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Wound Healing and Pharmacological Evaluation of Mallotus Philippinensis

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Abstract - The Mallotus philippinensis Muell. Arg (MP, Euphorbiaceae) In tropical and subtropical parts of the outer Himalayas, is a widely spread perennial shrub or small tree. Since then, a variety of medical benefits of Mallotus philippinensis have been shown. The purpose of the current investigation was to ascertain if fruit extract has the ability to heal wounds in rat models.

Keywords - Wound, Wound Healing, Mallotus Philippinensis, Pharmacological Evaluation

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INTRODUCTION

An injury known as a wound occurs when the skin is ripped, sliced, or pierced (resulting in an open wound), or when blunt force trauma results in a contusion (a closed wound). Depending on the degree of the wound, the wounded tissue might be repaired totally or partly throughout the complicated and prolonged process of wound healing. Three overlapping phases can be used to summarise the entire process: the inflammatory phase (which includes inflammation and hemostasis), the proliferative phase (which includes granulation, contraction, and epithelialization), and the remodelling phase, which results in an organised structure with increased tensile strength (1-3). It has been noted that a variety of variables, including microbial infection, inflammatory and immunological reactions, and immune responses might hinder and delay the healing process. Myeloperoxidase, cytokines, and free radicals are released by macrophages, which play a key role in the wound healing process by increasing reactive oxygen species (ROS), causing tissue damage from myeloperoxidase/destructive enzymes, and decreasing anti-oxidants, which promote healing by neutralising ROS (4).

Almost everywhere in the poor world, plants or herbal remedies are used to treat wound healing. In the ancient medical system, healers use crude extract from a variety of medicinal plants to treat wounds including ulcers, bites, burns, and lacerations. It will support the provision of healthcare for rural areas. Mallotus philippinensis Lam. Muell. Arg (Euphorbiaceae) (MP) are shrubs or small trees that may be found in woods, limestone hills, river valleys, or mountain slopes between 300 and 1600 metres above sea level. Traditional medicine has employed the red-colored powder known as kamala, which is made up of glandular hairs from the fruit capsule, for anthelminthic, cathartic, and many other pharmacological purposes. We discovered via our research investigation that MP were used as conventional healers in India. To treat wounds, the locals utilise the powdered fruit. Additionally, we found that MP fruit extract has potent anti-inflammatory and analgesic properties, which may be crucial for MP's therapeutic effects. As a result, we investigated the MP ethanol extract's capacity for wound healing. However, this herb is used to treat scabies, herpes ringworm, and other parasitic skin conditions. We also tested the MP extract's antioxidant and free radical-scavenging properties as part of our pharmacological inquiry, which is crucial for wound healing (5).

In addition to this work, study reported that significant phytochemicals like cinnamtannin B-1 and protocatechuic acid in ethanol MP bark extract that may influence the migration of mesenchymal stem cells from the bone marrow or perivascular regions into blood circulation and that have been shown to accelerate mouse wound healing. In vitro studies have shown that protocatechuic acid encourages the migration and growth of adipose tissue-derived stromal cells (ADSCs). According to these findings, MP's components could be able to reconstruct damaged tissues and provide novel treatment alternatives for regenerative medicine (6).

WOUND HEALING

The complex process of wound healing is how the skin (or another organ-tissue) recovers from damage. It involves the intricate alignment of several dynamic processes, many of which are yet unclear. After an injury, the body tries to give a wounded tissue its pre-wound properties as closely as

possible by restoring its structure and maintaining its function (7). Although these phases often overlap, normal wound healing may be broken down into three stages:

a) Inflammatory phase (also called 'lag phase')
b) Tissue formation phase ('proliferative phase')
c) Tissue re-modelling phase ('maturation phase')

