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PHYTOCHEMICAL PROFILE AND PHARMACOLOGICAL MECHANISMS OF CALOTROPIS GIGANTEA (LINN.) FOR WOUND HEALING POTENTIAL

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ABSTRACT

Wound occurs when the skin is disrupted by the any out source or sharp objects. There are type types of wounds, which is an acute wound and chronic wound. Acute wound is a type when the tissue is cut by knife or any sharp objects. Chronic wound types are referred as pressure or ulcer, which takes longer time than acute wound to cure. The wound healing has four different stages like Homeostasis, inflammation, proliferation and remodelling. Calotropis Gigantea, also known as Milkweed, the plant has been widely used in traditional medicine system to treat many aliments like wound healing, inflammation, scabies, spleen enlargement etc,. The study focuses on phytochemical and pharmacological activities of Calotropis Gigantea. Phytochemical investigation revealed that it has wide activities of flavonoids, alkaloids, glycosides, saponins and tannins from different parts of the plant like leaves, flowers, roots and barks. The pharmacological activity includes antimicrobial, cytotoxicity, antibacterial, anti-inflammation, anti-venom, antioxidant and wound healing. This article states that the Calotropis gigantea has significant therapeutic potential and may be a good source for the creation of new therapeutic drugs. However, to confirm its safety and effectiveness for contemporary medical applications, more clinical research and standardization studies are needed.

KEYWORDS: Wound healing, chronic and acute wounds, Calotropis Gigantea, Phytochemical activity and Pharmacological activity.

INTRODUCTION

A wound happens when the celluar, anatomical and functional continuity of live tissues are broken. It can be caused by an injury to the tissue that is physical, chemical, thermal, microbiological or immunological.[1] The burning are formed by heat related sources or chemicals, open wounds are created when skin is torn, sliced or pierced and closed wounds are created when blunt force trauma results in a contusion.[2] Almost all tissues undergo wound repair upon exposure to any type of damaging stimulation.[3]

The process where the cutaneous membrane or injured organ heals themself is known as wound healing. Under normal circumstances, the epidermis (outer layer of the skin) and the dermis (deeper or innermost layer), which acts as a barrier of defense the outer world. Any injury that breaches this layer of defense triggers the body's natural healing process right away. When the skin is injured, a series of intricate biochemical processes work together in a well- coordinated cascade to fix the damage.[4]

The natural physiological process of wound healing is started right away if this barrier of defense is breached by an injury. When the skin is injured, a series of intricate biochemical processes work together in a well-coordinated cascade to fix the damage. Platelets clump together to create a fibrin clot at the site of the damage within a few minutes of the injury. Hemostasis is achieved and the active bleeding is controlled by this clot. Beginning at the time of damage, the full wound healing process may take months or even years to complete.[5]

TYPES OF WOUNDS

There are two main types of wounds: acute wounds, which are cuts from knives and chronic wounds, which are skin ulcers. Metabolic problems are the cause of chronic wounds. These wound takes long time to heal than acute wound. The synthesis and breakdown of cells and extracellular matrix (ECM), such as collagen, are out of balance in chronic wounds.[6]

CHRONIC WOUND

The chronic wounds can be listed as: Pressure, vascular and diabetic ulcers, Ischemic wounds. More than 70% of chronic wounds in the lower extremities are venous/vascular ulcers, sometimes referred to as stasis ulcers or dermatitis.

Another type of chronic wound that is brought on by diabetic circumstances is diabetic ulcers. The primary mechanism underlying these wounds is the immune system's compromise and the development of neuropathic diseases in diabetics. Because of neuropathy and weakened immune systems in both of these disorders, a minor skin injury goes unreported, the body is unable to stop infections and a minor wound would turn into a chronic one.

The third type of persistent wounds, pressure ulcers, typically develop in individuals with paralytic disorders. Due to the body's immobility during paralysis, blood flow is restricted in certain tissues, primarily muscles and When tissue pressure surpasses capillary pressure, tissues become ischemic.

