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Review

Therapeutic promise of *Calotropis procera* (Aiton) W.T. Aiton latex for wound healing and keloid prevention: A narrative review

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ABSTRACT:

Background: A scar represents an alteration in skin architecture that occurs during the wound-healing process when the regenerated tissue does not fully resemble the original structure. Optimal healing requires a harmonious balance between the deposition and degradation of the extracellular matrix (ECM). Conditions such as keloids and hypertrophic scars (HTS) arise due to excessive collagen accumulation and dysregulated fibroblast activity, primarily influenced by growth factors like PDGF and TGF-β within the ECM. Disturbed maturation of granulation tissue further contributes to abnormal scar formation. *Calotropis procera* (Aiton) W.T. Aiton, a traditionally recognized medicinal plant in Ayurveda, ossesses bioactive latex constituents with significant wound-healing potential. Its soluble latex proteins exhibit hemostatic, pro-inflammatory, and anti-inflammatory actions that support sequential phases of healing. These properties highlight the therapeutic relevance of *Calatropis. procera* in managing pathological scar formation within holistic and integrative wound-care approaches. **Objectives:** This review compiles in vitro and in vivo studies on raw and processed latex of *Calotropis procera,* (Ait.) emphasizing its hemostatic and anti-inflammatory effects. It focuses on gallic acid, quercetin, and kaempferol as secondary metabolites in the lyophilized non-protein fraction, proposing their repurposing as bio-rational agents for anti-scar therapeutic and cosmetic applications. ***Results:*** Research supports the latex's hemostatic, pro-inflammatory, and anti-inflammatory activities in various animal models. Latex cysteine peptidases exhibit thrombin- and plasmin-like activities. It synergistically inhibits inflammatory cytokines such as COX-2, TNF-α, iNOS, and TGF-β, protecting against acute infections. Gallic acid modulates inflammatory mediators, while quercetin and kaempferol provide protective effects against scar formation. ***Conclusion:*** Current evidence supports the use of *Calotropis procera latex* as a hemostatic and anti-inflammatory agent with potential for further development as an anti-scar therapeutic and cosmetic drug. This review suggests its theoretical use in scar management warrants additional investigation.

KEYWORDS: Arka, *Calotropis procera* (Aiton) W.T. Aiton, keloid prevention, narrative review, wound healing.

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1. INTRODUCTION

Calotropis procera (Asclepiadaceae) and the use of latex obtained from the plant are reported in the traditional literature for the treatment of various ailments. *It* is an Indian shrub well-grown in tropical and subtropical regions. The traditional system of ayurvedic medicine accepts two varieties of the plant, i.e., *Shvetaarka* and *Raktaarka. Shvetaarka* is also identified by the synonyms, i.e., aak, arka, madar, akavana, akand, akanda, akan, ravi, tapana, bhanu, rui, and erikku. The plant has also been included in Hindu texts since the Vedic period. [1] The leaves of the plant are also used to be reported to worship of the Sun by the Hindu community and as a drug of choice for a variety of ailments. [2] *Calotropis proceraR. Br* is a well-recognized plant in the pharmacopeial compendium of Ayurveda. [3] The plant has its description in the early medieval period in Dhanwantari Nighantu, one of the oldest Indian materia medica. (10^{th}-13^{th} century A.D).

Traditional uses *of Calotropis procera*

Traditional medical systems utilized plant latex from the Asclepiadaceae family as therapeutic anti-microbial and medicinal agents for stopping bleeding from minor wounds and promoting wound healing. [4] Topically, the latex of *Calotropis procera* has been reported to be used for gum bleeding, as a hemostatic, and healer for fresh wounds by tribal people from rural areas. [5] The leaves, latex, and flowers are traditionally used as a poultice for sores and in toothache preparations [6] and for cracked feet and as a vermifuge. [7] Root bark has been reported by traditional therapists for elephantiasis. The secretions from root bark are reported to be used for skin diseases, asthma, leprosy, hemostasis, intestinal worm infestations, ascites, and anasarca. [8] Intake of flowers has been reported to increase appetite and improve digestion. Flower tops are reported for asthma, while boiled and oil-treated leaves have been proven effective in the treatment of paralysis. Leaf powder has been reported to be used as an alternative to ipecacuanha and is being used for wound healing, while juice is applied as an infanticide to induce abortion. Topically, the latex applied to fresh wounds induces hemostatic for healing. [5] Literature reports suggest that it has been used as a topical application for skin infections in Brazil for ages. Information is also available about drinking diluted latex with water as a traditional treatment for hyperglycemia. [9] Traditionally, milky latex was also assumed to have purgative and caustic actions, thus being used as an anti-inflammatory, antimicrobial, analgesic, anti-diabetic, anti-helminthic, anti-arthritic, and to treat baldness and toothache. Unprocessed latex has also been reported to be used as a poison on arrowheads among tribes and for tanners to remove hair from hides. [6] Toxicity studies on humans exist, causing Iridocyclitis. [10, 11]

