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Review on medicinal plants for wound healing activity

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Abstract
Wound is an anatomical and functional disruption of the skin followed by an injury. In response to the injury, wound healing is a complex process of tissue repair or remodelling. Historically, plants and plant-based constituents have been extensively used for the treatment and management of different types of wounds. In the current times, different types of biopolymers are being researched for developing economical, sustainable, stable, and effective delivery system for the treatment of wounds.. Traditional medicines have been used by humans, since ages and taking the wide spread of medicinal plants available for the same, they are valuable source even to deal with wound management. The present review article attempts to enlist medicinal plants which have been reported to be effective in the treatment of wounds. Pharmaceutical industry should use these medicinal plants to come up with an effective strategy to deal the still daunting task of wound management.

Keywords: wounds, inflammation, medicinal plants, plant constituents, wound healing

Introduction

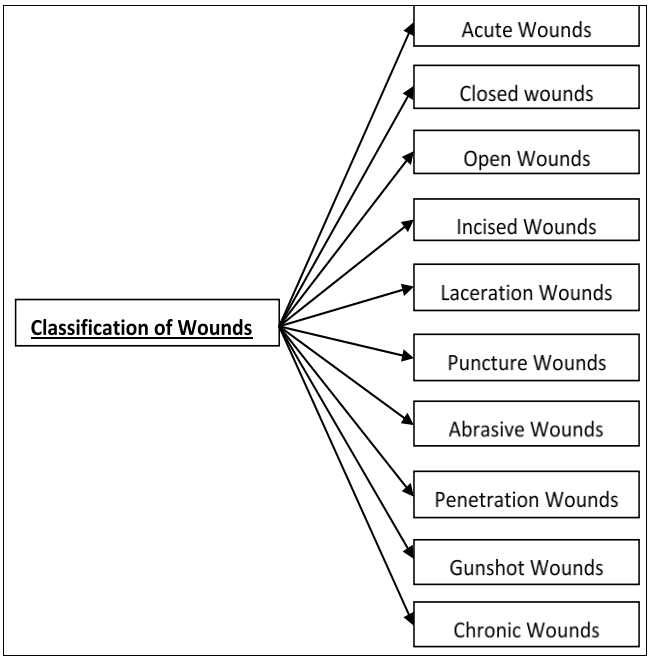
Wound healing still possess challenges for the Medical community, it is still challenge for the Pharmaceutical Industry, despite of being more advanced nowadays. Only 1-3 % of drugs listed in Western pharmacopoeias are intended for cure and healing of wounds. It is because of this challenge that Medicinal plants possess huge potential to come up with extensive solution for the Wound healing at present. Moreover, Medicinal plants are now considered as rich source for treatment of wounds. Proper and adequate nutrition is very important for dealing with wound and associated infection. Wound healing requires competency in wound repair functions or cellular repair functions, chemo-tactic factors, e.g., (Cytokines and growth factors) and local environment that promotes cell division, movement and differentiation. Depletion of proteins and nutrients due to diet or malabsorption syndromes, can impair wound healing and increase the risk of developing Ulcers, rough or think skin, alopecia's and nail dystrophies. Wound remains possible challenge for the medical community presenting the frequent cause of morbidity and mortality. It has been estimated that, Chronic wound affect 120 per 100000 people aged between 45 to 65 and rises to 800 people per 100000 people. The current estimation of chronic wounds is around 6 million people worldwide. Furthermore due to complications associated with wound, when healing does not occurs at natural pace, it may result into Chronic wounds, which are difficult to manage. Healing is complex process involving coordination between diverse immunological and biological systems. It involves cascade of carefully and precise regulated steps. A brief Steps in wound healing includes, Coagulations and Haemostasis phase: The principal aim of these mechanism is to prevent exsanguinations. It is a way to protect the vascular system, keeping it intact, so that the vital functions remains unharmed despite the injury. Another step is inflammatory phase, with an aim of establishing an immune barrier to the invading micro-organisms. Followed by Inflammatory phase is the Proliferation stage, the proliferative phase starts on the third day after wounding and lasts for 2 weeks. It is characterized by fibroblasts migration and deposition of newly synthesized extracellular matrix, acting as replacement for the provisional network composed of fibrin and fibronectin.

