

A REVIEW ON INDIAN MEDICINAL PLANTS AND THEIR ROLE IN WOUND HEALING ACTIVITY

Ajay Mandal^{1*}, Mrunal Sene P² and R.K. Jugeswor Mangang³

^{1,2}Department of Biotechnology Engineering, Acharya Institute of Technology, Bangalore-560107, INDIA.

³Department of Biotechnology, Presidency College, Bangalore-560024, INDIA.

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*Correspondence for

Author

Ajay Mandal

Department of
Biotechnology
Engineering, Acharya
Institute of Technology,
Bangalore-560107,
INDIA.

ABSTRACT

Plants and their extracts have immense potential for the management and treatment of wounds. These natural agents induce healing and regeneration of the lost tissue by multiple mechanisms. Wounds are inescapable events in life. Wounds may arise due to physical, chemical, microbial agents or immunological damage to the tissue. Healing of wounds is one of the important areas of clinical medicines explained in many Ayurvedic texts. Ayurveda, describes various herbs, fats, oils and minerals with anti-aging as well as wound healing properties. Wound healing is a process by which tissue regeneration occurs. Plants and their extracts have immense potential for the management and treatment of wounds. These phytomedicines 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. Hence in the current review a list of the plants used in traditional medicine for the treatment of wounds were screened. It is a beneficial work for researchers to provide many details about the wound healing herbs and development of safe and effective and globally accepted herbal drugs for cuts and wounds.

KEYWORDS

Wound healing, Phytoconstituents, Traditional uses, Medicinal Plants, Pharmacological actions.

INTRODUCTION

Wound

Wounds are major case of physical disabilities.^[1] A wound which is disturbed state of tissue caused by physical, chemical, microbial (or) immunological insults (or) typically associated with loss function. According to the wound healing society wounds are physical injuries that results in an opening (or) break of the skin that cause disturbance in the normal skin anatomy and function.^[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 re-epithelialization. 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 processes is still limited.^[10]

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] 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 non-phagocytic 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]

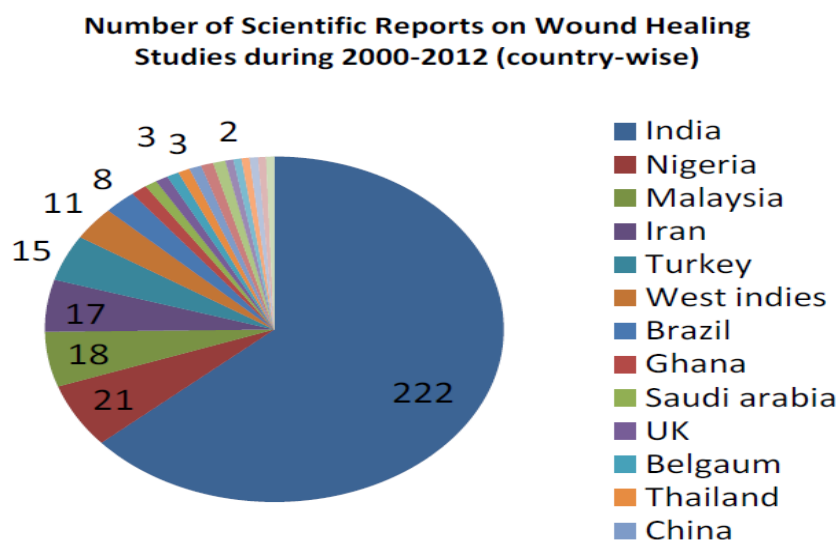
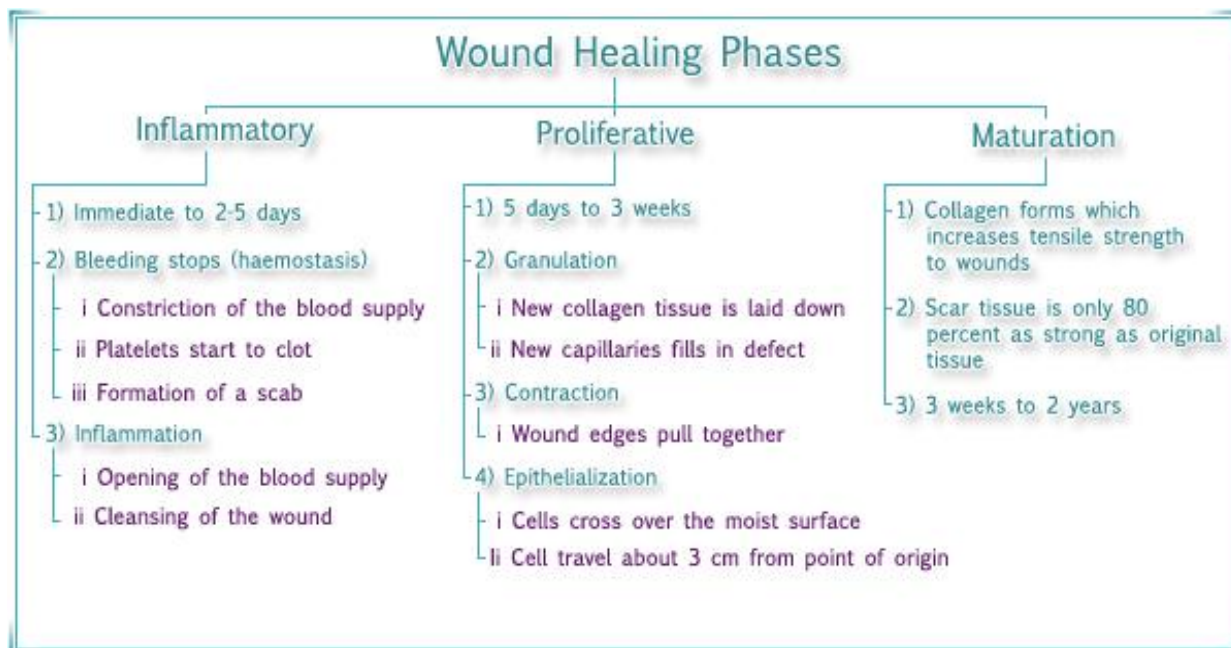