Another kind of chronic wound is an ischemic wound, which results in a lack of oxygen and glucose needed for cellular metabolism due to a restriction in the blood flow to the tissues.[6]

ACUTE WOUND

Acute wounds occurs when the external or environmental sources are in contact with the skin. These wounds heal in a certain order because the creation and destruction of cells and extracellular matrix are precisely balanced. Depending on the external or environmental source by which the injury occured, these wounds are split into numerous kinds.

1. Abrasions or scrapes, such as rope burns and skinned knees, are wounds caused by the skin rubbing against a rough surface.
2. Avulsions or contusions are injuries brought on by a forceful blow to the body or the removal of a body part. Examples of such wounds include bone fractures from hitting a ball, injuries from explosive materials, injuries by animal and the permanent tooth fall, nail or earlobe.
3. Cut or Crush, a person may have a part of their body crushed when a large object falls on them. or cut their bodily structures with a sharp object, causing wounds. This category includes injuries sustained at home, on the road and during surgery. This includes puncturing the skin with knives or nails. These wounds can be superficial or deep, causing damage to the dermis or epidermis, respectively.[7]
4. Another name for lacerations is "tearing of body structures." The wound requires a great force applied to the body. Both internal and external stimuli, such as childbirth or hitting the body, can trigger them.
5. Speed or Missile Wounds may result from a gunshot or other fast-moving item penetrating the body. These wounds include ballistic trauma and gunshot wounds.
6. Radiation Ionizing radiation's acute or long-term impacts might result in wounds or ulcers. It may impact the skin, soft tissues beneath it, and even deep structures like bone.[8]

PHASES INVOLVED IN WOUND HEALING

The Homeostasis, inflammatory, proliferative and remodeling phases are the three primary stages of wound healing.

People at the two extremes of the age spectrum—infants and the elderly—are more likely to sustain traumatic injuries. Chronic lower limb injuries increase the strain on healthcare systems as the population ages. While chronic wounds can cause the healing process to fail in a planned manner, acute wounds often do not interfere with the long-term restoration of the skin's anatomical and functional integrity. Numerous cell types with various roles move in tandem during the phases of homeostasis, inflammation, proliferation, re-epithelialization and remodeling as part of the wound healing process.[8]

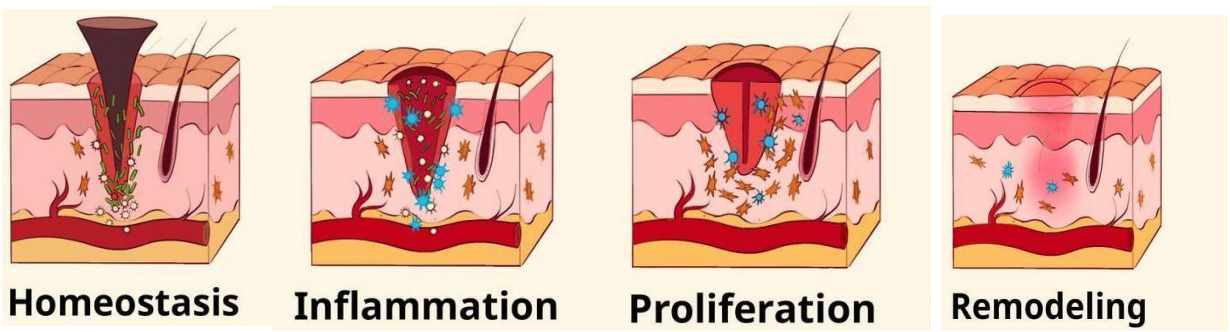

Figure 1: Stages of Wound Healing.

HAEMOSTASIS

After vascular damage, the body maintains the true nature of the circulatory system by hemostasis, an inherent and carefully controlled process. The process involves a number of cellular and noncellular elements. The followings are the some of the elements, they are the system of coagulation, platelets, vascular, fibrinolysis, kinin, complement and serine protease inhibitors. The alternate viewpoint states that the three main elements of hemostasis are the vascular system, cellular components and noncellular components.

