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Current Aspects of Wound Healing Agents From Medicinal Plants: A Review

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Wound is defined as the disruption of the cellular and anatomic continuity of a tissue. Wound may be produced by physical, chemical, thermal, microbial or immunological insult to the tissues. The process of wound healing consists of integrated cellular and biochemical events leading to re-establishment of structural and functional integrity with regain of strength in injured tissues. This review discuss about Wound healing potential of plants, which are helpful for researcher to development new Wound healing formulations for human use.

Keyword: Wound healing, Wounds, Burns, Indian medicinal plants, Ayurveda.

1. Introduction

Wounds generally termed as physical injuries that result in an opening or breaking of the skin. There are different types of wounds which range from mild to potentially fatal. Wound healing is impaired in diabetic patients with infection or hyperglycemia. Diabetes mellitus is one of the major contributors to chronic wound healing problems. The diabetic patients with ulcer become at high risk for major complications which include infection and amputation. In traditional medicine plants are generally used for treatment of various acute and chronic diseases and abnormalities in the body. Due to the present fast life of the humans a drastic increase in chronic disease conditions mainly diabetes has been determined. Most of these patients tend to face a tremendous problem when they get an infected wound. Hence in the current review a list of the plants used in traditional medicine for the treatment of

wounds and diabetes were screened. The work includes a list of traditionally claimed plants used for diabetes and wounds which are scientifically proved as well as scientifically not proved^[1].

1.1 Classification of Wounds:

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

1.1.1 Open Wound:

Though an open wound blood escapes the body and bleeding is clearly visible. Open wound is further classified in various types according to the object that occur the wound^[2].

1.1.2 Incised Wound:

It is an injury with no tissue loss and minimal tissue damage. It is caused by a sharp object such as knife. Bleeding in such cases can be profuse, so immediate action should be taken.

1.1.3 Abrasions or Superficial Wounds:

It is caused by sliding fall onto a rough surface. During abrasion the topmost layer of the skin i.e. epidermis is scraped off that exposes nerve ending resulting in a painful injury. Blood loss similar to a burn can result from serious abrasions.

1.1.4 Laceration Wound or Tears Wounds:

This is the nonsurgical injury in conjunction with some type of trauma, resulting in tissue injury and damage.

1.1.5 Puncture Wounds:

They are caused by some object puncturing the skin, such as needle or nail. Chances of infection in them are common because dirt can enter into the depth of wound.

1.1.6 Gunshot Wounds:

They are caused by a bullet or similar driving into or through the body.

1.1.7 Penetration Wounds:

Penetration wounds are caused by an object such as a knife entering and coming out from the skin.

1.2 Closed Wound:

In closed wounds blood escapes the circulating system but remain in the body. It includes Contusion or bruises, hematomas or blood tumor, Crush injury etc^[2].

1.2.1 Contusions or bruises:

Bruises are caused by a blunt force trauma that damage tissue under the skin.

1.2.2 Hematomas or blood tumor:

They are caused by damage to a blood vessel that consequently causes blood to collect under the skin.

1.2.3 Crush injury:

Crush injury is caused when great or extreme amount of force is applied on the skin over long period of time.

1.2.4 Acute Wounds:

Acute wound is a tissue injury that normally proceeds through an orderly and timely reparative process that result in sustained restoration of anatomic and functional integrity. Acute wounds are usually caused by cuts or surgical incisions and complete the wound healing process within the expected time frame^[3].

1.2.5 Chronic Wounds:

Chronic wounds are wounds that have failed to progress through the normal stages of healing and therefore enter a state of pathologic inflammation chronic wounds either require a prolonged time to heal or recur frequently. Local infection, hypoxia, trauma, foreign bodies and systemic problems such as diabetes mellitus, Malnutrition, immunodeficiency or medications are the most frequent causes of chronic wounds^[4,5].

1.3 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^[6].

1.3.1 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 (7). 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^[8,9].

1.3.2 Infection at the Wound Site:

Wound infection is probably the most common reason of impaired wound healing. Streptococcus aureus, streptococcus pyrogenes, Escherichia coli and pseudomonas aeruginosa^[10,11].

1.3.3 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^[12,13].

1.3.4 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^[14]. Systemic glucocorticoids interfere normal healing process by reducing collagen synthesis and fibroblast proliferation.

1.3.5 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^[15].

1.3.6 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^[16]. Acute and chronic liver diseases also associated with delay wound healing. Patients with altered immune faction have an increased susceptibility to wound infection.