2. METHODOLOGY

Table 1: Search Strategy Used for Identifying Relevant Literature on *Calotropis procera* Latex

Serial Number	Database /Source	Search Terms Used	Filters Applied	Notes
1	Scopus	"Calotropis procera" OR "Calotropis procera latex" AND ("wound healing" OR "keloid prevention" OR "wound repair" OR "scar inhibition")	Language: English; Full text available	Focused on pharmacological studies, in vitro, in vivo, and clinical studies, 1980-August 2025
2	PubMed	"Calotropis procera" OR "Calotropis procera latex" AND ("wound healing" OR "keloid prevention" OR "wound repair" OR "scar inhibition")	Language: English; Full text available	Included studies from 1980 to January 2025; excluded non-relevant plant parts
3	EMBASE	"Calotropis procera" AND ("wound healing" OR "keloid prevention" OR "wound repair")	Language: English	Included pharmacological, biochemical, and mechanistic studies 1980-August 2025
4	Web of Science	"Calotropis procera" AND ("wound healing" OR "keloid prevention")	Language: English	Focused on peer-reviewed articles, reviews, and clinical studies 1980-August 2025
5	ScienceDirect	"Calotropis procera" OR "Calotropis procera latex" AND ("wound healing" OR "scar prevention" OR "keloid treatment")	Language: English; Full text available	Emphasis on experimental studies and mechanistic insights 1980-August 2025
6	Google Scholar	"Calotropis procera" AND "wound healing" OR "keloid prevention"	Language: English	First 450 results screened for relevance; grey literature included 1980-August 2025

Chemical constituents present in the latex of *Calotropis procera*

After reviewing the various databases and phytochemical analysis of the latex has been reported to the existence of biologically active cardiac glycosides, phenols, saponins, alkaloids, triterpenes, tannins, anthocyanins, and steroids. [12]

Main cardenolide in crude latex includes uscharin, usharidin, calotropin, calotropagenin, 19-dihydrocalotropagenin, calotoxin, 12β-hydroxycoroglaucigenin, calactin, 15β-hydroxycalactin, voruscharin, uscharin, uscharidin, uzarigenin, syriogenin, dihydrouscharin, 15β-hydroxyuscharin, afrogenin, afroside. [13] Flavonoids in the aerial parts of the plant latex. Crude flavonoid fraction of dialyzed methanolic extract from aerial parts of plant identified as kaempferol-3-O-rutinoside, isorhamnetin-3-O- rutinoside, quercetin-3-O-rutinoside and the flavonoid 5-hydroxy-3,7-dimethoxyflavone- 4-O—glucopyranoside. [14] Di and Tri terpenes, 3β, 27-

dihydroxy-urs-18-en,13,28-olide, Urs - 19(29)-en-3yl acetate (calotropenyl acetate), multiflorenol, α,-β-calotropeol, 3-epimorenol, [2] β-amyri n, α-amyrin & germanicyl as terpenes. [15] Taraxast-20(30)-en-3(4-methyl 3-pentenoate). Enzymes detected as cysteine proteases included procerain and Trypsin, an enzyme with invertase-like activity. [16] Procerain exhibited tryptophan and tyrosine residues along with cysteines. Hydrocarbons reported are 4-Hydroxy-4-methylpentan-2-one, 2,3,4-timethylhexane, Decane, n-Pentadecane, 2,6,dimethyltetra-1,5 Decane, n-Eicosane,3,7,11-trimethyl-2,6,10,12-Petadecatrien-1-ol,2,6,10,15,19,23 Hexamethyl-2,6,10,14,18,22- tetra co sahexaene, 1,2,5-triisopropylbenzene, Z-2-propenyl-2-hydroxyethylcarbonate. [6] Other compounds detected are Phenols that can be used as antioxidants, nutraceuticals, and anti-inflammatory. Phenols present in latex are gallic acid, [12] heperidin, rutin and naringin. [15] They can be used as a good anti-inflammatory agent. Saponins detected are 3-epimorenol. [6]