Fig. Number of scientific report on wound healing studies during 2002-2012 (country-wise) ^[4]

MECHANISM OF WOUND HEALING

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

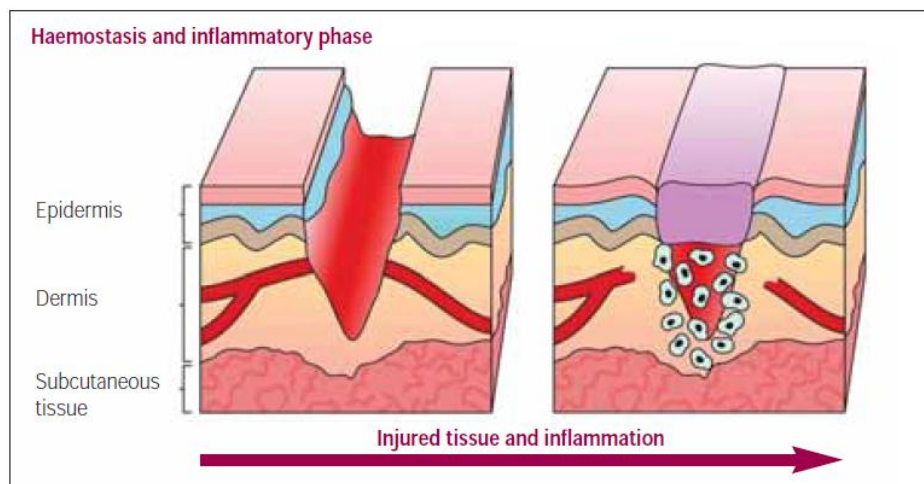
- The inflammatory phase
- The fibroplastic phase
- The remodelling phase



The inflammatory phase prepares the area for healing and immobilizes the wound by causing it to swell and become painful, so that movement becomes restricted. The fibroplastic phase rebuilds the structure, and then the remodelling phase provides the final form