1.4 Phases of Wound Healing:

1.4.1 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].

1.4.2 Fibroblastic phase:

The second phase of wound healing is the fibroblastic 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].

1.4.3 Epithelization phase:

Epithelial cell migration is one of the vital processes of wound healing. The stem cells of epithelium must detach from the edges of the wound and migrate into wound. Normally dermal basal cells adhere to each other and to the underline basal layer of the dermis. Following mobilization, epithelial cells begin to enlarge and migrate down and across the wound. Transected hair follicles also contribute to the number of migrating epithelial cells. Epithelial cell migrating across wound usually move along the basal lamina or fibrin deposits, this phenomenon is called contact guidance and is an important factor in epithelial migration. Epithelial migration is followed by increased mytosis of epithelium. Recent evidence suggests that a water soluble heatlabile substance called chalcone which is secreted at the wound site is responsible for regulation for mytosis^[19].

1.4.4 Proliferative phase:

Proliferative Phase (2 days to 3 weeks) includes: Granulation stage: Fibroblasts lay bed of collagen Fills defect and produces new capillaries Contraction stage: Wound edges pull together to reduce defect. Epithelialization stage: Crosses moist surface cell travel about 3 cm from point of origin in all directions^[20].

1.4.5 Contraction phase:

Wound contraction is caused by the action of differentiated fibroblasts (myofibroblasts) in the granulation tissue, which contain filaments of smooth muscle actin. Contraction of these fibroblasts makes the wound margins move toward the center of the wound^[21,22]. Wound contraction started sooner in ponies than in horses and it was significantly more pronounced in ponies. Additionally, it was significantly more pronounced in body wounds compared with

the limb wounds. As a result, second intention wound healing was significantly faster in ponies than in horses, and significantly faster in body wounds than in metatarsal wounds^[23]. Histology showed that myofi-broblasts were more organized in the wounds of the ponies: the myofibroblasts in the newly formed granulation tissue were transformed into a regularly organized pattern within 2 weeks, in which the cells were orientated perpendicular to the vessels and parallel to the wound surface. This appears to be a more favorable condition for wound contraction to occur. In the horses, myofibroblast organization took much longer. No differences were found in the number of fibroblasts, the amounts of smooth muscle actin and collagen^[24]. Further research was performed to investigate whether the differences in wound contraction between horses and ponies were caused by differences in the inherent contraction capacity of fibroblasts or the local environment of the fibroblasts. It was found that no differences existed in the inherent contraction capacity of fibroblasts from ponies and horses in vitro^[25]. However, the level of Transforming Growth Factor, the most important instigator of wound contraction, was significantly higher in the granulation tissue of pony wounds compared with horse wounds.

1.4.6 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^[26,27].

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^[28].

1.5 Parameters used in assessing wound healing activity

For the Study of Wound healing activity many *In-vitro* and *In-vivo* Models have been used.

In-vitro models keratinocytes assay, fibroblasts assay. *In vivo*- models incision models, excision models, dead space space models, burn models can be performed. Wound healing property can be checked by measuring tensile strength of skin, measurement of wound area, percentage of contraction, collagen content, protein estimation, Period of epithilization.

1.6 Medicinal Plants Having Wound Healing Activity:

1.6.1 *Allium cepa* Linn

The plant *Allium cepa* Linn. Belonging to family Liliaceae. It contains kaempferol, sitosterol, ferulic acid, myritic acid, prostaglandins. These constituents used as abortifaciant, bulb extract shown to have ecobolic effect in rats. *Allium cepa* Linn. Are proved to shown the anti-diabetic, anti-oxidant, anti-hypertensive, antithromobotic, hypoglycemic, antihyperlipidemic^[29].

1.6.2 *Kaemperia galanga*

The rhizome of *K. galangal* is a indigenous medicine. It is used as expectorant, diuretic, carminative, and also has anticancer, antihypertensive, larvicidal activity, treatment of various skin disorders, rheumatism and diabetes mellitus. It mainly contains flavonoids. *K. galangal* has shown

to possess anti-oxidant property. The flavonoids mainly responsible for the force-radical scavenging activity and also wound healing activity^[30].