Protein section of *Calotropis procera contains* basic proteins of molecular masses between 5 to 95 kDa. [17] Two cysteine peptidases named Procerain [18] and Procerain B [19]. Enzymatic activities of the Soluble Latex proteins were obtained by biochemical and spectroscopic studies through protocols decided by Ramos et al (M.V. Ramos et al., 2013). Major proteins recognized in *Calotropis procera's latex* are a group of three cysteine proteinases known by the names peroxidases, chitinases, osmotin and germin. LP$_{PI}$ is mainly composed of chitinases, and LP$_{PII}$ is composed of cysteine proteinases and less amount of osmotin. [11] LP$_{PIII}$ with residual protein activity. Dialyzable fraction of crude latex is composed of amino acids glutamic acid, aspartic acid, glycine, serine, histidine, arginine, alanine, threonine, tyrosine, proline, valine, ethionine, leucine, isoleucine, lysine and phenylalanine. [14]

Processing of latex of *Calotropis procera*

Calotropis procera has an endogenous production of latex, easy to be easily obtained from the plant with an approximate collection of 20 ml in 12 min. Yield is considered more as compared to *Hevea brasiliensis*. [9] The collected latex from plants' aerial portions in 1:1 ratio in distilled water at a-- temperature of around 25^0C to 28^0C is to be centrifuged at 5000 rpm (25^0 for 10 min), which leads to the separation of Rubber Fraction (RL). The obtained supernatant was then dialyzed with distilled water (1:1 v/v) at 8^0C for about 60 hours with dialysis membranes, and proteins with molecular weight up to 8000 Daltons were filtered. Latex collected in water is termed as DL (Dialyzable Latex), Non-Dialyzable Latex (NDL) is obtained by centrifuging this mixture again, and a clear supernatant is obtained that is devoid of RL but rich in soluble protein part. Acute toxicity is found to be absent in NDL and is lyophilized to be used for further pharmacological actions [21]

Centrifugation and dialysis separate highly insoluble RL, Soluble NDL with major latex proteins and DL with proteins of low molecular weight. [5] DL, NDL and RL fractionated could be separated by polyacrylamide gel electrophoresis in a PD-10 desalting column to isolate proteins responsible for pro-inflammatory and anti-inflammatory actions according to their molecular size. [21] Rubber fractions of latex contribute to more than

80% of the dry weight of latex, and the soluble protein part is less than 20% suggesting it as a rich protein source. Estimated protein content in RL, NDL & DL are 9.8 mg/dl, 0.32 mg/dl & 2.2 mg/dl, respectively. [17] When soluble latex proteins were subjected to fractionation by ion-exchange chromatography in CM Sepharose fast flow column, sub-fractions LPP1, LPPII, LPPIII were isolated at different absorbance profiles. [22]

Potential application of *Calotropis procera* for the treatment of wound of burns

In medical practice, it is reported that when skin replaces a lost tissue, the newly generated tissue does not exactly resemble the existing one, creating a scar, which could be long-lasting or non-treatable. [23] Healing through the formation of granulation tissue ensues with a proper balance among regular extracellular matrix deposition and degradation, and the wound matures without a scar. When this balance is disturbed, it leads to the formation of hypertrophic scars and keloids. [24] The mechanism behind the phenomenon of scar formation involves a non-uniform healing pattern. The reported incidence is approximately 40% post-surgery and about 91% after burns. [25, 26] Severe inflammation for a long period of time provides continuous wound healing signals, making wounds susceptible to HTS and keloids. [24] A solution to the Problem of Scar formation from herbal medicines could be a great advantage to the majority of the population**.** Sufficient literature exists with documented facts of many authors through pharmacological research for in-vitro and in-vivo studies support previously known traditional uses of the latex of *Calotropis procera*. It has anti-ulcer, anti-spasmodic activity along with anti-inflammatory, hemostatic and fibrinolytic potential. [5,21,27] Being a rich source of protein, latex has the distinguished properties of anti-inflammatory, proteolytic, and anti-scar potential. The NDL section of the latex from *Calotropis procera* contains quercetin, kaempferol, and gallic acid. Gallic acid is a natural phenolic compound that plays a role in inhibiting pro-inflammatory and anti-inflammatory mediators in latex. [28] Quercetin and kaempferol are bioflavonoids with a protective role in scar formation. [20] This paper presents a review of the literature on *Calotropis procera's* latex as a hemostatic with procoagulant, anti-oxidant, pro-inflammatory, and anti-inflammatory potential. [27, 29] *Calotropis procera latex* is repurposed as a bio-rational tool that can be helpful in healing burn wounds without scarring or keloid formation. This is being repurposed for the first time as a burn wound healer with anti-scar potential.