The last phase in wound healing process is the Remodelling phase. As the final phase of wound healing the remodelling phase is responsible for development of new epithelium and final Scar tissue formation.

Main text

Classification of wounds

Wounds are generally classified according to the underlying cause of the development of wounds.



Acute wounds
In acute wounds, there is tissue damage/injury that generally occurs through an orderly and timereparative phase that results in the anatomical and functional integrity being restored sustainably. Acute wounds are typically caused by the cuts or surgical incisions.

Closed wounds
The blood escapes from the circulatory system in closed wounds but stays inside the body. It becomes evident in the form of bruises.

Open wounds
Blood leaks from the body through an open wound and bleeding is clearly noticeable. The open wound may be divided further into categories according to the source causing the wound.

Incised wounds
This is a wound with no loss of tissue and minor damage to tissue. It is caused primarily by sharp objects like a scalpel or knife.

Tear or laceration wounds
This is the non-chirurgical injury in conjunction with other types of trauma which results in tissue loss and damage.

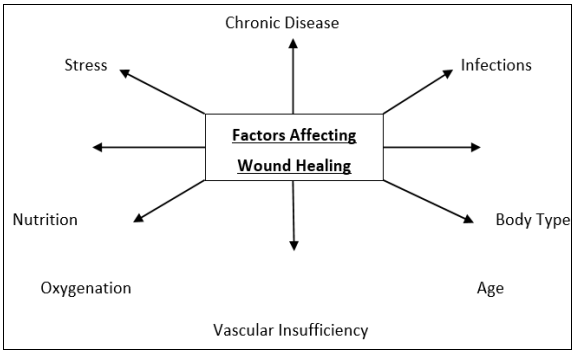
Puncture wounds
These are caused by an object which, like a nail or a needle, which punctures the skin. Since dirt may penetrate deep into the wound, chances of infection are common in them.

Abrasive or superficial wounds
Sliding slip onto a rough surface induces abrasion. During this time, abrasion is scraped off the top layer of the skin, i.e., epidermis which exposes nerve endings resulting in a painful injury.

Penetration wounds
Penetration wounds are chiefly caused by an object like a knife going in and out of the skin.

Gunshot wounds
They are typically produced by bullet or similar projectile which drives through or into the body.

Chronic wounds
Chronic wounds are wounds that have not gone through the usual healing stages and hence reach a state of pathologic inflammation. They need extended healing time



Oxygenation
Oxygen is essential for the metabolism of cells, particularly the production of energy through ATP, and is necessary for almost all wound healing processes. It protects wounds from infection, causes angiogenesis, increases differentiation of keratinocytes, migration and re-epithelialisation, improves proliferation of fibroblasts and synthesis of collagen, and facilitates contraction of wounds. The microenvironment of the early wound is deprived of oxygen and is very hypoxic owing to ingestion by metabolically active cells. Several systemic disorders will produce reduced vascular flow, including advancing age and diabetes, thereby setting the stage for inadequate oxygenation of the tissue. This superposition of inadequate perfusion produces a hypoxic wound in the sense of recovery. Chronic wounds are hypoxic in particular; tissue oxygen concentrations were measured transcutaneous in chronic wounds of 5 to 20 mm Hg, relative to control tissue concentrations of 30 to 50 mm Hg.

Infections
Micro-organisms that are typically sequestered on the skin surface gain access to the underlying tissues until the skin is wounded. If the wound is listed as having inflammation, colonization, local invasion/critical colonization, and/or spreading invasive infection determines the state of infection and replication status of the micro-organisms. Contamination is the presence of non-replicating microbes on a wound, while colonization is characterized as the presence without tissue damage of replicating microorganisms on the wound. An intermediate stage is local infection/critical colonization, with proliferation of microorganisms and the beginning of local tissue responses. The involvement of replicating organisms inside a wound with subsequent damage to the host is known as invasive infection. Inflammation is a natural part of the wound healing process and is necessary for the elimination of micro-organisms that are infected. However, inflammation can be prolonged in the absence of successful decontamination, because microbial clearance is incomplete. The sustained elevation of pro-inflammatory cytokines such as interleukin-1 (IL-1) and TNF-alpha will contribute to both bacteria and endotoxins and elongate the inflammatory process. The wound can reach a chronic state and refuse to heal if this persists. In addition, this prolonged inflammation contributes to an elevated level of matrix metalloproteases (MMPs), a protease family that can degrade the ECM. A decreased level of the naturally occurring protease inhibitors occurs in combination with the increased protease content. This change in protease equilibrium may cause the rapid deterioration of growth factors that occur in chronic wounds.