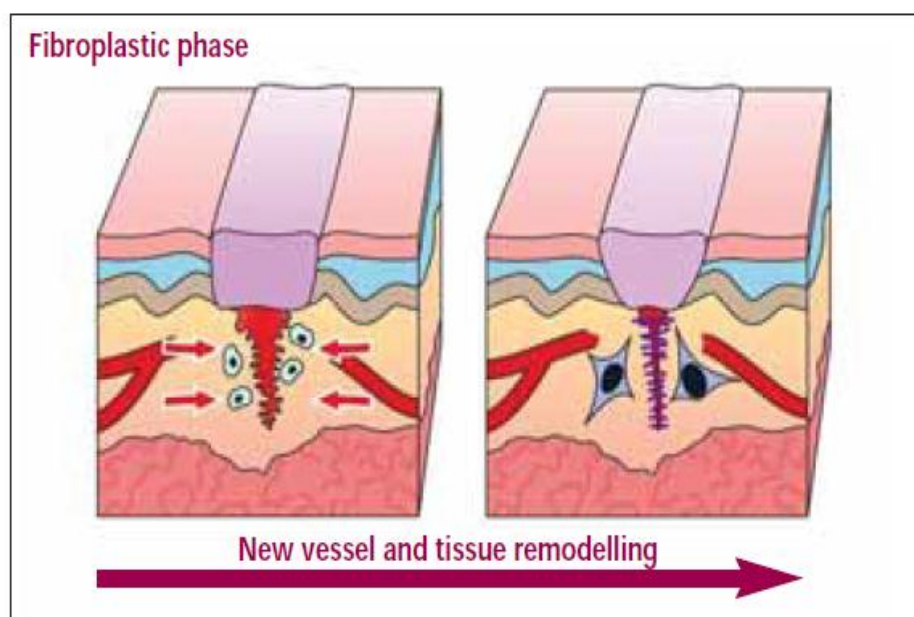
THE INFLAMMATORY PHASE

The inflammatory phase starts immediately after the injury that usually last between 24 and 48 hrs and may persist for up to 2 weeks in some cases The inflammatory phase launches the haemostatic mechanisms to immediately stop blood loss from the wound site. Clinically recognizable cardinal sign of inflammation, rubor, calor, tumor, dolor and function-laesa appear as the consequence. This phase is characterized by vasoconstriction and platelet aggregation to induce blood clotting and subsequently vasodilatation and phagocytosis to produce inflammation at the wound site.^[17]



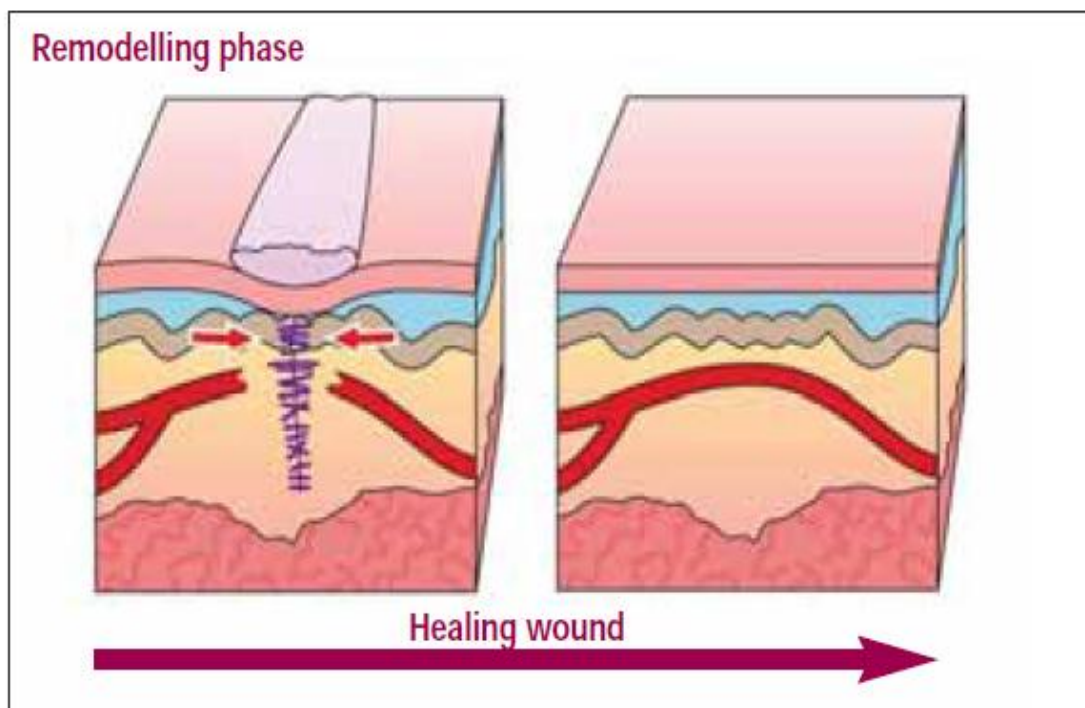
The fibroplastic phase

The second phase of wound healing is the fibroplastic phase that lasts upto 2 days to 3 weeks after the inflammatory phase. This phase comprises of three steps viz., granulation, contraction and epithelialisation. In the granulation step fibroblasts form a bed of collagen and new capillaries are produced. Fibroblast produces a variety of substances essential for wound repair including glycosaminoglycans and collagen. Under the step of contraction wound edges pull together to reduces the defects in the third step epithelial tissues are formed over the wound site^[18].



