PROSPECTIVE USE OF REUNDEU LEAVES (*Staurogyne elongata)* ON INFLAMMATORY MACROPHAGES IN SKIN EXCISION WOUND

(PENGGUNAAN PROSPEKTIF DAUN REUNDEU (Staurogyne elongata) PADA MAKROFAG INFLAMASI PADA LUKA EKSISI KULIT)

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Florence Meliawaty [1]*, Mistli Nur Robbani [1], Hartanto Endrowahyudi[2,] Euis Reni Yuslianti [3]
[1]Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Universitas Jenderal Achmad Yani
[2] Department of Conservative Dentistry, Faculty of Dentistry, Universitas Jenderal Achmad Yani
[3] Department of Oral Biology and Biomedical, Faculty of Dentistry, Universitas Jenderal Achmad Yani
*Corresponding author
florence.meliawaty@lecturer.unjani.ac.id

ABSTRACT

Healing of skin excision wounds involves complex stages, with inflammatory macrophages playing a key role in regulating the inflammatory response and tissue regeneration. *Staurogyne elongata* (Reundeu leaves), a medicinal plant native to Indonesia, contains bioactive compounds such as flavonoids, saponins, steroids, triterpenoids, and polyphenols, which exhibit antioxidant and antibacterial properties. This literature review aimed to explore the prospective role of S. elongata in modulating inflammatory macrophage activity during skin excision wound healing. Articles published within the last 10 years were retrieved from ProQuest, PubMed, ScienceDirect, and Science Publishing Group databases. The scientific implication is that *Staurogyne elongata* (Reundeu leaves) has potential therapeutic effects on skin excision wound healing by modulating inflammatory macrophage activity. Specifically, its bioactive compounds may promote the transition of macrophages from a pro-inflammatory (M1) to an anti-inflammatory (M2) state, leading to reduced inflammation and enhanced tissue regeneration. The results suggest that S. elongata could be developed as a natural, cost-effective adjunct treatment to improve wound healing outcomes, highlighting the need for further experimental validation, clinical studies, and pharmaceutical formulation development.

Keywords: excision; macrophages; reundeu; skin; *Staurogyne elongata*; wound healing

ABSTRAK

Penyembuhan luka eksisi kulit melibatkan beberapa tahap kompleks, di mana sel inflamasi makrofag memainkan peran penting dalam mengatur respons inflamasi dan regenerasi jaringan. Daun reundeu (Staurogyne elongata), tanaman obat asli Indonesia, mengandung senyawa bioaktif seperti flavonoid, saponin, steroid, triterpenoid, dan polifenol, yang diketahui memiliki aktivitas antioksidan dan antibakteri. Senyawa-senyawa ini berpotensi memodulasi aktivitas makrofag dengan mengurangi produksi sitokin pro-inflamasi (misalnya, TNF-α) dan meningkatkan sitokin anti-inflamasi (misalnya, IL-10), sehingga membantu transisi makrofag dari fenotipe pro-inflamasi (M1) menjadi fenotipe anti-inflamasi (M2). Transisi ini mempercepat proses inflamasi dan peningkatan regenerasi jaringan. Tinjauan pustaka ini bertujuan untuk menentukan prospek penggunaan daun reundeu (Staurogyne elongata) pada sel inflamasi makrofag pada penyembuhan luka eksisi kulit. Artikel yang digunakan bersumber dari basis data Proquest, Pubmed, Sciencedirect, dan Science Publishing Group yang mencakup publikasi kurang dari 10 tahun. Implikasi ilmiahnya bahwa Staurogyne elongata (daun reundeu) memiliki potensi efek terapeutik pada penyembuhan luka eksisi kulit dengan memodulasi aktivitas inflamasi. Secara spesifik, senyawa bioaktifnya dapat mendorong transisi makrofag dari keadaan pro-inflamsi (M1) menjadi anti-inflamasi (M2), menghasilkan pengurangan peradangan dan peningkatan regenerasi jaringan. Hal ini menunjukkan bahwa Staurogyne elongata dapat dikembangkan sebagai pengobatan alami dan hemat biaya untuk meningkatkan hasil penyembuhan luka, memerlukan validasi eksperimental lebih lanjut, studi klinis, dan pengembanngan formulasi farmasi.

