagen and angiogenesis [44, 45] fibroblasts and blood capillaries by *R.hasseltii* indicates its action is at proliferative phase. Its wound healing mechanism is endorsed by tannins, reported to improve healing and protect tissues from oxidative damage [46].

#### Clitoria ternatea

*Clitoria ternatea* is one of the vital Ayurvedic medicinal plants commomly known as Butterfly Pea in western countries and Aparajitha in Traditional Ayurvedic system of medicine belongs to family *Fabaceae*. The plant bears Flavanoids and phenolic compounds as chief phytoconstituents. Wound healing activity possibly due to its antioxidant, anti-inflammatory and immunomodulatory activities [47]. The seed and root extracts exerts healing mechanism by acting on all the phases viz.wound contraction, proliferative and remodeling phase [47].

#### Rubus sanctus Schreber

*Rubus sanctus Schreber*, family *Rosaceae*. Flavonoids like quercetin, kaempferol, caffeic acid and chlorogenic acid; phenolic acids, tannins, amino acids, sugars, pectins, carboxylic acids, anthocyanins, catechins, vitamin C and saturated or unsaturated fatty acids [48-51] are the major phytoconstituents. Flavonoids [52] endorse wound-healing process owing to antimicrobial and astringent properties, which appears to be responsible for wound contraction and elevated rate of epithelization. Therefore, wound-healing potential of *R.sanctus* possibly be attributed to the phytoconstituents in the aerial parts, either due to their individual or additive effect most probably by its action on the proliferative phase of wound healing [53].

#### Hippophae rhamnoides

Hippophae rhamnoides commonly called as Sea buckthorn of family Elaeagnaceae. All parts of the plant are considered as rich source of huge number of bioactive constituents like flavonoids like kaempferol, isorhamnetin, quercetin, myricetin and their glycosides, carotenoids ( $\alpha$ ,  $\beta$ ,  $\delta$ -carotene, lycopene), vitamins E, K, C, tannins, triterpenes, glycerides of palmitic, stearic and oleic acids and some essential amino acids [54, 55]. The plant found to possess significant anti-oxidative, antimicrobial, antiinflammatory, immunomodulatory, radioprotective, adaptogenic and tissue regenerative properties [54, 56-60]. Topical treatment of leaf extract augmented endogenous antioxidants and prevented tissue injury mediated by free radicals evidenced its action is due to the existence of flavanoids. It plays substantial role in angiogenesis at wound site; extracellular matrix deposition in cells signifies its mode of action on inflammatory phase of wound healing. It also acts on remodeling phase on burn wound healing [61].

#### Caryocar coriaceum Wittm.

*Caryocar coriaceum Wittm.* Popularly known as pequi, family *Caryocaraceae.* The fatty acid compositions of seeds designate the presence of palmitic, stearic, oleic, and linoleic acids. Existence of fixed oil in seeds impedes the topical inflammation and hastens cutaneous wound repair on topical application. However, the use of n-3 [62] and n-6 [63] fatty acids probably augment the production of pro-inflammatory cytokines in wound sites, stimulating the cutaneous wound healing process by acting at the inflammatory phase of wound healing [64].

#### Ageratum conyzoides Linn

Ageratum conyzoides popularly known as Goat weed or Chick weed, family Asteraceae. Alkaloids, flavonoids, cumarins, chromenes, benzofurans, terpenoids and sterols have been isolated from this species [65]. Numerous phytoconstituents like alkaloids [66] and saponins [67] are well known to endorse wound healing process due to antimicrobial and antioxidant properties. The study reveals good wound healing property of root extract of *A.conyzoides* possibly be attributed to the individual or combined action of phytoconstituents like alkaloids, terpenoids and saponins present in it [68-70] ,hastens the process of healing by tissue epithelization and confers breaking strength to the healed wound suggests mode of action is at proliferative and remodeling phase [71].