The Remodeling phase

This phase last for 3 weeks to 2 years. New collagen is formed in this phase. Tissue tensile strength is increased due to intermolecular cross-linking of collagen via vitamin-C dependent hydroxylation. The scar flattens and scar tissues become 80% as strong as the original.^[19,20] The wound healing activities of plants have since been explored in folklore. Many Ayurvedic herbal plants have a very important role in the process of wound healing. Plants are more potent healers because they promote 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 process.^[21]



FACTOR AFFECTING WOUND HEALING

- Improper diet.
- Infection at the wound site.
- Insufficient oxygen supply and tissue perfusion to the wound area.
- Drugs.
- Elderly age.
- Diabetes and other diseases conditions.

Wound healing is normal biological process in the human body. Many factors can adversely affect this process and lead to improper and impaired wound healing. A thought understanding of these factors and their influence on wound healing is essential for better therapeutic option for wound treatment.^[22]

Improper Diet

Wound healing is anabolic process that requires both energy and nutritive substrates. It is reported that serum albumin level of 3.5gm/dl or more is necessary for proper wound healing. Protein is essential for collagen synthesis on wound site. A state malnutrition may provide an inadequate amount of protein and this can decreased the rate of collagen synthesis wound tensile strength or increased chance of infection.^[23,24]

Infection at the Wound Site

Wound infection is probably the most common reason of impaired wound healing. Streptococcus aureus, streptococcus pyogenes, Escherichia coli and pseudomonas aeruginosa.^[25,26]

Insufficient Oxygen Supply and Tissue Perfusion to the Wound Area

Adequate blood supply and tissue perfusion is extremely important for wound healing. Excessive pain, cold and anxiety can cause local vasoconstriction and increased healing time. Smoking and use of tobacco decreased tissue perfusion and oxygen tension in wound.^[27,28]

Drugs

Many drugs are known to impair wound healing. Chemotherapeutic drugs are used in cancer are the largest group well known to delay wound repair^[29]. Systemic glucocorticoids interfere normal healing process by reducing collagen synthesis and fibroblast proliferation.

Elderly Age

Elderly age is found to associated with delay wound healing. It is reported that the fibroblast growth and activity diminishes and collagen production, wound contraction is slow in older individuals.^[30]

Diabetes and Other Diseases Conditions

Diabetic patients are more susceptible to wound healing. In study wound infection rate was found 11% higher in diabetic patients than in general patient's population^[31]. Acute and chronic liver diseases also associated with delay wound healing. Patients with altered immune function have an increased susceptibility to wound infection.

MEDICINAL PLANTS WITH SIGNIFICANT WOUND HEALING ACTIVITY

Plants or chemical entities derived from plants used in the treatment and management of wounds need to be identified and formulated. For this case, a number of herbal products are being investigated at present. Various herbal products have been used in the management and treatment of wounds for years.



Curcuma longa L. (Zingiberaceae)

The part used are rhizomes containing curcumin (diferuloyl methane), turmeric oil or turmerol and 1, 7-bis, 6- hepta-diene-3, 5-Dione. *Curcuma longa* also contains protein, fats, vitamins (A, B, C etc.) all of which have an important role in wound healing and regeneration. Turmeric has been used for treating the wounds in the rats.^[32]



Aloe Vera

It is one of the oldest healing plants known to mankind Also acemannan (β -(1,4)-acetylated polymannose) — the major polysaccharide of *A. vera*— stimulates expression of VEGF and other wound healing-related factors (e.g.,keratinocyte growth factor-1 and type I collagen) in gingival fibroblasts. This can be especially beneficial in the case of oral wound healing. Thus, crude *Aloe vera*extract or isolated proangiogenic components may have potential pharmaceutical applications for the management of wounds.^[33]



Sesamum indicum (Pedaliaceae)

Sesamum indicum is a member of family Pedaliaceae. sesame oil obtained from the seeds of the plant is highly nutritive as it is rich source of natural oxidant such as sesamin and sesamol^[34]. The methanolic extract of root of sesamumindicum was obtained and was incorporated in gel and ointment bases. These preparations were evaluated for in vivo wound healing on rat using excision wound model^[35].