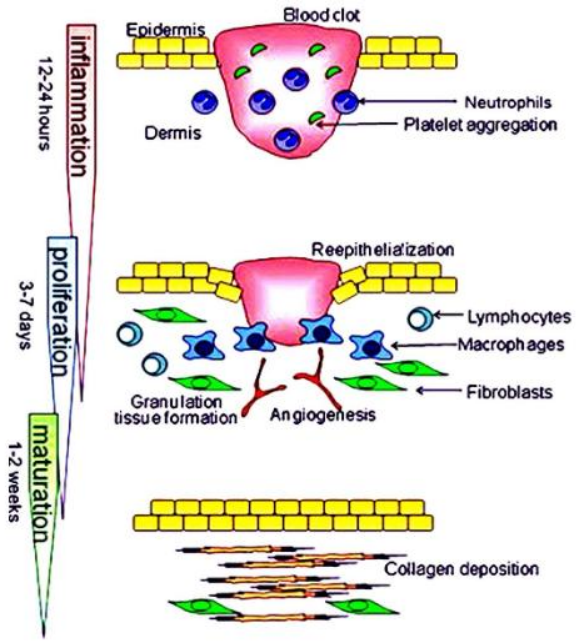

Figure 1: Phases of wound healing process

Blood initially contacts collagen when skin is broken or wounded, causing blood platelets to release inflammatory substances first. The clotting system kicks in to limit blood loss even before the inflammatory phase has started. Hemostasis is accomplished by a cascade of clotting components operating sequentially to produce a fibrin clot. On their cell membranes, platelets produce glycoproteins that enable them to adhere to one another and group together to create a mass. In this first mass, fibrin and fibronectin cross-link and create a plug that catches other plasma proteins and particles, halting further blood loss. At the location of wound healing, this fibrin-fibronectin plug serves as the primary structural support for inflammatory cells. This plug serves as a matrix for migratory cells to spread out throughout and release more inflammatory and growth factors. The clot gradually dissolves and is replaced by granulation tissue, which is followed by collagen.

Damaged platelets and platelets stuck in blood clots produce substances necessary for the start of healing, such platelet derived growth factor, when they are injured (PDGF). The early influx of neutrophils and subsequent influx of other cells to the wound site are both crucially influenced by PDGF and interleukin-8 (IL-8). When neutrophils reach the site of the wound, they take the lead in producing pro-inflammatory cytokines such tumour necrosis factor (TNF) and interleukin-1 (IL-1). These cytokines seem to stimulate the chemokine and growth factor synthesis that starts the healing process. Monocyte chemo-attractant protein-1 (MCP-1) is one chemokine that is activated by IL-1, and after a day of damage, over 20% of all cells express MCP-1 (resident and infiltrating cells) (8).

The recruitment of macrophages to the site of the injury is greatly aided by MCP-1. Once there, the macrophages support the neutrophils' phagocytic activity and convert into a significant source of the growth factors that help the wounded area regenerate and heal. Additionally, wounding causes the basal keratinocytes to release KGF, which encourages the formation of primary and secondary keratinocytes, which repair the injured tissue. The synthesis of all of these cytokines and growth factors is, however, highly interconnected, irrespective of the cell source, so that changes in one component may have an impact on the production of one or more of the others and affect the overall integrity of the healing wound (9).

NORMAL WOUND HEALING

Wound

A wound is a loss of skin integrity brought on by an illness or an accident. A key bodily mechanism known as wound healing is responsible for repairing the epidermis and dermis cells' normal structure and function after they have been damaged by burns, fractured bones, muscular tension, or skin breaches. When these wounds don't heal, it leads to consequences including septicemia and toxaemia and delays wound recovery (10).

Classification of Wounds

Health care practitioners categorise wounds in a variety of ways. Depending on the kind of healing and the procedure involved, they are classified as either chronic or acute wounds.

Traumatic injuries (mechanical wounds, burns, and chemical wounds) and surgical wounds that heal within four weeks make up the majority of acute wounds.

Chronic wounds that leave scars and take longer than three months to heal, the main contributing factors include

- Venous or arterial insufficiency
- diabetes
- Increased bacterial load
- Inappropriate treatment
- Local-pressure/trauma

Basic mechanism of wound repair

The healing process of an acute wound is a complicated and ongoing chain of events. An damage to live tissue sets off this cascade of

processes, each one more complicated than the last.

- Vasculoprotective properties of hemostasis
- Inflammation and debridement of the skin B.
- Proliferation and rebuilding C.
- D. Collagen remodelling and maturation

➢ **Haemostasis**

When the coagulation system is activated to halt bleeding, the injured arteries contract fast, causing platelets to aggregate and a clot/plug to develop. Fibrin and fibronectin combine to produce a plug that serves as a matrix scaffold for cellular migration to the site of damage. The plug's platelet aggregates are critical for both halting bleeding and kicking off inflammation. Several growth factors, cytokines, and chemokines are released during platelet activation. Endothelial, monocyte, lymphocyte and macrophage activation is induced by these complement proteins. This results in a proper inflammation response in the body.

➢ **Inflammatory phase (Day 0-5)**

This is the body's first line of defence and serves to set up the injured region for recovery. Platelet degranulation occurs as a result of the blood's contact with collagen at the wound site. Injured tissue releases histamine, which produces vasodilation and, as a result, increased redness, heat, discomfort, and swelling, as well as limited mobility. All cells in the body generate more prostaglandins and Bradykinins as a result of the damage to the cell membrane, which prolongs the effects of vasodilation.