Vascular System

The vascular system in hemostasis is predominantly composed of endothelial cells, the path blood arteries and control clotting by regulating both procoagulant and anticoagulant activities, such as the release of von Willebrand factor for platelet adhesion and tissue plasminogen activator for fibrinolysis. Smooth muscle allows vasoconstriction to limit early blood loss, whereas subendothelial connective tissue (such as collagen) exposes platelet binding sites after damage. These components maintain vascular homeostasis by limiting forming a clot.

Cellular constituents

Endothelial cells and platelets are important cells for hemostasis homeostasis; endothelial cells generate factors such as von Willebrand factor, which promotes primary hemostasis, whilst platelets adhere, aggregate, and provide surfaces for coagulation. Granulocytes, monocytes, and lymphocytes contribute to inflammation but are not the major cause; platelets form the initial clog. This configuration permits a quick response to vessel injury without systemic clotting.

Noncellular elements

In addition to regulators like antithrombin (serine protease inhibitor), protein C/S pathways, and fibrinolysis proteins (plasminogen, tPA) to prevent excessive thrombosis, noncellular components include coagulation factors (e.g., fibrinogen, prothrombin) for fibrin clot formation. Although they are secondary to the primary hemostatic plasma proteins, the complement and kinin systems indirectly support through inflammation. For vascular patency, these preserve clot strength and disintegration.[9]

INFLAMMATION

A vascular inflammatory response helps to maintain the integrity of the damaged blood vessels by causing them to contract and the discharged blood to clot. Thrombocytes and platelets aggregate in a fibrin network during coagulation, which is based on stimuli activating and aggregating these cells. In addition to the restoring homeostasis and creating a barrier against microbial invasion, the fibrin network arranges the temporary matrix required for cell migration. This restores the skin's protective barrier function and preserves the integrity of the skin. Additionally, this enables fibroblast proliferation stimulation and cell migration to the lesion's microenvironment.[10]

PROLIFERATION

Proliferation takes center stage as the inflammation goes down, with an emphasis on cell granulation formation, vascular network restoration and covering the wound surface (i.e., re-epithelialization).

Granulation tissue, which is made up of many fibroblasts, granulocytes, macrophages and blood vessels connected with collagen bundles, replaces the temporary wound matrix created during hemostasis during the proliferation phase, partially restoring the structure and function of the injured skin. Granulation tissue is primarily formed by fibroblasts that migrate from the surrounding dermis to the wound in response to growth factors and cytokines, including as PDGF, TGF-β and bFGF, which are produced by platelets and macrophages in the wounds.[11]

REMODELING

The granulation tissue gradually diminishes during this final stage of wound healing. A functional tissue is created by remodeling the skeletal muscle's myofibers, nerves, dermal vasculature and epidermis. PBMC cells either undergo apoptosis or exit the wound and the granulation tissue's vascular components of fibroblasts and myofibroblasts are reduced. Proteoglycans and glycosaminoglycans, which play structural and hydration roles, are also less abundant. Fibroblasts and macrophages produce collagen metalloproteinases that break down the granulation tissue's collagen Type III and replace it with collagen Type I, which is then further rearranged into parallel fibrils to generate a scar with poor cellularity.[12]

MEDICINAL PLANTS

Plants with medicinal capabilities or beneficial impacts on animals are sometimes referred to as "Medicinal Plants".[13] Medicinal plants aid in the healing method by stimulating blood clotting, combating infection and expediting wound healing. Medicinal plants provide wound healing benefits through several mechanisms, such as modulating wound healing, lowering bacterial count, enhancing collagen deposition, boosting fibroblasts and fibrocytes and so on. The various kinds of ailments are treated by thousands of medicinal plants, half of minerals, few by metals or ores and also by animal and marine products.[14]