Functions of RL, DL & NDL

Studies suggest DL & RL to be involved in inflammation. NDL, a rubber-free section containing high molecular weight soluble proteins, does not have any adverse effects and is supposed to be a cause for the anti-inflammatory activity. DL, when subjected to electrophoresis on a PD-10 desalting column, was found to induce migration of neutrophils, while no such activity was seen in RL and NDL. Carrageenan-induced peritonitis was reported to be reversed with a pre-treatment with NDL and RL, but the same activity was absent with DL.

Wound healing process

Wound healing is initiated by hemostasis. Immediately after injury Platelet degranulation releases various glycoproteins. As platelet aggregation progresses coagulation cascade is activated. Fibrinogen is broken down to insoluble fibrin, forming a clot. As healing progresses, this clot serves as a provisional matrix. Damaged cells and platelets serve as chemotactic stimuli for fibroblasts, endothelial cells, and keratinocytes. The provisional matrix is degraded by proteinases and is removed from the wounded site as a scab. Physiologically, plasmin and matrix metalloproteinases (MMP) are key enzymes that dissolve fibrin clot. [5] Growth factors released from platelet degranulation activate fibroblasts to produce collagen in the ECM and form a supporting matrix. Thus, healing begins with hemostasis in a sequence of steps. [30]

Hemostasis & Inflammation

Beginning with vasoconstriction, platelet aggregation, adhesion, and degranulation follow. The inflammation and coagulation processes are found to be interrelated to each other. As per modern physiology, TNF-α, IL-1β, and IL-10 are presented to have a central role in the inflammatory process. [31] Macrophages activate TNF-α to release IL-1β for an inflammatory response. IL-1β has a chemotactic property for neutrophils and stimulates gene expression for iNOS & COX-2. [32] IL-10, an anti-inflammatory cytokine [33] released during uncontrolled bacterial infections, downregulates the inflammatory cell response. [34] Cellular infiltrations cause neutrophils to release ROS. [35] Released TNF-α, IL-1, IL-6 (pro-inflammatory cytokines), and complement system activation promote coagulation. [5] Haemostasias is mediated by extrinsic and intrinsic pathways of blood clotting, which activate the coagulation cascade (fig. no.1). Clotting factors from the coagulation cascade act on damaged cells and platelets to progress towards the formation of insoluble fibrin fibers that further form a clot. The meshwork of the temporary matrix is sealed off by fibronectin and vitronectin to halt bleeding. Coagulation factors, complement system, and chemotactic stimuli released by growth factors act on keratinocytes, endothelial, and fibroblast cells that form a provisional matrix which is degraded by plasmin, and the interweaving fibers are removed from the site as a scab. [30]

Re-epithelialization & Granulation tissue formation

Platelet degranulation and macrophages activate cytokines (PDGF & TGF-β). ECM deposition is the task considered by Macrophages and platelets. In early stages macrophages and platelets function to form fibronectin and in later stages they function to form collagen and proteoglycans. The function performed by PDGF & TGF-β from macrophages and platelets activate fibroblasts for this process. PDGF influences proliferation, chemotaxis and collagenase expression by fibroblasts. Synthesis of matrix proteins and proteases are increased by TGF-β that down-regulate the process of matrix degradation and stimulates the secretion of tissue inhibitor of metalloproteinases (TIMP), for inhibition of matrix degradation. [36] Primarily PDGF, TGF-β along with IGF-I & FGF function to recruit fibroblasts to migrate to the matrix. Appointed

fibroblasts change their morphology and begin to synthesize reparative granulation tissue (collagen, elastin and proteoglycans) that helps in vascular growth [37] revealing the fibrogenesis process. This allows a balance to be maintained between ECM production and degradation. Any disturbance in the balance between the production and degradation phase leads to derangement [36] the wound healing process and thus forms scars. The process of epithelialization is stimulated by EGFs, TGFα & KGFs (Keratinocyte's growth factors).

Remodeling process

Conversion process for a granulation tissue into the scar. It occurs by proteolytic enzymes MMPs and serine proteases. Early remodeling occurs during the formation of fibronectin. The capillary endothelium of damaged tissues decreases in oxygen levels. [30] Macrophages, keratinocytes and endothelial cells release signals from TGF-β, VEGF and bFGFs that stimulate angiogenesis. Angiogenesis depends upon plasmin, MMPs and oxygen availability. MMP-2 & MMP-9 are seen to play an essential role in physiological angiogenesis. They activate TGF-β, an important growth factor that regulates matrix deposition. Neovascularization provides nutrition, signals, and cells for coordinated tissue repair. [30,36] After wound closure, MMP-2 & MMP-9 continue to play a significant role in the remodeling process by their ability to digest ECM. [24] Expression of MMPs is very less in undamaged tissues and elevated in active physiological conditions during different phases of wound healing. In early phases, MMP-9 degrades collagen, fibronectin, and elastin. It can cleave ECM.