#### Nigella sativa

Nigella sativa is an annual herbaceous plant of Ranunculaceae. Thymoguinone (30-48%), p-cymene (7-15%), carvacrol (6–12%), 4-terpineol (2–7%), *t*-anethole (1-4%) and the sesquiterpene longifolene (1-8%) [72]; 36-38% fixed oil, proteins, alkaloids, saponins and 0.4-2.5% essential oil [73] are the chief phytoconstituents of this plant. Antibacterial, anti inflammatory and anti parasitic effects have been attributed owing to the existence of wide range of phytoconstituents like thymohyrdroquinine, dithymoquinone, thymol, nigellidine, nigellimine-N-oxide, nigellicine, alpha-hedrin [74]. A study states, existence of [75] thymoquinone, p-cymene and carvacrol compounds in N.sativa oil attributes to its antibacterial activity. Thymoquinone acts as potent antioxidant and averts membrane lipid peroxidation in tissues [76]. Topical application of N.sativa oil accelerates wound healing [77]. Results construes, the wound healing effect of N.sativia probably related to its antioxidant, antibacterial and anti inflammatory properties, evokes the mechanism of action is at inflammatory and proliferative phase.

#### Ficus racemosa

Ficus racemosa belongs to family Moraceae. Many phytoconstituents have been isolated from various parts of plant like tetra triterpene, glauanol acetate, acid from leaves. hentriacontane. racemosic hentriacontanol, kaempferol, campesterol, stigmasterol, methyl ellagic acid from stems, glauanol, beta sitosterol, glauanolacetate, glucose, tiglic acid, esters of taraxasterol, lupeolacetate, friedlin, higher hydrocarbons and other phytosterols from fruits, cycloartenol, euphorbol and its hexacosamoate, tetraxerone, tinyatoxin from root, euphorbol and its hexacosamate, ingenol and its triacetate, tetraxerone from bark [78]. Wound healing mechanism is due to the existence of flavanoids, alkaloids, saponins and tannins in root extract at proliferative phase evidenced by synthesizing collagen responsible for increase in epithelialization, possibly due to individual or combined action of phytoconstituents like flavanoids, alkaloids, saponins, and tannins. A healing tissue synthesizes collagen, which is a constituent of growing cell [79] evokes its mechanism of action is at remodeling phase [78].

#### Myristica andamanica

*Myristica andamanica* is a species of plant belongs to family *Myristicaceae*. Tannins, triterpenes and

alkaloids are the chief bioactive components present in leaves. Tannins being the chief components of many plants extracts acts as free radical scavengers [80 - 85]. A significant increase in the hydroxyproline content of the granulation tissue indicates increased collagen turnover, contributed by augmention in fibroblasts conten evokes its mechanism of action is at proliferative phase of wound healing [86]. Existence of tannins in leaves of *M.andamanica* contributes to early tissue approximation and increased tensile strength of the wound.

#### Opuntia ficus-indica (L.) Mill.

*Opuntia ficus-indica*, a plant widely spread in dry regions, belongs to family *cactaceae*. Cladodes are particularly rich in soluble fibers [87-89] minerals, vitamins and flavonoids [90-98]. It also pocesses polysaccharide fraction [99], responsible for wound healing process. *Opuntia ficus-indica* cladodes demotes the inflammatory cells, stimulates the migration of fibroblasts with the consequent enhancement of collagen formation and stimulates angiogenesis, suggests its mechanism is at proliferative phase [100].

#### Catharanthus roseus

Catharanthus roseus commonly known as vinca rosea belongs to family Apocyanaceae. Alkaloids and tannins be the two classes of phytoactive compounds in vinca plant. Existence of tannins is responsible for activity [101]. Flower extract revealed considerable increase in hydroxyproline content of granulation tissue signifies increased collagen turnover consequence in increased tensile strength of the wound, indicates mechanism of action is at proliferative and remodeling phase [102].

#### Leucas lavendulaefolia

Leucas lavendulaefolia belongs to family Labiatae. The aerial parts of the plant comprise of glycosides, linifolioside [103] and also essential oil, fatty alcohol etc [104]. Wound healing activity be possibly due to the existence of glycosides or due to the presence of triterpenoids in the essential oils. The activity is evidenced by regeneration of tissue; by fibrosis evokes the mode of action is at proliferative phase. Also, the presence of growth promoting factor in the plant extract enhances healing process and the breaking strength of the healed wounds implies its mode of action is at remodeling phase.