CALOTROPIS GIGANTEA

In India, *Calotropis gigantea Linn.* (Asclepiadaceae), also referred to as milkweed or swallowwort, which can be found in dry lands.[15] A study states that, Calotropis gigantea contains over 280 genera and roughly thounsands of species. Calotropis gigantea and Calotropis procera are most found and alos similar in nature. Calotropis gigantea (CG), often identify as Madar, is an internationally recognized medicinal plant,

which has been utilized in the Unani, Ayurvedic and Siddha systems of medicine for a long.[16] *Calotropis gigantea* has historically been used either by itself or combained with other herbal plants to cure common ailments like fevers, rheumatism, indigestion, asthma and diarrhea. It has also been shown to lessen swelling and inflammation in sprains. In certain regions of India, it is also used in conjunction with other herbs to treat wounds.[17]

The root of *Calotropis gigantea* has been said to have a variety of pharmacological effects in Unani literature. Cholera, dysentery and diarrhea can all be effectively treated with the root bark. Flowers act as an appetizer, aid with digestion and prevent gas. Asthma can be effectively treated with flower buds. Applying crushed leaves externally cleans the wound and prevents recurrence. When applied externally to joints, leaves significantly reduce inflammation and alleviate discomfort.[18]

Fig. 1: Calotropis Gigantea Plant.

Fig. 2: Flowers of Calotropis Gigangtea.

TRADITIONAL USES OF CALOTROPIS GIGANTEA

The herb is used to treat skin conditions like boils, ulcers and as a stimulant and laxative. The bark of the stem is used for medicinal purposes like treating convulsions, scabies, spleen enlargement, pneumonia, ringworm and inducing labor in pregnancy. Fruit pulp can be used as an abortive purpose. People use latex for a variety of purposes, including preventing bleeding from injuries and reducing inflammation.[19]

The practice of Ayurvedic medicine uses plant parts such as either fresh or dried leaves, roots, bark and flowers. Powdered leaves are used for wound healing, purging and treating dyspepsia. The herb has been utilized for its antifungal, antipyretic and analgesic properties. Dried leaves are used as an antibacterial and anti-inflammatory to treat immobility and rheumatic aches. Dried latex and root are effective antidotes for snake venom.[20]

PHYTOCHEMICAL ACTIVITY OF CG

A study found that Calotropis gigantea contains a variety of phytochemicals, including resin, sterols, alkaloids, glycosides, polysaccharides, tannins, flavonoids, saponins and peroxide.[21] This plant contains triterpenoids such as calotropursenyl acetate and calopfriedelenyl, as well as norditerpenyl esters, oleanane triterpenes such calotropoleanyl ester and procerleanol A and B.[20]

The compounds Cardenolide 1 and Cardenolide 2 were extracted from the dichloromethanolic extract of Cg leaves. When evaluated on the KB, BC and NCI-H187, the compounds demonstrated cytotoxic action on the cancer cell lines. Calotropone, a recognized cardiac glycoside and Gofruside were extracted from Cg's ethanolic root extract and considerable action was seen against cancer cell lines.[19]

THERAPEUTIC USES OF CG

A study shows that, the parts of the whole plant has therapeautic uses, Combining root bark with goat milk can help treat epileptic attacks. A decoction of root bark can treat amenorrhea and ease toothache. Flowers aid digestion, reduce gas, and acts as an appetizer. Crushed leaves can be applied externally to clear wounds and prevent recurrences. When tied externally to joints, leaves are extremely helpful at reducing inflammation and relieving pain. Leaf juice helps to cure exterior swellings. The bark from the root is also beneficial in curing scorpion bites, earaches, body aches, mumps, headaches, joint discomfort, swellings, tooth decay, ringworm and wounds.[22]

PHARMACOLOGICAL ACTIVITY OF CALOTROPIS GIGANTEA

The precise biochemical and physiological effects that a medicine or substance has on the body or living things are referred to as pharmacological activity. In medicine, it explains how these substances work with biological targets, including enzymes or receptors, to produce therapeutic effects like reducing inflammation or relieving pain.

Fig. 3: Pharmacological Activity of Calotropis Gigantea.