1.6.3 *Raxid paeomiae* root

It is the dried root of *paeonia lactiflora pallas* (*paeonaceae*) family. It is having anti-pyretic, hepatoprotective, antifertility, antispasmodic, antifibrinolytic, and anti-inflammatory and also used for the healing of wounds, and also diuretic. The *Raxid paeomiae* root extract treated wound contraction. *Raxid paeomiae* root extract was also promoting epithelialisation either by facilitating the proliferation of epithelial cells^[31].

1.6.4 Aloe Vera Leaf

It is one of the oldest healing plants known to mankind. It is used topically for cuts, burns, insects stings, bruises, acne and blemishes, poisoning, welts, skin lesions, eczema, sunburns. Aloe Vera plant to rub on the wounds of his soldiers and also traditionally use for stomach and intestinal disorders and also it has to enhance immune systems. Aloe Vera leaf contains Vitamin C, Vitamin E and amino acids which are essential for wound healing^[32].

1.6.5 *Rubus sanctus*

Rubus species (*Rosaceae*), it is mainly used for the treatment of diabetes mellitus, rheumatism, sore throat, hemorrhoid, diarrhea Roots decoction of *Rubus sanctus* is used as herbal tea to elevate pain and to heral rheumatism. *Rubus* species, having antimicrobial, anticonvulsant, muscle relaxant, antiinflammatory, antinociceptive activities. It mainly contains phenolic carboxylic acids,like ellagic acid, phenyl propanoids, caffeic acid^[33].

1.6.6 *Vinca rosea*

Vinca roseai is also called as *Catharanthus roseus* L. belonging to family Poyanaceae. It is mainly contains alkaloids, tannins, triterpenoids. It is mainly used for the treatment of Hodgkin's disease, malignant lymphomas, neuroblastoma, rhabdomyosarcoma, win's tumor and cancers and also use in European countries used in the conditions like headache, diabetes. And also it is vasodilating and memory enhancing properties have been shown to alleviate vascular dementia and Alzheimer disease^[34].

1.6.7 *Hyptis suaveolens* (L.) Poit

The plant, *Hyptis suaveolens* (L.) poit belongs to family Lamiaceae. The extract of *Hyptis suaveolens* contains steroids, alkaloids, carbohydrates, proteins, flavonoids, tannins, glycosides, leaves of this plant used as stimulant, carminative, sudorific, galactagogue, parasitic cutaneous disease, leaf extracts used as a relief to colic and stomachaches leaves and twigs are acts as antirheumatic and antispasmodic, anti-inflammatory antifertility. Decoction is used for the appetizer and leaves of the plant also used to repel mosquitoes and control insect pests of stored grains. Tribalmen continue to use the plant in the treatment of wound^[35].

1.6.8 *Tectona grandis* leaves

Tectona grandis is commonly known as Indian teak, and belongs to family "verbinaceae". It contains mainly carbohydrates, tannins and anthraquinone glycosides. *Tectona grandis* is used as anti-inflammatory agents and also used topically for the treatment of burns. It is mainly used for the injuries like burn, inflicted wound and skin ulcers. The extract applied topically (or) given orally promoted the breaking strength, wound contraction and collagenation^[36].

1.6.9 *Morinda citrifolia* Linn.

Morinda citrifolia is also known as Indian mulberry, belongs to family "Rubiaceae". It

mainly contains saponins, tannins, tri terpenes, alkaloids, flavonoids. It is mainly used for the bowel disorders, including arthritis, atherosclerosis, bladder infections, boils, burns, cancer, chronic fatigue syndrome, circulatory weakness, cold, congestion, constipation, diabetes, eye inflammations, fever, fractures, gastric ulcers, gingivitis, headaches, heart diseases, hypertension, immune weakness, indigestion, intestinal parasites, kidney disease, malaria, menstrual cramps, mouth sores, respiratory disorders, ringworms, sinusitis, sprains, stroke, skin inflammation and wounds^[37].

1.6.10 *Musa sapientum* (Plantain banana)

Musa sapientum var. paradisiacal belong to family Musaceae. It contains flavonoids (leucocyanidin) sterylacyl glycosides and sitoindisides I-IV. Sitoindoside IV was reported to mobilize and activate peritoneal macrophages with increase in DNA and [3H] thymidine uptake. Flavonoids are known to reduce lipid peroxidation flavonoids are also known to promote the wound healing process mainly due to their astringent and antimicrobial property, which results to be responsible for wound contraction and increased rate of epithelialisation^[38].

1.6.11 *Morinda citrifolia* Linn.