Kata kunci: *eksisi; kulit; makrofag; reundeu; staurogyne elongata; penyembuhan luka*

INTRODUCTION

The prevalence of wounds worldwide is increasing every year. The Singapore Wound

Association conducted a study on the incidence of wounds, obtaining data on wounds of 300 per 100,000 people in the general population, 15 per 100,000 people for venous wounds, 56 for arterial wounds, 168 for diabetic wounds, and 183 for pressure wounds.[1] A study conducted in West Africa by Toppino et al in 2022 found that the prevalence of skin injuries reached 13% of the population, with the majority caused by mechanical injuries, particularly among children.[2] According to the Indonesian Ministry of Health in 2018, the prevalence of wound patients in Indonesia was 8.2%, including abrasions or bruises caused by skin friction with rough surfaces (70.9%), cuts caused by sharp objects (25.4%), and lacerations caused by blunt force trauma (23.2%).[3]

One type of wound that is often encountered is an excision wound.[4] An excision wound is a wound caused by the cutting of tissue by a sharp object.[5] Wound healing is a complex process involving coordinated interactions between various immunological and biological systems. The wound healing mechanism also involves inflammatory and vasoactive mediators.[6] The stages of wound healing consist of hemostasis, inflammation, proliferation, and maturation. The hemostasis phase is the initial stage of healing, where the body attempts to stop bleeding by forming a blood clot. The inflammatory phase then occurs to clean the wound area of debris and pathogens. Inflammatory cells include neutrophils, eosinophils, macrophages, basophils, mast cells, and lymphocytes.[7] Macrophages play a crucial role in the inflammatory phase as immune cells responsible for phagocytosing dead cells and microorganisms causing infection. Macrophages also release inflammatory mediators that help initiate the tissue regeneration process. Certain drugs or compounds can increase or decrease macrophage activity [8]

Indonesia is recognized as one of the countries with the second-highest biodiversity in the world, boasting numerous native medicinal plants. The tradition of using traditional medicine has been around for centuries. It is an integral part of local culture, with the prevalence of traditional medicine use generally ranging from 20% to 28% worldwide.[9] In various countries, including Indonesia, medicinal plants are the primary source of raw materials for traditional medicine due to their bioactive content that is beneficial to health. Indonesia is home to approximately 30,000 plant species, with 7,000 of these possessing medicinal properties.[10]

One plant that has attracted attention is reundeu leaves. *Staurogyne elongata* is the scientific name for the plant known as reundeu in Sundanese, which contains antioxidants.[11,12] Reundeu leaves are often used as a side dish for daily consumption, and are also used as an antiseptic ingredient due to their antibacterial properties. According to research conducted by Maulani et al. in 2017 in Sumedang, the phytochemical screening of reundeu leaves (*Staurogyne elongata*) revealed the presence of flavonoids, saponins, polyphenols, steroids, and triterpenoids, as well as antibacterial properties.[13] This antibacterial property is crucial in the wound healing process as it inhibits the growth of

microorganisms causing infection while supporting tissue regeneration.

The use of reundeu leaves (*Staurogyne elongata*) as a wound healing agent for excision wounds is one of the alternatives in both modern and traditional medicine in Indonesia. The antibacterial properties of reundeu leaves (*Staurogyne elongata*) have the potential to enhance wound healing efficacy while reducing the risk of complications such as infection. Research on the potential use of reundeu leaves (*Staurogyne elongata*) in inflammatory macrophage cell excision wound healing is still limited; therefore, the author is interested in investigating the potential use of reundeu leaves (*Staurogyne elongata*) on inflammatory macrophage cells in skin excision wound healing. The objective of this study is to determine the potential use of reundeu leaves (*Staurogyne elongata*) on inflammatory macrophage cells in skin excision wound healing.

METHOD

The research design employed was a literature review, utilizing national and international sources. A literature review study is an activity that involves searching for books, scientific articles, and other sources related to a particular issue, field of research, or theory to produce a description, summary, or evaluation of those sources that are relevant to the research issue being studied.[14] The search was conducted through the Proquest, PubMed, Sciencedirect, and Science Publishing Group databases using the keywords "Daun Reunde OR *Staurogyne elongata*" AND "Inflammatory Cells OR Inflammation OR Macrophages" AND "Wound Healing OR Skin Excision Wounds" AND "Anti-inflammatory OR Anti-inflammatory Activity." This search was limited by inclusion criteria such as articles: journals <10 years old, RCT, and quasi-experimental. Meanwhile, the exclusion criteria were articles that did not involve the analysis of anti-inflammatory activity, macrophages, or wound healing processes.

RESULT

This literature review identifies and analyzes relevant studies on the use of reundeu leaves in the healing of excised wounds, particularly in relation to inflammatory macrophages. The findings from the selected articles are summarized in Table 1.