Leukocytes begin to adhere to the dilated endothelium walls of the blood vessels at the location of the lesion. Preventing the spread of infection from the wound and cell debris is a primary goal of this stage. Following damage, granulocytes and polymorphonuclear leukocytes are recruited within 24 to 48 hours due to the activation of complementary and traditional molecular cascades. Responses by monocytes to chemo attractants continue to reach the site of damage (e.g. fragments of the ECM and coagulation components of the PDGF, platelet factor IV, collagen and elastin immunoglobulin G (IgG) fragments, leukotrienes and TGF-). They are involved in the shift from inflammatory response to wound healing, which is where they come in. Cytokines and growth factors released at the site of damage activate fibroblasts, endothelial cells and keratinocytes to repair the damaged blood supply. Besides that, they secrete substances like collagenase and NO into the ECM, which aids in the debridement of tissue (11).

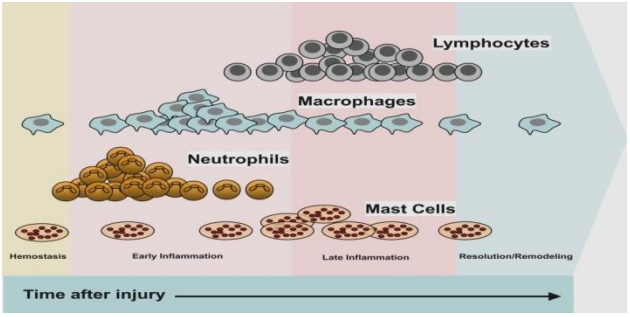

Figure 2: The array of white blood cells at the site of injury

➢ **Epidermal Proliferation (3-14 days)**

Proliferative phase involves just a few kinds of cells, but the inflammatory stage involves many. It starts three days after the injury and lasts for three weeks. Wound remodelling and replacement with fresh, newly generated bone tissue are two components of this process. The following five events describe it:

(1) Neovascularization: Since healing needs functioning blood capillaries to supply the injured cells, angiogenesis (neo-vascularization) occurs concurrently throughout all stages of the healing process. It begins in the inflammatory phase. It has been shown that during haemostasis, thrombocytes produce PDGF and TGF-, which activate macrophages and start neo-vascularization. TNF- and other crucial growth factors are secreted by the macrophages.

(2) Fibroblast mobility: Hyaluronan (HA), fibronectin, and then collagen, as well as the proteolytic enzymes known as matrix metalloproteinases (MMPs), which aid in fibroblast movement within the matrix, are secreted by myofibroblasts near the site of the injury.

(3) Granulation tissue formation: After a few days, a microvascular network spreads out at the damage site, and new buds and sprouts cover the area that was wounded. The wound develops as collagen builds up in the granulation tissue.

The capillary loop density decreases, making the fully formed scar seem whiter than the surrounding tissue. The effectiveness of the healing process depends on the colour of the scar. In freshly created granulation tissue, glycosaminoglycans (GAGs), hyaluronan (HA), proteoglycans, and newly formed capillaries, endothelial cells, myofibroblasts, and macrophages are imbedded.

(4) Epithelialization: Within 12 hours after wounding, undamaged keratinocytes start to divide and transfer from the surrounding margins, establishing a new basement layer stratified epithelium around the edge of the wound. This process is known as epiboly. If the location is oxygen-rich, has an unbroken basal lamina, is moist, and does not need debridement, the

pace of epithelization will be enhanced. The collagenases and proteases (matrix metalloproteinases-MMPs) that the keratinocytes release progressively disintegrate the scab, which finally sheds from the spot.

(5) Collagen production: The migrating fibroblasts migrate over the whole wound, activating the fibroblasts and causing them to begin producing collagen. As soon as a wound occurs, collagen begins to play a crucial role in healing it. Collagen exposure to blood promotes platelet aggregation and activates chemotaxis. Collagen then serves as the ECM's structural foundation in wounded tissue. Type III collagen is produced by fibroblasts. Wound tissue cannot move freely because of recently cross-linked collagen fibres.

- **Reconstruction phase: (7 days – 1 year)**

As matrix tissue matures, fibronectin and HA are broken down, inflammatory cells depart, and collagen bundles are cross-linked, increasing the tissue's ability to withstand wounds (12).

When the borders of the wound are drawn together by the contractile connective tissue, healing occurs. TGF-, PDGF, and FGF are a few of the factors that regulate contraction. Additionally, capillary development is stopped, and the reduced blood flow at the spot results in an avascular scar. For around a year, the scar tissue continues to remodel (13).