Age
The elderly population (people over 60 years of age) is growing more than any other age group (a significant risk factor for delayed wound healing is the World Health Organization and elevated age). Several cellular and molecular-level clinical and animal studies have explored age-related changes and delays in wound healing. It is widely accepted that the impact of aging induces a transient pause in wound healing in stable older people, but not a genuine disability in terms of the consistency of healing.

Stress

Stress has a considerable influence on human well-being and social behaviour. Stress is associated with multiple disorders, such as cardiovascular disease, cancer, compromised wound healing, and diabetes. Several studies have reported that stress-induced neuroendocrine immune equilibrium dysfunction is critical for well-being. Stressors can contribute to harmful mental conditions, such as depression and anxiety, which can in turn alter physiological mechanisms and/or behavioural behaviour that affect health outcomes. Stressed people are more likely to have risky behaviours, including irregular sleep schedules, insufficient diet, less exercise, and a higher risk for consumption of alcohol, nicotine, and other medications, in addition to the direct effects of anxiety and depression on endocrine and immune function.

Body type

Body form can also influence the healing of wounds. For instance, an obese patient can experience a compromise in wound healing due to low adipose tissue blood supply. In addition, there is protein malnutrition in some obese patients, which further impedes recovery. Conversely, the absence of oxygen and nutrition stores can interfere with wound healing when a patient is emaciated.

Chronic diseases

A few of the chronic conditions that can compromise wound healing include coronary heart disease, peripheral vascular disease, stroke, and diabetes mellitus. To have the right plan, patients with chronic illnesses should be monitored closely through their course of care.

Vascular insufficiency

Various wounds or ulcers—such as arterial, diabetic, pressure, and venous ulcers—can affect the lower extremities. Decreased blood supply is a common cause of these ulcers. The clinician must identify the type of ulcer to ensure appropriate topical and supportive therapies.

Nutrition

Food has been recognized for more than 100 years as a very significant aspect that impacts wound healing. The most apparent thing is that malnutrition or specific nutritional shortages following trauma and surgery can have a profound impact on wound healing. Special nutrients are also needed in patients with chronic or non-healing wounds and with nutritional deficiencies. The metabolism of energy, carbohydrates, proteins, fats, vitamins, and minerals will all affect the healing process.

Mechanism / Pathophysiology of wound healing

Wound healing is a complex mechanism that can be categorized as an allergic response, propagation, and remodelling in three parallel phases. The inflammatory process initiates a proliferative wound repair response further characterized by vascular responses like blood coagulation and haemostasis. Cellular activities include leukocyte infiltration with the release of antimicrobials and cytokines. During the proliferative process, the epithelium is formed to coat the wound surface with the subsequent growth of granulation tissue to fill the wound space. The generation of granulation tissue includes fibroblast proliferation, collagen deposition as well as other extracellular matrices, and the development of new blood vessels. The remodelling process begins to restore structural integrity and functional competence to the tissue when the new tissue is established inside the wound. The 3 stages of wound healing, however, are not simple linear procedures, but instead, vary in time. Acute wounds, like burns, other severe injuries, and wounds sustained by surgery, relate to those injuries that heal quickly. An example of a typical acute wound is a neat and uninfected incisional surgical wound approximated by operative sutures. While the desired end product of organized healing is tissue production with similar structure and functions as with retained skin, but regeneration is rare (with significant exceptions, such as early fatal (healing). Thus, healing results in an outcome that is structurally and functionally adequate but not equivalent. Wound healing processes tend to be strictly regulated at the wound site by various growth factors and cytokines released. Changes that interfere with regulated timely healing processes increase tissue damage and delay recovery. The different phases (inflammatory phase, proliferative phase, remodelling phase) of wound healing. Blood-borne cells—neutrophils, macrophages, and platelets— play crucial roles during the coagulation and inflammatory phases (A) of the healing. These cells provide the growth factors and interim matrices required for the recruitment into the wound bed of epidermal and dermal cells. The proliferative process (B) starts around 3 days after injury and is characterized by increased rates of proliferation, migration, and extracellular matrix (ECM) synthesis of keratinocytes and fibroblasts in response to autocrine, juxtracrine, and paracrine growth factors. In this process, angiogenesis/neovascularisation occurs too. The tissue has a granular texture (granulation tissue), due to the involvement of blood vessels. Eventually, inside the granulation tissue, differentiated fibroblastic cells (myofibroblasts) begin to remodel the extracellular matrix at about 1 to 2 weeks after injury. Extracellular matrix remodelling accompanied by resident cell apoptosis leads to an a cellular scar formation. Medicinal plants and their metabolites used in the treatment of different types of wounds.