Table 1. Results of the literature review

No	Article Title	Author (Year)	Method	Research Results
1	Rational selection of bioactive principles for wound healing applications:	Viaña-Mendieta P, Sánchez ML, Benavides J (2022)[15]	This review explores the roles of growth factors (EGF, bFGF, VEGF, TGF-β1) and antioxidants (astaxanthin, beta-carotene, EGCG, delphinidin, curcumin) in wound healing, highlighting the potential benefits of combining these agents to enhance repair outcomes.	Growth factors regulate cell proliferation, migration, angiogenesis, and inflammation during wound healing, while antioxidants support these processes. Combining them may produce additive or synergistic effects, thereby accelerating healing and improving tissue quality.
2	Functional Hallmarks of Healthy Macrophage Responses	Sheu KM, Hoffmann A (2022)[16]	The review explores how macrophages generate tailored immune responses, adapt to their environment, and retain memory of past stimuli, focusing on the molecular mechanisms involved and their effects on immune-related diseases.	This review highlights the macrophage-specific immune responses, contextual adaptation, and memory, examining how disruptions in these processes contribute to disease, and emphasizes key molecular pathways and their diagnostic implications.
3	Macrophages in health and disease.	Park MD, Silvin A, Ginhoux F, Merad M. (2022)[17]	This review analyses macrophage heterogeneity by examining tissue-resident macrophages' origins and roles in health and disease, emphasizing how local tissue environments shape their differentiation and function, and how their imbalance drives inflammation, autoimmunity, fibrosis, and cancer.	Macrophages exhibit diverse phenotypes shaped by tissue context, functioning along homeostatic or inflammatory pathways. Altered signaling timing can shift the balance toward chronic inflammation, with M1/M2 imbalances linked to diseases such as SLE, systemic sclerosis, type 1 diabetes, and fibrosis. Their immunological memory further influences disease progression.
4	Macrophages: shapes and functions	Lendeckel U, Venz S, Wolke C (2022)[18]	This review highlights macrophages as key innate immune cells, focusing on their activation, polarization, and diverse roles in inflammation, tissue repair, and cancer.	Macrophage activation determines function: M1 are pro-inflammatory and glycolytic, while M2 are anti-inflammatory, support repair, and exhibit oxidative properties. In tumors, macrophages commonly adopt M2-like roles that promote cancer, influenced by their location.
5	Discoid Domain Receptors	Ma Y, Gong H, Cheng L,	This review explores how DDR1 and DDR2 regulate macrophage function	DDR1 and DDR2 modulate macrophage inflammation by inducing cytokines and

	Signaling in Macrophages-Mediated Diseases	Zhang D (2025)[19]	through collagen interactions, activating signaling pathways that influence adhesion, migration, cytokine release, and polarization in inflammation, fibrosis, and cancer.	regulating movement through collagen signaling, contributing to immune defense and diseases such as cancer and fibrosis, primarily via the p38 MAPK pathway.
6	Macrophage Polarization and Its Role in Liver Disease	Wang C, Ma C, Gong L, Guo Y, Fu K, Zhang Y, et al (2021)[20]	This review summarizes liver macrophage origins, M1/M2 polarization, and key molecular pathways – such as TLR4/NF-κB, JAK/STAT, TGF-β/Smads, PPARγ, Notch, and microRNAs- that regulate these states in the liver environment.	Liver macrophages, including Kupffer and monocyte-derived cells, polarize into pro-inflammatory M1 or repair-focused M2 types, influencing liver diseases such as injury, hepatitis, MAFLD, fibrosis, and cancer, and representing crucial therapeutic targets.
7	The Phagocytic Function of Macrophage Enforcing Innate Immunity and Tissue Homeostasis	Hirayama D, Iida T, Nakase H (2017)[21]	This review highlights macrophage phagocytosis in immunity and tissue maintenance, focusing on pathogens and debris clearance, macrophage origins, and their dual roles in defense and repair.	Macrophages are essential immune cells that clear pathogens and dead cells, while promoting tissue repair, balancing inflammation, and facilitating healing to support immune defense and tissue health.
8	Antigen Cross-Presentation by Macrophages	Muntjewerff EM, Meesters LD, van den Bogaart G (2020)[22]	This review summarizes how macrophage antigen cross-presentation activates CD8+ T cells, detailing animal studies, key macrophage markers (CD169, F4/80), CD8+ activation measures, and strategies to enhance responses through receptor targeting and nanogel-based antigen delivery.	Macrophages from spleen, lymph nodes, and tumors, especially CD169+ subsets, cross-present antigens to activate CD8+ T cells. Cross-presentation relies on endosomal pathways and enzymes, such as ACE, with ongoing research investigating their roles in T cell activation, tolerance, and implications for cancer and antiviral therapies.
9	Macrophage plasticity, polarization, and function in health and disease	Shapouri-Moghaddam A, Mohammadian S, Vazini H, Taghadosi M, Esmaeili SA, Mardani F, et al (2018)[23]	This review overviews macrophage biology, emphasizing molecular mechanisms behind M1 pro-inflammatory and M2 anti-inflammatory polarization, their impact on inflammation, healing, fibrosis, tissue damage, and	Macrophages exhibit high plasticity, shifting between pro-inflammatory M1 and various anti-inflammatory M2 subtypes. This balance is vital for healing, with disruption linked to chronic diseases like fibrosis and cancer. Polarization is regulated by signaling pathways (TLR, STAT,