IMPAIRED WOUND HEALING

When the inflammatory and repair processes balance one another (chronic inflammation, for example, in smoker's bronchitis or liver damage brought on by alcohol), a situation of wound healing occurs. When excessive quantities of collagen are produced, the result is fibrosing inflammation (such as liver cirrhosis), while excessive granulation tissue production is a sign of granulomatous inflammation (e.g., in tuberculosis, foreign bodies). Local stress may result in the wound reopening following abdominal procedures if the scar tissue is of poor quality, such as when collagen production is inhibited by corticoids or there is an irregularity of collagen cross-linking in vitamin C deficiency. Larger scars, particularly those on the face, may cause aesthetic issues, especially when there is an excessive amount of scarring (keloid). On the cornea (visual impairment), the heart valves (stenosis, regurgitation), or the belly, for example, scars may sometimes cause serious functional issues (adhesions or strictures of the gut). If a pathogen-caused inflammation cannot be contained locally, it will spread to the whole body, often via the lymphatic system, and sepsis will develop (14).

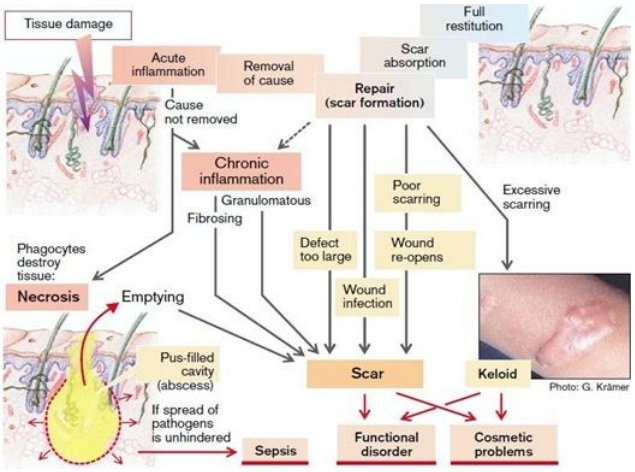

Figure 3: Inflammation: Disorders and after-effects

MAJOR FACTORS AFFECTING WOUND HEALING

Malnutrition

Nutritional deficiencies, such as a deficiency in protein and fatty acid levels, impede wound healing, according to this study. A wound's tensile strength and infection risk are both affected by the presence of proteins, which are necessary for collagen synthesis, fibroblast formation, and other critical immunologic processes. Arachidonic acid is the primary substrate for the production of eicosanoid molecules during wound healing, which necessitates the presence of fatty acids.

Wound Infection

Infection at the site of trauma might impede the healing process. Inflammation and epithelialization are influenced by the microorganisms already present. Biofilms (bacterial colonies embedded in an extracellular matrix structure made up of polymeric components) that emerge as a result of poly-microbial wound infection and prolonged colonisation hinder wound healing.

Ischemia and inadequate Perfusion

Wound healing requires a sufficient amount of blood flow. Pressure injuries, inadequate arterial supply, venous hypertension, smoking, and other factors may all contribute to ischemia.

Drugs

The chemotherapeutic medicines, in particular, have been shown to have a negative impact on wound healing. Glucocorticoids have been shown to interfere with all phases of wound healing, including the formation of new tissue.

Medicines linked with retarded wound repair:

- Chemotherapeutics

- Systemic corticosteroids
- Analgesics (NSAIDs) (e.. naproxen, acetyl salicylic acid)
- Anticoagulants
- Bisphosphonates
- Morphine

Age related

Older people are more likely to have wounds that don't heal properly. It has been shown that in senior adults, there is a longer duration of inflammation, a decrease in fibroblast production, and a decrease in matrix deposition.

Metabolic diseases

Chronic diabetic foot ulcers may be caused by wound-related infection in patients with diabetes. Inflammation in the liver is also connected to a decreased ability to heal wounds. Patients with reduced immune systems are more susceptible to wound infection and less able to mend their wounds.

Irradiation

During cancer therapy, ionising radiation might delay the healing of wounds. Ionizing radiation damages cells by causing double-stranded cellular DNA to be disrupted and free radicals to be produced, leading to apoptosis and necrosis (15).

HERBAL ANTIOXIDANTS

Antioxidants made from plants have recently become the subject of much research. It has been shown to be effective in the prevention and treatment of a wide range of ailments in both individuals and the broader population. An antioxidant is a chemical that depletes electrons from other atoms in order to prevent free radicals and/or ROS/RNS from causing damage. Antioxidants have both intracellular and extracellular functions (extracellular).