Morinda citrifolia is also known as Indian mulberry, belongs to family; Rubiaceae. It mainly contains saponins, tannins, triterpenes, alkaloids, flavonoids. It is mainly used for the bowel disorders, including arthritis, atherosclerosis, bladder infections, boils, burns, cancer, chronic fatigue syndrome, circulatory weakness, cold, congestion, constipation, diabetes, eye inflammations, fever, fractures, gastric ulcers, gingivitis, headaches, heart diseases, hypertension, immune weakness, indigestion, intestinal parasites, kidney disease, malaria, menstrual cramps, mouth

sores, respiratory disorders, ringworms, sinusitis, sprains, stroke, skin inflammation and wound^[39].

1.6.12 *Radix paeoniae*

Aqueous extract of roots of *radix paeoniae* was screened for wound healing by excision, incision and dead space wound models on wistar rats. Parameters studied were tissue breaking strength, epithelialization, wound contraction and granulation tissue dry weight. The test group demonstrated significant wound healing activity as compared to nitrofurazone ointment treated control group^[40].

1.6.13 *Quercus infectoria*

Quercus infectoria is a small tree (Fagaceae). It is mainly used for the treatment of anti-inflammatory disorders and also used as dental powder, toothache treatment, gingivitis. Pharmacologically it acts as astringent, antidiabetic, antiviral, antitremorine, local anaesthetic, antibacterial, antifungal, anti-inflammatory and larvicidal activities. It mainly contains tannin (50-70%) and small amounts of gallic acid and ellagic acid^[41,42,43].

1.6.14 *Hippophaerhamnoides L.*

Hippophaerhamnoides L. (family *Elaeagnaceae*) commonly known as seabuckthorn (SBT). Leaves, ripe fruits and seeds from seabuckthorn have been found to be a rich source of a large number of bioactive substances including flavonoids (isorhamnetin, quercetin, myricetin, kaempferol and their glycoside derivatives), carotenoids (α , β , δ -carotene, lycopene), vitamins (A, C, E and K), tannins, triterpenes, glycerides of palmitic, stearic and oleic acids and some essential amino acids. The high content of bioactive substances has been reflected in its extensive exploitation by

traditional medicine. Seabuckthorn has antioxidant and anti-inflammatory activity and has been reported to be useful in treating skin wounds^[44,45,46,47].

1.6.15 *Catharanthus roseus*

Catharanthus roseus plant is a key source of monoterpenoid indole alkaloid, vincristine and vinblastine which found useful in treatment of cancer. In a study of ethanolic extract of flower of this plant in a dose of 100mg/kg/day demonstrated to possess wound healing property^[48,49].

1.6.16 *Lycopodium serratum*

Lycopodium serratum is commonly known as club moss. Wound activity of aqueous and ethanolic leaf extract of *Lycopodium* was studied by excision, incision and dead space wound model on rats as compared to the aqueous extract and controls the ethanolic extract showed significant decrease in the period of epithelialization and an increase in wound contraction rate, tissue breaking strength and hydroxyl proline content at the wound site^[50].

1.6.17 *Sesamum indicum*

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. The methanolic extract of root of *sesamum indicum* 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^[51,52,53].

1.7 Medicinal Plants Having Wound Healing Activity

The medicinal plants having wound healing activity is given in **Table 1** [54].