Phases Involved in Wound Healing

Normal wound healing involves there are 4 overlapping phases. They are,

- Haemostasis phase
- Inflammatory phase
- Proliferative phase v Remodelling phase

1. Haemostasis Phase

It is the first phase, Bleeding usually occurs when the skin is injured and serves to flush out bacteria and antigens from the wound. Platelets are the cells that are deputed for sealing off the damaged blood vessels. They secrete vasoconstrictors that stimulate the constriction of broken blood vessels and thereby help to reduce blood loss. Within the first few minutes of injury, platelets in the blood begin to stick to the injured site. They change into an amorphous shape, more suitable for clotting, and they release chemical signals to promote clotting. This results in the activation of fibrin, which forms a mesh and acts as “glue” to bind platelets to each other. This makes a clot that serves to plug the break in the blood vessel, slowing/preventing further bleeding.

2. Inflammatory Phase

The inflammatory phase starts immediately after the injury that usually last between 24 and 48 h and may persist for up to 2 weeks. This phase is characterized by vasodilatation and phagocytosis to produce inflammation at the wound site. The inflammatory cells migrate to the injury site to scavenge bacteria, and prepare the injury site for healing. Neutrophils is the first cells to appear at the injury site, cleanse debris and bacteria to provide a good environment for wound healing. In the following, macrophages accumulate and facilitate phagocytosis of bacteria damage tissue and apoptotic neutrophils then leads to removal of chemokines from the area of inflammation, preventing further leukocyte influx. Several cytokines and growth factors are known to be secreted by macrophages. Such growth factors include TGF-β, TGF-α, basic FGF (bFGF), VEGF and PDGF. These growth factors activate and attract local endothelial cells, fibroblasts and keratinocytes, and enable wound healing by causing cell proliferation.

3. Proliferative Phase

Proliferative phase (2 days to 3 weeks) includes

- Granulation stage: Fibroblasts lay bed of collagen matrix and produces new capillaries.
- Contraction stage: Wound edges pull together to reduce defect.
- Epithelialisation stage: keratinocytes divides and migrate about 3cm from point of origin in all directions.

4. Remodelling 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. During maturation and remodelling, collagen is realigned along tension lines, and cells that are no longer needed are removed by programmed cell death, or apoptosis.

Traditional use of medicinal plants in wound healing

For more than 5000 years, Egyptians, indigenous peoples of Africa, Asia, Romans, and the Americas have used medicinal plants as first-line therapy for inflammation, burns, ulcers, and surgical wounds. They contain many natural bioactive compounds that help fasten the process of wound healing and regenerate tissue at the wound site. Some examples of medicinal plants and their wound healing effects are listed below

1. Tridaxprocumbens

Tridaxprocumbens Linn is a common plant found in tropical areas of all countries, growing primarily during rainy season. It is commonly known as ‘Coat button’ in English. It belongs to the family Asteraceae.