Terminalia bellirica Roxb. (Combretaceae)

Terminalia bellirica Roxb. belonging to the family Combretaceae, commonly known as belliricmyrobalan. Fruit is astringent, antiseptic, rejuvenative, brain tonic, expectorant and laxative. It is used in coughs, sore throat, dysentery, diarrhoea and liver disorders. It is also

useful in leprosy, fever and hair care. In folk medicine it has been used for the treatment of skin diseases as antiseptic and on all types of fresh wound. An ethanol extract of *Terminalia bellirica* Fruit has properties that render it capable of promoting accelerated wound healing activity compared with placebo control. [36]



Azardica indica [37]

It is commonly called as Neem and the plant has diverse medicinal properties. Neem oil contains margosic acid, glycerides of fatty acids, butyric acid and trace of valeric acid. Various active principles are nimbidin, nimbidal, azardirachtin, nimbin, azadirine, gedunin, salanin. They have diverse medicinal activities. Neem oil is especially beneficial for curing skin ailments. Oil is used for dressing for foul ulcers, eczema and skin diseases like ringworm, scabies and mange in dogs. It is a powerful insect repellent, antibacterial, anti-fungal, anti-viral, anti-inflammatory and also strengthens the body's overall immune responses. Neem oil contains fatty acids which build collagen, promote wound healing and maintain the skin's elasticity. The active ingredients of neem oil help in the process of wound healing and the skin is able to retain its suppleness as the wounds heal. Neem oil has a high content of essential fatty acids. They keep the site moist and give a soft texture to the skin during the healing process. Alcoholic extract of neem is useful in eczema, ringworm and scabies. Neem leaf extracts and oil from seeds has proven anti-microbial effect. This keeps any wound or lesion free from secondary infections by microorganisms. Clinical studies have also revealed that neem inhibits inflammation as effectively as cortisone acetate, this effect further accelerates wound healing.



Aristolochia bracteolata- (Family Aristolochiaceae)

It is a perennial herb and twining plants found in the tropical and temperate regions of the world. Eight species are known to occur in India, of which *A.bracteolata*, *A.indica*, *A.tagala* are of medicinal importance. They generally contain alkaloids and reputed to be useful in the treatment of snakebites. The leaf paste is used by the tribals and the villagers in the Chittoor district of Andhra Pradesh for the rapid healing of cuts and wounds ^[38]. *A.bracteolata* leaf extract has got wound healing activity, supported by an enhancement in the levels of antioxidant enzymes in the granulation tissue.^[39]



Anogeissus latifolia- (Family: Combretaceae)

This is a deciduous tree, found in drier areas. Wound healing potential of ethanolic extract of *Anogeissus latifolia* bark for treatment of dermal wounds in rat was studied on excision and incision wound. The results obtained indicated that the plants accelerate the wound healing process by decreasing the surface area of the wound and increasing the tensile strength ^[40].

Areca catechu- (Family: Leguminosae) The effects of Areca catechu (betel nut) extract and its two constituents namely arecholine and polyphenols in male Wistar rats were studied on three wound models (excision, incision and dead space wound) and it was found that except arecholine both polyphenol and the crude extract promoted wound healing by increasing wound breaking strength, percent wound contraction and hydroxyproline level in the granulation tissue.^[41]



Butea monosperma- (Family: Leguminosae)

The topical administration of an alcoholic bark extract of Butea monosperma increased cellular proliferation and collagen synthesis at the wound site, evidenced by increase in DNA, total protein and total collagen content of granulation tissues. The extract treated wounds were found to heal much faster as indicated by improved rates of epithelization and wound contraction which was also confirmed by histopathological examinations. In addition, the plant also showed antioxidant properties by its ability to reduce lipid peroxidation.^[42]



Calendula officinalis- (Family: Araceae)

Studies carried out on fractions isolated from the flowers of *Calendula officinalis* in combination with allantoin in Wistar albino rats by inducing skin wounds surgically showed that this combination markedly stimulates physiological regeneration and epithelization. The ethanol extract and gel from the stem bark of *Calendula officinalis* and *Stryphnodendron barbadetinum* were found to be effective, in the treatment of domestic sun burn cases in Brazil and in the treatment of patients with various ulcers and skin lesions ^[43]. The effect of tinctures of *Calendula officinalis* has compared with *Hypericum* species on wound healing in male albino rats. It was concluded that the tincture of *Hypericum* enhanced the wound breaking strength and reduced the period of epithelization more effectively as compared to tincture of *Calendula*.^[44]