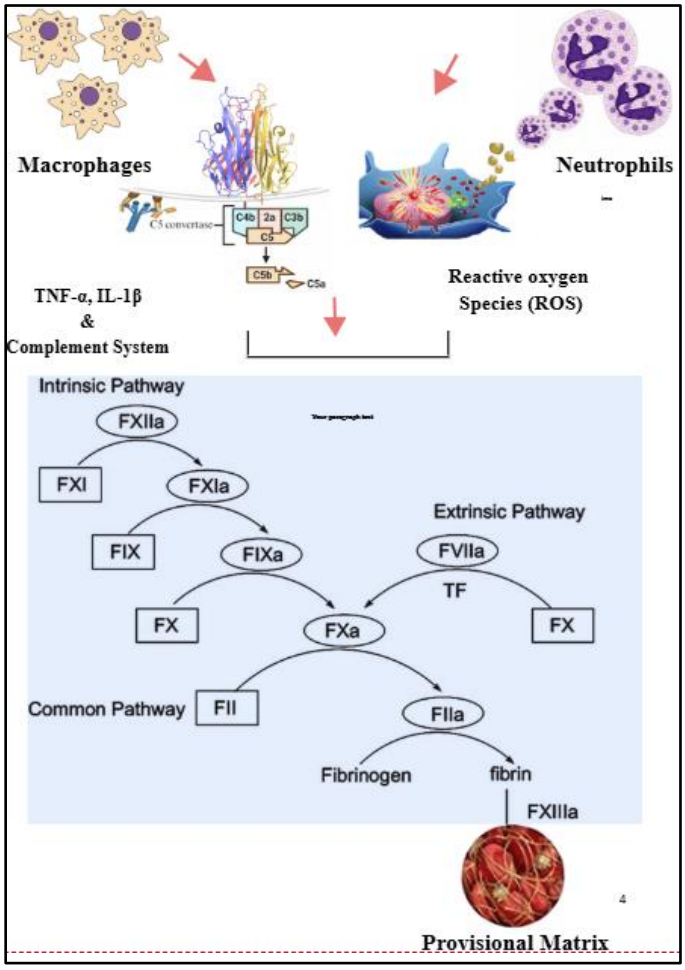

Figure 1. Graphical representation of wound healing

It plays an inhibitory role in wound healing. TIMP binds all MMPs and inhibits them by adhering to ECM proteoglycans. *Late remodeling* requires MMP-2 to degrade collagen. It involves a reduction in the number of fibroblasts by apoptosis. Fibroblasts change their phenotype to my fibroblasts that express α-smooth muscle actin, causing wound contraction that reduces the scar area. They are eliminated in later stages, thus reducing my fibroblasts. [30,36] Scar formation is prevented when collagen type III fibres are replaced by collagen type I fibres, bundles of which are arranged in

the dermis. Plasmin and Proteinases digest ECM (laminin & fibronectin), making the release of GF and cytokines from it. TGF-β activates factor V and IX, [38] 2005, regulating MMPs that downregulate ECM deposition. MMP-9 has a regulatory (inhibitory) role in wound healing and is known to digest fibrin. [30] Physiologically, plasmin and MMP help in wound healing. [39] All MMPs are activated by IL-1, IL-6, TNF-α, PDGF, TGF-β, bFGFs and deactivated by IL-4 and corticosteroids.

Progress of wound toward HTS & keloids

Role of Hemostasis

The molecular events between stimulators, inhibitors and co-factors regulate the formation of fibrin deposits. The physiologically regulated co-ordination between coagulation and fibrinolysis ensures the blood flow is maintained.