Chemical constituents: Alkaloids, flavonoids, carotenoids, Kaempferol, lutein, ferulic acid, tannins, stigmasterol and caffeic acid,

Scientific Classification

- **Kingdom –** Plantae
- **Subkingdom -** Tracheobionta
- **Division -** Magnoliophyata
- **Class -** Magnoliopsida
- **Subclass -** Asteridae
- **Order -** Asterales
- **Family -** Asteraceae
- **Genus -** Tridax

Medicinal uses: wound healing, antimicrobial, antidiabetic, anti-inflammatory.

2. Adhatoda Vasica

Adhatoda Vasica Nees belonging to family Acanthaceae. It is small evergreen shrub found many regions of India & throughout the world. Methanolic, Chloroform & diethyl ether extract of Adhatoda Vasica plants were evaluated for its wound healing activity in the form of ointment dosage form in excision wound.

Chemical Constituents:

Alkaloids, Flavonoids, Tannins, Vasicinone, Vasicinol, Adhatodine, Vasicine, Maiontone

Scientific Classification

- **Kingdom** - Plantae
- **Subkingdom** - Tracheobionta
- **Division** - Magnoliophyta
- **Class** - Magnoliopsida
- **Subclass** - Asteridae
- **Order** - Lamiales
- **Family** - Acanthaceae
- **Genus** - Adhatoda
- **Species** - Vasica

Medicinal Uses

Vasica improved breaking strength, tensile strength, absorption & extensibility in the wound repair tissue. In addition, the level of elastin, collagen, hydroxyproline, hexosamine & zinc were greatly increased in the animals treated with Adhatoda.

3. Hypericum Perforatum

Known as St. John's wort, is a flowering plant in the family Hypericaceae & the type of species of the genus Hypericum. The name 'Perforatum' is given to the plant due to the presence of transparent areas on the leaves & petals. These transparent areas comprises of the oil glands. The oil glands may also be present as small dots on the lower surface of the leaves.

Chemical Constituents

Napthodianthrones, Flavanoids (Kaempferol, quercitin, isoquercitin, lateolin, myricetin, hyperin, rutin & hyperoside), Phloroglucinol, Tannins, Essential oil.

Scientific Classification

- **Kingdom -** Plantae
- **Subkingdom -** Tracheophyta
- **Division -** Magnoliophyta
- **Class -** Magnoliopsida
- **Subclass -** Rosidae
- **Order -** Malpighiales
- **Family -** Hypericaceae
- **Genus –** Hypericum
- **Species -** Hypericum Perforatum

Medicinal Uses

St. John's wort has the antidepressant, antiviral, antibacterial, antiinflammatory & is known to have wound healing & skin healing properties.

4. Ginkgo biloba

Ginkgo biloba extract is derived from the leaves of the Ginkgo biloba tree, Family-
Ginkgoaceae, the world most ancient tree species that is commonly found in China, Japan & Korea.

Chemical Constituents

Flavonoids (quercetin, kaempferol & isorhamnetin), Terpenoids (Ginkgolide A, ginkgolide B, ginkgolide C & bilobalide).

Scientific Classification

- **Kingdom -** Plantae
- **Subkingdom -** Viridiplantae
- **Division -** Tracheophyta
- **Class -** Ginkgoopsida
- **Subclass -** Ginkgooidae
- **Order -** Ginkgoales
- **Family –** Ginkgoaceae
- **Genus -** Ginkgo L.
- **Species -** Ginkgo biloba L.

Medicinal Uses

The free flavonoids present in Ginkgo biloba have been reported to have pro-healing activity. Because, of anti-inflammatory properties, it helps to treat acne, eczema & many type of skin-inflammation. Ginkgo biloba exhibits variety of interesting pharmacological activities such as antioxidant, membrane stabilizing, increase in blood fluidity & improvement in cognition.

5. Calendula officinalis

Calendula officinalis Linn.or pot marigold is a common plant belonging to Asteraceae family, native to southern Europe.

Chemical Constituents

The plant species has been reported to contain a variety of phyto-chemicals, including carbohydrates, phenolic compound, lipids, steroids, tocopherols, terpenoids, quinines & carotenoids. The major active constituents of plant include triterpendiol esters, saponins & flavonoids including rutin & hyperoside.