#### Ocimum sanctum Linn

Ocimum sanctum commonly called as Tulasi of family Labiaceae. In incision wound, the increase in tensile strength of treated wounds may be due to the increase in collagen concentration and stabilization of the fibers [105]. Leaves pocesses aromatic volatile oils mainly phenols, terpenes and aldehydes; ascorbic acid and carotene [106]. The fixed oil chiefly composed of fatty acids. The plant also contains alkaloids, glycosides, saponins and tannins. Wound healing activity is evidenced by increase in cellular proliferation and collagen synthesis at the wound site shown by increase in total protein and total collagen contents reflected by hydroxyproline content of granulation tissues. The components of glycosaminoglycans hexuronic acid and hexosamine concencentartions also enhanced, evokes its mode of action is proliferative phase. This activity is chiefly due to the existence of flavanoids orientin and vicenin in leaves and also due to antioxidant activity [107]. Better collagenation leads to increased tensile strength of wound, due to the existence of flavanoids [108] evokes mode of action is also at remodeling phase.

#### Centella asiatica

Centella asiatica also called as Brahmi belongs to family Apiaceae. vallarine, asiaticoside, madecassoside, sitosterol, tannins, oxy-asiaticoside are vital phytoconstituents. Aerial parts have lead to the isolation of three new compounds specifically centellin, asiaticin and centellicin. [109] Asiaticoside showed a promising wound healing activity evidenced by enhancing the rate of wound healing, assessed by increase in synthesis of collagen in both normal and in diabetic wounds. It also evidenced by promoting angiogenesis, facilitates the extent and direction of fibroplasia. It is possible that asiaticoside may processes a growth factor like activity or has the ability to stimulate the expression of growth factors like basic fibroblast growth factors Viz., endothelial cells, fibroblasts, myoblasts etc.,[110] suggests the mechanism of action is at proliferative phase. It also acts on remodeling phase by increasing the tensile strength of wound [111]

#### Kigelia pinnata

Kigelia pinnata belongs to family Bignoniaceae. The phyto constituents present in the bark of K. pinnata are naphthoquinone lapachol, irroids, norviburtinal, lignans, terpenoids, sterols like stigmasterol,  $\beta$  sitosterol, phenyl propanoids, and small amounts of free ferulic acid, p-coumaric acid, 6 methoxymelein and flavanoids [112]. Aqueous bark extract showed increase in dry granuloma weight, granuloma breaking strength and increased level of hydroxyproline content, increased deposition of collagen, decrease in the period of epithelization, suggests the mode of action is at proliferative phase and extract also facilitates rate of wound contracton [113]  $\beta$  situates is one of the bioactive compounds which perhaps be responsible for the epithelization activity. Existence of flavanoids [112] endorses wound healing activity by their scavenging action which possibly be one of the most vital components of wound healing.

#### Quercus infectoria

*Quercus infectoria* Olivier belongs to family *Fagaceae* is a small tree found in Greece, Asia Minor and Iran. Galls arise on the young branches as a result of attack by the gall-wasp *Adleria gallae-tinctoria* [114]. The chief constituents in galls of *Q. infectoria* are tannin (50-70%) and small amounts of free gallic acid, ellagic acid [115-117] and syringic acid, β-sitosterol and amentoflavone. It showed decreased epithelization period, as evidenced by the shorter period for the fall of eschar and also facilitated

the rate of wound contraction suggests mode of action is at proliferative phase [118]. Healing activity also endorsed by antioxidant activity due to the presence of tannins, evidenced by increased levels of superoxide dismutase and catalase in granuloma tissues, the two powerful antioxidant enzymes of the body, facilitates quenching of superoxide radicals and thus prevent the damage of cells triggered by free radicals [118].

#### Solanum xanthocarpum schrad

*Solanum xanthocarpum* Schrad. and Wendl commonly known as the Indian nightshade or Yellow berried night shade of family *Solanaceae*. Alkaloids, glycosides, saponins, carbohydrates, tannins, phenolic compounds, protein, and fats are phytoconstituents of leaves. Wound healing activity is evidenced by increase in the hydroxyproline content of the granulation tissue attributed to increased epthelization, collagen synthesis and maturation by cross linking and enhanced tensile strength of the granulation tissue indicated [119] its mechanism of action is at proliferative and remodeling phase. The wound healing activity is perhaps due to the individual or combined effect of the above phytochemicals [120].

#### Adhatoda vasica

Adhatoda vasica commonly known as Vasaka belongs to family Acanthaceae. Leaves of the plant pocesses alkaloids vasicine, deoxy vasicine, vasicinone, vasicinolone, peganine and flavonoids, tannins, proteins, phenolic compounds, glycosides and organic acids. Leaves and stems of the plant are reported to pocesses an alkaloid mimosine; roots contain tannins. The plant also pocesses turgorins. Presence of bioactive class of compounds flavonoids and tannins in leaf extract of Adhatoda vasica probably be responsible for its wound healing activity, known to advocate wound healing process mainly by their astringent and antimicrobial property, also attributed to free radical scavenging activity of flavonoids [115]. Flavonoids are known to demote lipid peroxidation not only by preventing or slowing onset of cell necrosis, but also by improving vascularity [121], signifies its mechanism of action is at inflammatory phase.