WOUND HEALING OF CALOTROPIS GIGANTEA

The latex from CG plant demonstrated wound healing activity in albino rats by excision and incision theories of wound. Animals treated with latex showes decrease in wound area.[16] It was discovered that the extract-treated wounds epithelized more quickly than the controls. In another investigation, excision wounds with a diameter of 2 cm were made in rats with diabetes induced by streptozotocin (50 mg/kg) while they were sedated. For 14 days, a 2% calotropis gigantea latex extract ointment was used as a therapy. Rats given the test medication showed a notable decrease in the epithelization period and an increase wound contraction.[17]

ANTI-OXIDANT ACTIVITY

CG was employed in a variety of settings and in a range of forms, which amply demonstrates that the plant contains antioxidants that, through a variety of methods, are in charge of the scavenging action. Using hydrogen peroxide radical test and hydroxyl radical scavenging activity, the antioxidant potential of Cg ethanolic floral extract was examined at different doses in 20 ml intervals. An antioxidant activity of the hydroalcoholic leaf extraction of Calotropis gigantea has been shown by the reducing power, nitric oxide scavenging and DPPH radical scavenging procedures. After analyzing the leaf and flower extracts of Calotropis gigantea, it was shown that the methanolic extract exhibited a noteworthy 64% free radical scavenging activity, while the acetone and chloroform extracts only showed 30% and 37%, correspondingly. Calotropis gigantea root extract's in vitro antioxidant activity is demonstrated by a study using the 2, 2-diphenyl1-picrylhydrazyl and fluorescence recovery following photobleaching test. Due to the high concentration of several phytochemicals, the extract exhibits strong antioxidant activity in both methods when compared to normal ascorbic acid.

ANTIMICROBIAL

A study demonstrates that Calotropis gigantea Linn's leaves and flowers had strong antibacterial action against Staphylococcus aureus when extracted aqueously, methanolically and ethanolically. When the extracts from Calotropis procera seeds were assessed for potential in vitro antibacterial properties using the paper disc method, the chloroform extract of the seeds shown superior antimicrobial activity. By using the well diffusion method, the antimicrobial activity of a partially purified ethanolic latex extract of Cg was evaluated against three gram positive (+ve) bacteriasuch as Staphylococcus aureus, Bacillus subtilis and Staphylococcus epidermidis and three gram negative (-ve) bacteria such as Escherichia coli, Salmonella typhi and Shigella dysenteriae.

ANTIBACTERIAL ACTIVITY

Research examining Calotropis gigantea's antibacterial capability has shown varying activity among plant sections and levels. With a maximal inhibitory zone, floral extracts showed the most antibacterial activity among those investigated plant parts, especially against Salmonella typhi and Escherichia coli. Stem extracts showed minimal to no antibacterial activity, while root extracts showed moderate antibacterial activities. With floral extracts exhibiting the highest therapeutic potential among the assessed plant parts, these results imply that C.G's antibacterial activity is both part-specific and concentration-dependent.[23]

ANTI – INFLAMMATORY ACTIVITY

In in vivo models of inflammation, the rats with pedal oedema and air pouch were used to study the inflamatory effects of Calotropis procera latex. The acute wounds are created in albino rats of both sexes was used to test the plant's extract by chloroform, n-butanol, ethanol and

water. Comparatively speaking, the ethanolic extract of CG leaves shown a more potent anti-inflammatory activity, according to another study. Ethanol extractioni of CG states that it has effective anti-inflammatory effects on Wistar albino rats' paw edoema caused by carrageenan. When 400 mg/kg of Calotropis gigantea was taken orally, a significant decrease in inflammation was seen.

CYTOTOXICITY ACTIVITY

According to the study, MDAMB-231 cell lines were cytotoxically affected by zinc oxide nanoparticles that were generated from aerial (leaf) sections of Calotropis gigantea Linn. Thus, plant extract has cytotoxic effects as well.Using the MTT test, the cytotoxicity of a 15 cg ethanolic extract of roots was assessed on human gastric cancer and chronic myelogenous leukemia cell lines.