Scientific Classification

- **Kingdom -** Plantae
- **Subkingdom -** Tracheobionta
- **Division -** Magnoliophyta
- **Class -** Magnoliopsida
- **Subclass -** Asteridae
- **Order -** Asteraceae
- **Family -** Asteraceae
- **Genus -** Calendula
- **Species -** C. officinalis

Medicinal uses

wound healing, Anti- inflammatory activity, Anti-oxidant, Antimicrobial activity.

6. Azadirachta Indica

Azadirachtaindica, commonly known as neem or nimtree. It belongs to the family Meliaceae. It is typically grown in tropical and semi-tropical regions.

Chemical Constituents: Nimbidin & sodium nimbidate.

Scientific Classification

- **Kingdom -** Plantae
- **Subkingdom -** Tracheobionta
- **Division -** Magnoliophyta
- **Class -** Magnoliopsida
- **Subclass -** Rosidae
- **Order -** Sapindales
- **Family -** Meliaceae
- **Genus -** Azadirachta
- **Species -** Indica

Medicinal uses: wound healing, anti-inflammatory, antibacterial. antiseptic, antifungal.

7. Curcuma longa

Curcuma longa is a flowering plant of the ginger family Zingiberaceae. It requires temperature between 20 to 30 degree Celsius. It is native to the Indian subcontinent and southeast Asia.

Chemical Constituents

Curcumin, zingiberene, cineole, sesquiterpenes.

Scientific Classification

- **Kingdom** - Plantae
- **Subkingdom** - Tracheobionta
- **Division** - Magnoliophyta
- **Class** - Liliopsida
- **Subclass** – Zingiberidae
- **Order** - Zingiberales
- **Family** - Zingiberaceae
- **Genus** - Curcuma L
- **Species** – C. longa L.

Medicinal uses: wound healing, antioxidant, Alzheimer's disease, anticancer.

8. Aloe vera

Aloe vera is a succulent plant species of genus aloe. An evergreen perennial, it is originated from Arabian peninsula but grows wild in tropical climates around the world and is cultivated for agriculture and medicinal uses.

Chemical Constituents: Aloe-emodin, Aloin, Aloesin, Emodin.

Scientific Classification

- **Kingdom -** Plantae
- **Subkingdom -** Tracheobionta
- **Division -** Magnoliphyta
- **Class -** Liliopsida
- **Subclass -** Liliidae
- **Family -** Aloaceae
- **Genus -** Aloe L
- **Order -** Liliales
- **Species -** Aloe vera (L)

Medicinal uses: Wound healing, Heartburn relief, Lower blood sugar.

9. Liquorice

Liquorice is the common name of Glycyrrhiza glabra, a flowering plant of the bean family Fabaceae, from the root of which a sweet, aromatic flavouring can be extracted.

Chemical Constituents

Triterpene, Saponins, Glycyrrhizin, Glycyrrhetic acid, Glabridin, Liquiritin, Flavonoids.

Scientific Classification

- **Kingdom** - Plantae
- **Subkingdom** - Tracheobionta
- **Division** - Magnoliophyta
- **Class** - Magnoliopsida
- **Subclass** – Rosidae
- **Order** - Fabales
- **Family** - Leguminosae
- **Genus** – Glycyrrhiza
- **Species** – Glycyrrhiza glabra.

Medicinal Uses

Anti- inflammatory, Anti- diabetic, Anti- depressant, Anti-Hepatoprotective effect, Anti-Ulcer.

10. Honey

Honey is sugar secretion deposited in honey comb by the bees, Apis mellifera, Apis dorsata & other species of Apis, Family: Apidae.

Chemical Constituents

Glucose & fructose, succinic acid, acetic acid, dextrin, formic acid, Enzymes, Vitamins.

Scientific Classification:

- **Kingdom** - Animalia
- **Division** - Endopterigota
- **Class** - Insecta
- **Subclass** - Pterygota
- **Order** - Hymenoptera
- **Family** - Apidae
- **Genus** - Apis
- **Species** - Apis mellifera

Medicinal Uses

Used as a demulcent, sweetening agent & It is used as Antiseptic and applied to burns & wounds.

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