Role of PDGF, TGF-β & MMPs

During the proliferative phase, two of the most significant growth factors that control fibroblast activity are PDGF and TGF-β. In fact, keloid fibroblasts exhibit more growth-factor receptors than normal fibroblasts and react more quickly to growth factors like PDGF and TGF-β, due to which keloid fibroblasts remain up-regulated from the start of wound healing. TGF-β inhibits matrix degradation by secreting TIMP (Tissue inhibitors of metalloproteases) and downregulating the secretion of proteases responsible for matrix breakdown. TGF-β exists in three isoforms in mammals, named TGF-β1, TGF-β2, andTGF-β3. TGF-β1 & β2 stimulate collagen and proteoglycan synthesis of the ECM and prevent its degradation during early phases of wound healing[40]. TGF-β3 reduces connective tissue deposits in the later part of wound healing. The healing process enters the proliferative phase after 48 - 72 hours, which lasts for 3-6 weeks. Hypertrophic scars (HTS) and keloids show a persistent increased number of TGF-β in their fibroblasts [40,41] and overexpressed TGF-β1 &β2 and low β3 are found in fibroblasts of keloids, respectively. [42,43] Hypertrophic scars have low TGF-β2mRNA expression compared to keloid fibroblasts and normal skin, while keloid fibroblasts have low TGF-β3 mRNA compared to hypertrophic scars and normal skin. After about a week of injury, TGF-β isoforms expression and their receptors in fibroblasts are considered responsible as activity modulators in HTS and keloids. [24] An increased number of TGF-β receptors in fibroblastskeeps them in an upregulated tone from the beginning of the healing process in wounds that develop into HTS & keloids. High MMP-2 and low MMP-9 are found in HTS & keloids. MMP-2 & 9 are known to activate TGF-β. [30] MMP-2 activity is seen in prolonged tissue remodeling, and MMP-9 acts as an inhibitor in wound healing that degrades excess collagen, fibronectin, and elastin.

Hypertrophic scarring has an incidence rate of 91% after burns. HTS and keloids possess excess production of fibroblast proteins, fibronectin which suggests persistent wound healing signals. Pathologically, HTS & keloids are a failure of organized downregulation of healing signals. [44] Histologically, hypertrophic scars have type-III collagen fibres while keloids have type I & type III unaligned collagen fibres along with abundant myofibroblasts.

Role of SMAD (signal transduction pathway)

The signal transduction pathway is g group of intracellular regulatory proteins acting as a downstream regulator of TGF-β1 receptors in the cells that respond to them. SMAD 7 associates with TGF-β1 receptors and provides negative feedback for collagen synthesis. [24] SMAD3 are mediators that stimulate TGF-β in fibroblasts. Downregulating SMAD 3 gene expression inhibits ECM deposits by fibroblasts of keloids. SMAD 3 protein inhibition and SMAD 7 overexpression helps to contribute to the unusual response of TGF-β and prevent pathologic fibrosis that leads to scarformation. [45]

Latex as a hemostatic for wound healing

Promoted by inflammatory response of the body's hemostasis process involves endothelial cell damage, platelet aggregation, coagulation cascade, neutrophil infiltrations, productionof ROS, release of proteases and coagulation. [19] The defensive role of plant latex is attributed to hydrolytic enzymes, among which proteases play a major role. Aqueous extracts of dry latex and proteins recovered from fresh latex both contain this activity. [29]

Initially, in-vitro studies explored the Latex of the Asclepiadaceae family to possess proteolytic activity due to cysteine peptidases present in it. According to research by Shivaprasad and co-workers. [46] They were discovered to cleave Arg-16-gly and Arg-14-gly bonds in the A, B, and sub-parts of fibrinogen chains and release fibrinopeptide A & B, which causes fibrin to form. In vitro studies of latex of *Calotropis procera* using azocasein as a substrate revealed that the proteolytic activity of latex proteins was contributed by 4 cysteine peptidases. [17] Further, in-vitro studies by marico Ramos in 2012 were conducted to explore cysteine peptidases by fibrinogen agarose plate and spectrophotometric assays in sub-fractions P_{II} & P_{III} of thelatex of *calotropis procera*. *(Ait.) Calotropis procera's (Ait.)* Latex proteins (LPP_{II} & LPP_{III}) exhibited thrombin and plasmin-like properties, thus promoting the hemostasis process and clot hydrolysis and reducing the clotting time in a dose-dependent manner. However, prolonged exposure of cysteine peptidases to fibrinogen exhibits hydrolysis of fibrinogen chains in the order of Aα > Bβ > ϒ. The cysteine peptidases can induce a fibrin clot when exposed to fibrinogen. The same study's fibrinogen experiments demonstrated that the latex proteins LPP_{II} & LPP_{III} had a procoagulant impact similar to activated plasma thromboplastin time (APTT) assays presented reduced plasma coagulation time, while the PT assays provided no change, so they were believed to trigger coagulation factors IX, XI & XII by latex protein sections (LPP_{II} & LPP_{III}) that reduce clotting time via the intrinsic pathway. [5] In the absence of inflammation, latex presented a procoagulant effect without any change in platelet count. [21] The activity of LPP_{II} and LPP_{III} sections on plasma coagulation time was concurrently examined in a recent in vivo study conducted to explore the effect of latex proteins to down regulate inflammation in acute infections. [31] The LPP_{III} section of latex works in the acute inflammatory process and is believed to trigger factor VII through TF signaling, which aids in the development of procoagulant activity in latex. Similar results were

seen on treatment with LPP_{III} & LPP_{III} -IAA, ruling out the role of LPP_{III} in proteolysis.