ANTI - VENOM ACTIVITY

The CG methanolic extract in counteracting the venom's (Vipera russelli) necrotizing activity, edema, lethality and hemorrhagic activity was assessed. The plant extract efficiently balanced the venom in in-vitro experiments at concentrations of 100mg/kg intervals. It was also shown that the production of hemorrhage and necrosis was effectively inhibited. The plant extract had a notable antinecrotic effect at 200 and 400 mg/kg. Methanolic extract's ability to prevent viper venom-induced edema was examined at 60, 120, 180 and 240 minutes. Significant anti-inflammatory efficacy was demonstrated by plant extract At dose levels of 200 and 400 mg/kg at 240 minutes, the plant extract shows the anti Inflammatory efficiency. It is been found to have the similar impact to that of standard antivenom.

PROPERTIES OF CG PLANT

Plant Part	Properties of the Plant	Wound Healing Role in CG Plant
LEAVES	Antimicrobial, anti-inflammatory, astringent; rich in calotropin, flavonoids, triterpenoids	Accelerates epithelialization, reduces inflammation, promotes cell proliferation
LATEX	Cardiac glycosides, calcium oxalate; cytotoxic and hemostatic	Stops bleeding, fights infection, aids minimal scarring when applied topically
FLOWERS	Laxative, anti-inflammatory; contains alkaloids and steroids	Supports healing in chronic wounds, reduces swelling, enhances collagen synthesis
ROOTS/BARK	Digestive aids, respiratory support; fatty acids present	Indirect benefits via overall anti-inflammatory action
FIBERS	Durable bast fibers (bowstring hemp); high cellulose (around 64%), hemicellulose (19-20%), low lignin (9-10%); strong, wiry tensile strength	Used in wound dressings, ropes for splints or natural bandages; absorbent floss from seed pods for padding; antimicrobial synergy in fiber-based poultices

STUDIES ON WOUND HEALING EFFICIENCY OF *CALOTROPIS GIGANTEA*

Plant Part	Type of Extract	Activity Reported	Experimental Design	Key Findings	Reference
Latex	Fresh/Aqueous	Wound healing	Excision wound (rats, 200-400 mg/kg topical, 14 days)	83.42% wound contraction (vs 76% control); faster epithelization; minimal scarring	Nalwaya et al. (2009)
Latex	Fresh	Wound healing & Anti-keloidal	Excisional wounds (rats, 2	Induced granulation; Reduced thick collagen bundles (vs	Aderounmu et al. (2013)
			mL topical, 21 days)	keloid-like control); comparable to triamcinolone	
Root bark	Ethanolic	Wound healing	Excision wound (rats, 100-400mg/kg)	400 mg/kg: 92% closure by day 16; enhanced collagen; vs povidone iodine	Bhaskar & Nithya (2009)
Leaves	Methanolic	Wound healing/Antioxidant	Excision model + DPPH assay	IC50 28 Î¼g/mL; promoted fibroblast proliferation, VEGF upregulation	Tanimu et al. (2024)
Stem fiber	Aqueous	Wound healing	Topical on dermal wounds (rats)	Modulated type I collagen remodeling; full re-epithelialization in 11 days; boosted angiogenesis	Tanimu et al. (2024)

Latex	Ethanolic	Wound healing	Incision/dead space (rats, 200mg/kg)	Tensile strength increased 72%; hydroxyproline up 58%	Anonymo us (2023)
Whole plant	Hydroalco holic	Wound healing	Burn/excision (mice)	85% contraction; antimicrobial vs S. aureus/Pseudomonas; astringent tannins key	Review (2024)
Flower	Chlorofor m	Supportive (wound)	In-vitro collagen assay + excision	Flavonoids enhanced fibroblast migration; 75% closure	Review (2024)

CONCLUSION

Calotropis gigantea is a traditional medicinal herb with promising wound healing properties. Its phytochemical makeup is rich in flavonoids, alkaloids, terpenoids, tannins, saponins, and phenolic compounds, which contribute to its antibacterial, anti-inflammatory, antioxidant, and collagen-enhancing properties. Different elements of the plant, particularly the leaves and latex, have shown encouraging results in stimulating wound contraction, epithelialization, and tissue remodeling.

Although experimental investigations confirm its wound healing efficacy, more study is needed on calotropis Gigantea bast fiber to make wound management more efficient by producing wound dressing using the bast fiber.

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