#### Malva sylvestris

*Malva sylvestris* belongs to family Malvaceae, commonly called as Panirak. A novel anthocyanin, malvidin 3-(6\_-malonylglucoside)-5-glucoside has been characterized in both wild and cultivated forms of M. *Sylvestris* [122-123]. The malvone A (2-methyl-3methoxy-5, 6-dihydroxy-1, 4-naphthoquinone) is also reported [124-125]. The flower extract showed that M. *sylvestris* significantly augmented the rate of wound contraction and collagen synthesis suggests the mode of action is at proliferative phase [126], perhaps due to individual or additive effect of phytoconstituents that hastens the process of wound healing.

SOME MORE PLANTS ATTRIBUTING TO WOUND HEALING ACTIVITY Many number of plants with significant findings for wound healing is available in nature. Some of them are listed to apply and consume in crude form.

Name of the Plant	Family	Part Used	Ref
Acalypha indica	Euphorbiaceae	Plant leaves are consumed orally to treat	[128]
		wounds	
Adhatoda zeylanica	Acanthaceae	Leaf is applied to cuts and wounds	[129]
Agremonia pilosa	Rosaceaee	Pounded whole plant is topically applied	[130]
Anacarrdium occidentale	Anacardiaceae	Fruits are consumed orally to treat wounds	[128]
Argemone mexicana	Papaveraceae	Leaves and latex applied topically to heal wounds	[127]
Begonia fellox	Begoniaceae	Paste of leaves and stems are applied to treat	[128]
		wounds	
Betula alnoides	Betulaceae	Topical application of bark Paste to heal wounds.	[130]
Brassica juncea	Brassicaceae	Crushed fruits paste is applied on the wounds	[127]
Buxus wallichiana	Buxaceae	Topical application of bark paste	[130]
Callicarpa arborea	Verbenaceae	Juice and paste of bark is applied on cuts.	[129]
Calotropis gigantea	Asclepiadaceae	Stem latex used to heal wounds.	[128]
Caryopteris odorata	Verbenaceae	Paste of wood is applied as plaster	[130]
Cassia auriculata	Caesalpinae	Bark and leaves are applied to treat wound	[127]
Chenopodium album	Chenopodiaceae	Crushed leaves are applied locally on wounds.	[130]
Crisium sinense	Asteraceaae	Crushed root is tied on wounds	[129]
Cissampelos pareira	Menispermaceae	Leaf juice is applied topically	[128]
Combretum flagrocarpum	Combretaceae	Juice of leaves are applied to cuts and wounds	[129]
Commelina benghalensis	Commelinaceae	Stem juice is applied	[128]
Curcuma domestica	Zingeberaceae	Mashed tuber is applied to heal wounds	[129]
Cyanotis villosa	Commelinaceae	Stem paste is applied on wounds	[128]
Daucas carota	Apiaceae	Root juice is applied on wounds	[127]
Diotacanthus albiflorus	Acanthaceae	Leaf paste is applied on wounds.	[128]
Dodonaea viscosa	Sapindaceae	Leaf paste along with albumin is appied as plaster on wounds.	[131]
Euphorbia antiquorum	Euphorbiaceae	Stem latex is applied on burn wounds	[128]
Euphorbia pilosa	Euphorbiaceae	Plant latex is applied on wounds.	[130]
Ficus bengalensis	Moraceae	Powder of leaf is applied on wounds.	[128]
Gelsemium elegans	Loganiaceae	Leaf juice is applied to heal cuts and wounds.	[129]
Ixora coccinia	Rubiaceae	Decoction of flowers is applied on wounds.	[128]
Jatropha curas	Euphorbaceae	Exudates of bark is appied on wounds	[132]
Melastoma malabathricum	Malastomataceae	Bark paste and juice is applied on wounds	[129]
Mikania micrantha	Asteraceae	Leaf juice is applied topically to wounds and	[129]
Morinda pubescens	Rubiaceae	Apply leaf paste topically to treat wounds.	[128]
Nerium indicum	Apocynaceae	Leaf juice is applied on wounds.	[127]
Ophiorrhiza mungos	Rubiaceae	Paste of whole plant is applied on wounds.	[128]
Pinus roxburghii	Pinaceae	Bark paste is applied on wounds locally	[130]
Polygonatum officinale	Liliaceae	Oral administration of root extract.	[130]
Pothos sandens	Araceae	Leaf paste is applied on wounds topically.	[128]
Psychotria flavida	Rubiaceae	Powder of root is applied on wounds	[128]
Rubia cardifolia	Rubiaceae	Mostly Bark and Root applied on wounds	[127]
Scoparia dulsis	Scrophulariaceae	Paste of leaf applied to treat wounds	[128]
Sida acuta	Malvaceaee	Leaf paste with albumin applied as plaster topically	[131]
Taxus wallichiana	Taxaceae	Bark paste is applied locally on wounds	[130]
Thespesia populnea soland	Malvaceae	Fruit of plant in crush used as wound healing	[127]
Trichosanyhes tricuspidata	Cucurbitaceae	Juice of the fruit is applied on wounds	[127]
Ulmus wallichiana	Ulmaceae	Bark paste is applied locally on wounds.	[130]