Latex acts as an anti-inflammatory, antioxidant and bactericidal

Considering the Studies conducted two decades back. Insoluble and soluble proteins present in the latex of *Calotropis procera* were suggested to be a cause for the pro and Anti-inflammatory activity seen. The anti-inflammatory activity was considered in dried latex. [27] Methanolic extracts of dried latex were tested on various inflammatory mediators [47] and inflammatory models. [29] The pro-inflammatory activity was seen in dried latex, later acknowledged as dialysed latex (DL)[21,48] and the anti-inflammatory activity was due to non-dialysable latex NDL. [17, 21] Anti-nociceptive, [49] anti-histaminic [48] and anti-oxidative effect [17, 27, 50] have constantly been highlighted in literature concerned with latex of *Calotropis procera. (Ait.)* Latex is also known to have a protective potential to avoid sepsis. The study presented LP to downregulate IL-1β for anti-inflammatory actions. [51] Platelet degranulation activates macrophages. Mediators released from platelets accelerate the inflammatory response of the body. [52] LP-treated septic mice had longer clotting times and higher platelet counts. [51]

In vitro studies explored superoxide dismutase (SOD) [17] and ascorbate peroxidase (to a lesser extent) in latex helps to reduce the formation of reactive oxygen species (ROS) that cause tissue damage. In-vivo studies of *Calotropis procera* latex validate the protective anti-inflammatory effect of soluble high molecular weight latex to reduce edema and MPO levels. [27] Various sections of latex separated by ion exchange chromatography were examined for leucocyte infiltrations. [22, 51, 53] In vivo studies of LPP_{I} fraction initiate expression of iNOS, activating macrophages, which are bactericidal. The findings were supported by the previous similar findings of the latex protein section to inhibit neutrophil infiltrations through Nitrous oxide (NO) production. [54] Inhibition of the pro-inflammatory cytokines TNF-α, IL-1β, COX-2, and iNOS was found in a study on latex proteins. [38] Later, it was found that the inhibitory activity on cytokines was due to sub-fractions LPP_{II}-IAA sub-section of the latex. [55] LPP_{III} also downregulates IL-1β and serves as an anti-inflammatory action. This section of latex causes the release of IL-10, an immunoregulatory cytokine from healthy and infected cells. [31,51] Recent researches validate that Latex administration increases mRNA expression of TNFα and IL-1. IL-6 and iNOS participate in microbial clearance. [56]

Action of *Calotropis procera* latex towards the prevention of HTS & Keloids

TGF-β produces matrix proteins that are released by platelet degranulation and aid in wound healing in the early stages of injury [36] and serves as a chemoattractant for fibroblasts, monocytes, lymphocytes and neutrophils. TGF-β, along with IGF-I, recruits fibroblasts that migrate to the ECM further and synthesize granulation tissue. The LNP section is rich in secondary metabolites as gallic acid, quercetin and Kaempferol are present. [12] Quercetin reduces the expression of TGF-β receptors in keloid fibroblast cells and strongly prevents the formation of the Smad2-

Smad3-Smad4 complex and its nuclear translocation. Blocking the IGF-1 and TGF-β signaling pathways by quercetin may be helpful to reduce the appearance of scars.

3. DISCUSSION:-

Calotropis procera. latex has long been recognized in traditional medicine for its wound-healing potential; however, its therapeutic translation requires careful consideration of toxicity, route of administration, and fraction-specific biological activity. Earlier toxicological reports, particularly involving intraperitoneal and intravenous administration in animal models, raised safety concerns, including mortality in goats. Recent fractionation-based studies provide clarity by demonstrating that toxicity is not uniform across latex components. Specifically, the LPPI fraction appears non-toxic, while LPPII shows route-dependent toxicity primarily due to its proteolytic activity when administered intraperitoneally, with oral administration proving comparatively safer because of digestive proteolysis of latex proteins. Chemical inhibition of proteolysis (IAA treatment) further supports the safety of latex proteins for parenteral use, highlighting the importance of processing and delivery strategies.