Human health has been shown to be adversely affected by the use of synthetic antioxidants. A wide variety of phytochemicals make up herbal antioxidants, from basic phenolic compounds to more complicated polyhydroxyphenolic compounds. In addition to their anti-oxidant properties, these polyphenols cause oxidative damage. Hydroxyl ion concentration and placement on the benzene ring determine antioxidative action. The antioxidant capacity of the phenol ring rises as a result of the addition of the hydroxyl group. In order to isolate bioactive phytochemicals from plants, it is necessary to evaluate the oxidation inhibitor characteristics of the plants and their fractions.

MALLOTUS PHILIPPINENSISIS

Tropical and sub-tropical regions are home to a broad range of this plant's distribution, from Punjab and Uttar Pradesh to Burma and Singapore. In addition to China, the Malaya Islands, Australia, Pakistan, and the Andaman Islands, it is also said to be expanding. By releasing seeds that fall to the ground at the beginning of the hot season, plants are able to reproduce naturally. In April, new seeds are sown for artificial propagation. In the first year, the more strong seedlings are suitable for transplantation; smaller seedlings may be retained in the nursery for another year. Reproduction through root suckers is also possible for this species, however it grows much more slowly. In addition to its ability to survive heavy shade, this plant is drought- and frost-resistant. In addition to Fomesconchatus, I. rimosus, and E. caryophylli, the tree is susceptible to attack by numerous other rot-causing fungus, such as Hexagonia discopoda and Polyporus dustus as well as Stereum and Ganodema applanatum (16). The average yearly girth increase in India was 0.65 cm, and the average girth after 16 years was less than 15 cm. Mean annual diameter increment for trees in the 10-20 cm class of M. philippensis in the Philippines has been found to be 1.4 cm. M. philippensis, which has been established in India, is frost-hardy and drought-resistant, and it can coppice well and produce root suckers. The bacterium M. philippensis is not fire resistant.

CONCLUSION

Microbes are more likely to assault a wound when it is exposed to the outside environment, altering the normal healing process. MP has been shown to have a broad spectrum of antibacterial action against human pathogens, which may minimise skin infections and speed up the healing process after wounds.

REFERENCES

1. Suntar I. Traditional Medicine for Wound Management. Evi Based Compl Alternative Med. 2017;2017:1.
2. Sougrat R, Morand M, Gondran C, Barre P, Gobin R, Bonte F, Dumas M, Verbavatz JM. Functional expression of AQP3 in human skin epidermis and reconstructed epidermis. J Invest Dermatol. 2002;118:678-685.
3. Gould J. Keeton W. Biological Science. 6th ed. New York: WW Norton and Co.; 1996.
4. Strodtbeck F. Physiology of wound healing. Newborn Infant Nurs Rev. 2001;1:43-52.
5. Waugh A, Grant A. Ross and Wilson: Anatomy and physiology in Health and Illness. 12th ed. Edinburgh: Churchill Livingstone Elsevier; 2001.
6. Thivierge B, Turkington CA. Medical Encyclopaedia on line. 30 Nov 2007.
7. Boateng JS, Matthews KH, Stevens HNE, Eccleston GM. Wound healing dressings and drug delivery systems: A review. J Pharmaceutical Sci. 2008;97:2892-2923.

8. Dealey C. The care of wounds-A guide for nurses. 3rd ed. UK: Blackwell publishing Ltd.; 2005:56-57 p.
9. Witte MB, Barbul A. General principles of wound healing. Surgical Clinics of North America. 1997;77(3):509-28.
10. De la Torre J, Sholar A. Wound healing: chronic wounds. Emedicine.com. Accessed on 20 November, 2013.
11. Jie L, Juan C, Robert Kirsner MD. Clinics in Dermatol. 2007; 25: 9-18.
12. Buchstein N, Hoffmann D, Smola H et al. Alternative proteolytic processing of hepatocyte growth factor during wound repair. Am J Pathol. 2009;174(6):2116-28.
13. Snyder RJ, Lantis J, Kirsner RS et al. Macrophages: A review of their role in wound healing and their therapeutic use. Wound Repair Regen. 2016;24(4):613-29.
14. Eming SA, Koch M, Krieger A et al. Differential proteomic analysis distinguishes tissue repair biomarker signatures in wound exudates obtained from normal healing and chronic wounds. J Proteome Res. 2010;9(9):4758-66.
15. Rayment EA, Upton Z, Shooter GK. Increased matrix metalloproteinase-9 (MMP-9) activity observed in chronic wound fluid is related to the clinical severity of the ulcer.Br JDermatol.2008;158(5):951-61.
16. Jiang L, Dai Y, Cui F et al. Expression of cytokines, growth factors and apoptosis-related signal molecules in chronic pressure ulcer wounds healing. Spinal Cord. 2014;52(2):145-51.

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