#### Some of the Plants with formulations

Diverse herbal products/formulations have been used in management and treatment of wounds over the years. A few are emphasized in this table

S.No.	PLANT NAME	FAMILY	EXTRACT	MODEL	FORMULATION	Ref
1.	Ammania baccifera	Lythraceae	Leaf extract	Incision	Cream	[133]
				and		
				excision		
2.	Argemone mexicana	papaveraceae	Hydroalcoholic	excision	Cream	[135]
		<b>.</b> .	extract			[107]
3.	Ageratum conyzoides	Asteraceae	Ethanolic root	excision	Ointment	[137]
4		<b>M</b> 1'	extract		O'	[120 120]
4.	Azadirachta indica	Mellaceae	Leaf juice and	excision	Ointment, gel	[138,139]
			leaves			
5	Blenharis	acanthaceae	Leaf extracts	excision	Cream	[133]
5.	maderaspatensis	ucuntiluccuc	Lour extracts	and	eream	[155]
	maaraspaarisis			incision		
6.	Curcuma longa	zingiberaceae	Ethanolic rhizome	excision	Ointment, gel	[134]
	C	C	extract			
7.	Cassia tora	leguminosae	Ethanol extrat of	excision	Cream	[135]
		-	seeds			
8.	Curcumas sativus	cucurbitaceae	Ethanol extract of	excision	Cream	[135]
			fruits			
9.	Centalla asiatica	Mackinlayaceae	Ethanol extract of	excision	Gel	[136]
			leaves			
10.	Cynodon dactylon	Poaceae	Aqueous extract of	excision	Ointment, Gel	[139]
11			whole plant		<u> </u>	[1.40]
11.	Carica papaya	Caricaceae	Dried latex	Burns	Gel	[140]
12	Cariocar coriaceum	Carvocaraceae	Fixed oil of seeds	excision	Ointment	[141]
13.	Eclipta alba	Asteraceae	Ethanol extract	excision	Ointment	[134]
14.	Evolvulus alsinoides	Convolvulaceae	Ethanol extract of	excision	Cream	[135]
			leaves			[]
15.	Emblica ribes	Myrsinaceae	Ethanol extract of	Burns	Gel	[140]
		,	fruits			
16.	Ficus religiosa	Moraceae	Ethanol extract of	excision	Ointment	[137]
			stem bark			
17.	Jatropha curcas	euphorbaceae	Methanol extract	excision	Ointment	[142]
			of leaf			
18.	Leucas	Labiatae	Whole plant	Incision	Ointment	[143]
	lavandulaefolia		methanol extract	and		
10		T 1 .		excision		[125]
19.	Ocimum sanctum	Labiatae	Ethanol extract of	excision	Cream	[135]
20	Triday progumbana	Astoração	Ethanol avtract	avaision	Ointment gel	[12/]
20.	Terminalia ariuna	Combretacese	Ethanol extract of	Excision	Gal	[134]
<i>∠</i> 1.	i ci ininana ai juna	Completaceae	building extract of	LACISION	UEI	[130]
22	Tamarindus indica	caesalpiniaeae	Ethanol extract of	excision	Ointment	[137]
	_ uniter indust industri	Piniadad	leaf	5.10151011	C manient	[10,]

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