The coordinated hemostatic and inflammatory actions of Calotropis latex are central to its wound-healing efficacy. Latex cysteine peptidases exhibit thrombin- and plasmin-like activities, facilitating fibrin formation and ECM remodeling, thereby supporting early hemostasis and controlled inflammation. The inflammatory response induced by latex is tightly regulated through macrophage and neutrophil modulation, cytokine balance, nitric oxide signaling, and antioxidant mechanisms that limit oxidative tissue damage. Importantly, the anti-inflammatory effects arise from synergistic actions of LPPI, LPPII, and LPPIII fractions, rather than bactericidal activity.

Pathological scarring, including hypertrophic scars and keloids, is driven by prolonged inflammation, delayed epithelialization, and persistent TGF-β signaling in fibroblasts. The presence of gallic acid, quercetin, and kaempferol in Calotropis latex provides a plausible mechanistic basis for anti-scar activity. These secondary metabolites downregulate pro-fibrotic cytokines, inhibit fibroblast proliferation and collagen synthesis, promote angiogenesis, and reduce oxidative stress. Although extensive evidence supports the hemostatic and anti-inflammatory roles of latex, the specific contribution of these metabolites to scar prevention remains underexplored. Targeted experimental and clinical investigations are therefore essential to validate their role in anti-scar and anti-keloidal therapy, particularly in burn wound management.

4. CONCLUSION

Calotropis procera. latex, traditionally used for wound management, shows significant hemostatic, anti-inflammatory and tissue-repair potential. Toxicity concerns reported in earlier studies were largely associated with intraperitoneal or intravenous administration. Recent findings indicate that the LPPI fraction is non-toxic, while LPPII produces proteolytic tissue effects only through intraperitoneal routes and remains safe orally due to natural digestive proteolysis. Rubber-based insoluble components appear responsible

for inflammatory or allergic reactions, which can be minimized through basic purification methods.

Latex proteins exhibit thrombin-like and plasmin-like activities, supporting fibrin formation and controlled fibrinolysis, aligning with modern insights into leukocyte-mediated coagulation. Anti-inflammatory effects arise from coordinated actions of latex fractions: LPPI initiates early inflammation through NO release, LPPII suppresses major pro-inflammatory mediators, and LPPIII enhances IL-10 production, preventing excessive tissue injury. Antioxidant enzymes further reduce ROS-associated damage.

Importantly, secondary metabolites—gallic acid, quercetin, and kaempferol—present in the latex demonstrate strong anti-scar and anti-keloidal activity by regulating fibroblast behavior, limiting collagen overproduction, modulating TGF-β pathways, and promoting healthy angiogenesis. Although the wound-healing potential of C. procera latex is well documented, the anti-scar properties of these phytoconstituents remain underexplored.

Overall, *Calotropis procera* and its bioactive compounds offer promising integrative therapeutic value for burn wound healing and scar modulation, warranting further experimental validation.

Abbreviations:

API- Ayurvedic Pharmacopoeia of India

APTT- Activated partial thromboplastin time

COX- Cycloxygenase

2D- Two Dimensional

DL- Dialysable latex

EGFs- Endothelial growth factors.

EGF- Epithelial growth Factor

ECM- Extracellular matrix.

FGF- Fibroblast Growth Factor

GIT- Gastro-Intestinal Tract

HPLC Hypertrophic - High Performance Liquid Chromatography

GF- Growth Factor

HGF- Hepatocyte growth factor.

HTS- scars

IGF-1- Insulin like Growth Factor

IgE- Immunoglobulins-E

IL-1- Interleukin-1

IL-6- Interleukin-6

IL-10- Interleukin-10

IL-1β- Interleukin-1 Beta

iNOS- Nitric Oxide Synthase

KGFs - Keratinocyte's growth factors.

LP- Latex proteins

$LP-_{PI}$ – Latex proteins- part-1

$LP-_{PII}$ – Latex proteins – part-2

$LP-_{PIII}$ – Latex proteins- part-3

LNP- Latex non-proteins

MeDL- Methanolic extracts of dry latex

MMP- Matrix metalloproteinases

MPO- Metalloperoxidases.

MS- Mass Spectrometry

NDL- Non-dialysable latex

PDGF- Platelet derived growth factors.

PMNs- Polymorphonuclear Leukocytes

ROS- Reactive oxygen species

RL- Rubber latex

SOD- Superoxide dismutase.

SMAD- Signal Transduction Pathway

PAGE- Polyacrylamide Gel Electrophoresis.

TIMP- Tissue inhibitors of Metalloproteases

TNF-α- Tumor Necrosis Factor-alpha

TNF-β- Tumor Necrosis Factor- Beta

UV- Ultra-Violet

VWF- VON-Willebrand Factor

VEGFs- Vascular endothelial growth factors.

PAF- Platelet Activating Factors.

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