Table 1: Medicinal Plants having wound healing activity

Sr. No.	Name of the Plant	Family	Part Used
1.	<i>Adhatodavastica</i> Linn.	<i>Acanthaceae</i>	Leaves, Stem
2.	<i>Hippophaerhamnoides</i> L.	<i>Elaeagnaceae</i>	Leaves, Fruit
3.	<i>Aloe Vera</i>	<i>Liliaceae</i>	Leaves
4.	<i>Hibiscus Rosasinesis</i>	<i>Malvaceae</i>	Leaves, Root
5.	<i>Tribulusterrestris</i> Linn.	<i>Zygophyllaceae</i>	Leaves
6.	<i>Gymnemasyvestre</i> R.Br.	<i>Asclepiadaceae.</i>	Leaves
7.	<i>Lawsoniainermis</i> Linn.	<i>Lythraceae,</i>	Leaves
8.	<i>Euphorbia Hirtal.</i>	<i>Euphorbiaceae</i>	Leaves
9.	<i>Adhatodazeylanica</i> M.	<i>Acanthaceae</i>	Leaves
10.	<i>Agrimoniapilosa</i> Ledeb	<i>Rosaceae</i>	Whole Plant
11.	<i>Alstoniascholaris</i> R.Br.	<i>Apocynaceae</i>	Latex
12.	<i>Anacardiumoccidentale</i> L.	<i>Anacardiaceae</i>	Fruit
13.	<i>Areca Catechu</i> L.	<i>Arecaceae</i>	Fruit
14.	<i>Argemonemexicana</i> L.	<i>Papaveraceae</i>	Latex
15.	<i>Aristidasetacea</i> Retz.	<i>Poaceae</i>	Leaves
16.	<i>Barleriaprionitis</i> L.	<i>Acanthaceae</i>	Leaves
17.	<i>Begonia Fallox</i> DC.	<i>Begoniaceae</i>	Stem
18.	<i>Betulaalnoides</i> B.H.	<i>Betulaceae</i>	Bark
19.	<i>Brassica Juncea</i> L.	<i>Brassicaceae</i>	Fruit
20.	<i>Buxuswallichiana</i>	<i>Buxaceae</i>	Bark
21.	<i>Calendula Officinalis</i> L.	<i>Asteraceae</i>	Flower
22.	<i>Callicarpaarborea</i> Roxb.	<i>Verbenaceae</i>	Bark
23.	<i>Calotropisgigantea</i> L.	<i>Asclepiadaceae</i>	Sem
24.	<i>Calotropisprocera</i> Br	<i>Asclepidaceae</i>	Leaves
25.	<i>Cassia Alata</i> L.	<i>Caesalpiniae</i>	Leaves
26.	<i>Cassia Auriculata</i> L.	<i>Caesalpiniae</i>	Leaves, Bark
27.	<i>Chasaliacurviflora</i> Wall.	<i>Rubiaceae</i>	Root
28.	<i>Chenopodium Album</i> Linn.	<i>Chenopodiaceae</i>	Leaves
29.	<i>Combretumflagrocarpum</i>	<i>Combretaceae</i>	Leaves
30.	<i>Commelinabenghalensis</i>	<i>Commelinaceae</i>	Stem
31.	<i>Eupatorium Odoratum</i> L.	<i>Asteraceae</i>	Leaves
32.	<i>Euphorbia Antiquorum</i> L.,	<i>Euphorbiaceae</i>	Stem
33.	<i>Euphorbia Hirta</i> L.	<i>Euphorbiaceae</i>	Latex
34.	<i>Euphorbia Pilosa</i>	<i>Euphorbiaceae</i>	Latex
35.	<i>Ficusbengalensis</i> L.,	<i>Moraceae</i>	Leaves
36.	<i>Jatrophacurcas</i> L.	<i>Euphorbiaceae</i>	Bark
37.	<i>Melastomamalabathricum</i>	<i>Malastomataceae</i>	Bark
38.	<i>Menthaviridis</i> L.	<i>Lamiaceae</i>	Leaves
39.	<i>Solanumxanthocarpum</i> Linn.	<i>Solanaceae</i>	Fruit
40.	<i>Morindapubescens</i>	<i>Rubiaceae</i>	Leaves
41.	<i>Raxidpaeomia</i>	<i>Paeonaceae</i>	Root

42.	<i>Murrayapaniculatalinn.</i>	<i>Rutaceae</i>	Leaves
43.	<i>Neriumindicum Mill</i>	<i>Apocyanaceae</i>	Leaves
44.	<i>Ophiorrhizamungos L.,</i>	<i>Rubiaceae</i>	Whole Plant
45.	<i>Pinusroxburghii</i>	<i>Pinaceae</i>	Bark
46.	<i>Psychotriaflavida</i>	<i>Rubiaceae</i>	Root
47.	<i>Rubiaccordifolia L.</i>	<i>Rubiaceae</i>	Bark,Root
48.	<i>Thespesiapopulneasoland</i>	<i>Malvaceae</i>	Fruit
49.	<i>Trichosantheatricuspidata</i>	<i>Cucurbitaceae</i>	Fruit
50.	<i>Tridaxprocumbens L.</i>	<i>Asteraceae</i>	Leaves

2. Conclusion

Most of the natural plants in this review are those with wound healing potentials. Plants are more potent healers because they promote the repair mechanism in the 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 healing tissue synthesizes more collagen to provide tensile strength. The demand of herbal drugs is increasing day by day in developed as well as developing countries because they are safer and well tolerated as compared to those allopathic drugs. These plants should be subjected to animal and human studies to derermine their effectiveness.

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