***Carallia brachiata* Merrill (Rhizophoraceae)**

The bark is mentioned to be useful in the treatment of itching, cuts and wounds, oral ulcers, inflammation of throat and stomatitis. From the bark, new proanthocyanidins (fig. 5) were reported to possess free radical scavenging activity. A new megastigmane diglycoside (3-hydroxy-5, 6-epoxy- β -ionol-3-O- β -apiofuranosyl (1 \rightarrow 6)- β -glucopyranoside), two megastigmanes, condensed tannins, flavonoids and glyceroglycolipids were isolated from the leaves. The presence of alkaloid hygroline in the leaves was also reported.^[47]



Gymnema sylvestre R.Br. (Asclepiadaceae)

Gymnema sylvestre R. Br. is a member of Asclepiadaceae. The leaf has been widely used in Ayurvedic traditional medicine leaves of the plant as anti-diabetes, astringent, bitter, acrid, thermogenic, anti-inflammatory, anodyne, digestive and liver tonic. Tannins and saponin are the chief chemical constituents present in *Gymnema sylvestre* and are known to possess wound healing property. In excision wound models, the percentage of wound area was found to be significantly increased in the animal grouped treated with the extract (16.73%)^[48].



Ocimum sanctum Linn. (Labiatae)

Ocimum sanctum Linn. belonging to the family Labiatae, is a herbaceous plant commonly known as tulsi is found throughout the semitropical and tropical parts of India. Different parts of the plant are traditionally used in Ayurveda and Siddha systems for the treatment of diverse ailments like infections, skin diseases, hepatic disorders and as an antidote for snake bite and scorpion sting. The ether extract and essential oil of the leaves exhibited antibacterial activity against a number of bacterial species. A methanol extract and an aqueous suspension of *Ocimum sanctum* leaves were found to have anti-inflammatory, analgesic and immunostimulatory properties. The extract of *Ocimum sanctum* significantly increased the wound breaking strength in incision wound model. The extract treated wounds were found to epithelialize faster and the rate of wound contraction was significantly increased as compared to control wounds. Significant increase in wet and dry granulation tissue weight, granulation tissue breaking strength and hydroxyproline content in dead space wound model was observed.^[49]



Allium Cepa Linn. (Liliaceae)

Allium cepa Linn belongs to the family of Liliaceae. It contains kampferol, β -sitosterol, ferulic acid, myritic acid, prostaglandins. These constituents used as abortifaciant and bulb extract shown to have ecobolic effect in rats. *Allium cepa* Linn is proved that anti diabetic^[50] Anti oxidant, anti hypertensive, anti thromboic, hypoglycaemic & hyper lipidemic Activities.^[51] Phytochemical screening of *Allium cepa* Linn revealed the presence of tannins, flavonoids, alkaloids, proteins & other important constituents. Flavonoids have been documented which is believed to be one of the most important components of wound healing. The enhanced wound healing may be due to free radical scavenging action and the

antibacterial property of the Phytoconstituents present in it which either due to their individual or additive effect fastens the process of wound healing. This could be the reason for prohealing activity of *Allium cepa* Linn.



Catharanthus roseus (Apocyanaceae)

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.^[52] 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.^[53]



Ficus racemosa

Ficus racemosa belongs to family *Moraceae*. Many phytoconstituents have been isolated from various parts of plant like tetra triterpene, glauanol acetate, racemosic acid from leaves,

hentriacontane, 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.^[53] 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^[54] evokes its mechanism of action is at remodeling phase.^[53]

CONCLUSION

The present review clearly revealed that nature provides huge number of plants that show significant wound healing activities. Ayurvedic herbal plants have a very important role in the process of wound healing. Plants are more potent healers because they promote the repair mechanisms in a natural way. The healing process can be physically monitored by assessing the rate of contraction of the wound, period of epithelization, tensile strength, histopathology, and weight of granuloma in different wound models. The demand of herbal drugs is increasing day by day in the developed as well as developing countries because they are safer and well tolerated as compared to the allopathic drugs. This review is an approach towards the herbal plants having wound healing potentials involving the observation, description, and experimental investigation of indigenous drugs and their biological activities. It is based on botany, chemistry, biochemistry, pharmacology, and many other disciplines that contribute to the discovery of natural products of biological activity.

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