			clinical implications for disease treatment.	NF-κB) and environmental and epigenetic factors.
10	ROS/TNF-α Crosstalk Triggers the Expression of IL-8 and MCP-1 in Human Monocytic THP-1 Cells via the NF-κB and ERK1/2 Mediated Signaling	Akhter N, Wilson A, Thomas R, Al-Rashed F, Kochumon S, Al-Roub A, et al (2021)[24]	This in vitro study stimulated human THP-1 monocytes with TNF-α, H_2O_2, or hypoxia to induce oxidative stress, measuring IL-8, MCP-1 expression, ROS, and NF-κB/ERK1/2 activation. The antioxidant NAC was used to assess the involvement of oxidative stress, while ER stress markers, including CHOP, ERN1, and HIF1A, were also analyzed.	IL-8 and MCP-1 expression in THP-1 cells increased significantly in response to combined TNF-α and H_2O_2 or hypoxia, associated with increased ROS production. It activated NF-κB and ERK1/2 pathways and triggered ER stress. NAC pre-treatment reduced chemokine levels, indicating a ROS-dependent mechanism, suggesting that the ROS–TNF-α interaction promotes inflammation via these pathways and ER stress.
11	Penyembuhan Luka Sayat Pada Kulit Tikus Putih (Rattus norvegicus) yang Diberi Ekstrak Daun Kirinyuh	Amfotis ML, Made N, Suarni R, Arpiwi NL (2022)[25]	This study tested Kirinyuh leaf extract (10%, 20%, 30%) on rat incision wounds across five groups, including controls. Macroscopic healing was assessed on days 3, 6, and 9, while microscopic healing was assessed on day 10. Wound contraction was statistically analyzed, and other observations were documented.	Kirinyuh leaf extract significantly enhanced incision wound healing in mice, with a 30% concentration yielding the best improvements in epidermal thickness, fibroblast proliferation, and collagen synthesis, comparable to 10% povidone iodine. The study identifies 30% as the optimal dose for effective healing.
12	Formulasi Krim Ekstrak Etanol Daun Reundeu (*Staurogyne elongata* (Blume) O.Kuntze) dengan Variasi Konsentrasi Parafin Cair dan Setil Alkohol	Wardani D, Nurul N, Sujana D, Nugraha YR, Nurseha R (2021)[26]	The cream was prepared by melting varying ratios of liquid paraffin and cetyl alcohol (F1: 5%/2%, F2: 10%/4%, F3: 15%/8%) with Reundeu leaf ethanol extract. Stability was tested at room temperature and 40°C for 4 weeks. Physical properties assessed included emulsion type, color, odor, texture, spreadability, homogeneity, viscosity, pH, and adhesion.	All formulas were oil-in-water emulsions. Formula F1 (5% paraffin, 2% cetyl alcohol) showed the best stability, texture, spreadability, and skin-safe pH. Higher paraffin and cetyl alcohol levels in F2 and F3 increased viscosity but reduced spreadability. All formulas remained stable for 4 weeks.
13	Efektivitas Ekstrak Daun Sirih Tanah (Piper sarmentosum	Laili TD, Bhakti PC, Yani S, Irawiraman H,	This post-test only study used Wistar rats divided into control and treatment groups receiving 20%, 30%, or 40% betel leaf extract (EDST).	EDST treatments at 20%, 30%, and 40% resulted in significantly lower macrophage counts compared to controls, with the 40% treatment showing the most

	Roxb.ex Hunter) terhadap Jumlah Makrofag Pasca Pencabutan Gigi Tikus Wistar.	Paramitha S (2021)[27]	Rats were sacrificed on days 3, 5, and 7 post-extraction for histological macrophage counts. The extract was prepared by macerating dried leaves in ethanol. Data were analyzed using ANOVA and related tests.	significant reduction. By day 7, macrophage counts had decreased to 5 in the 40% group, compared to 55 in the controls, likely due to the presence of anti-inflammatory compounds such as essential oils, tannins, saponins, and flavonoids.
14	Antibacterial Bioactivity from Extract of Reundeu Caret (Staurogyne longata) and Honje (Etlingera hemisphaerica)	Sinaga E (2021)[28]	This study assessed the antibacterial activity of Reundeu caret and Honje extracts via disc diffusion against four bacterial strains. At various concentrations, the extracts demonstrated effectiveness based on inhibition zone diameters, supporting their traditional use by the Baduy tribe.	Reundeu caret and Honje extracts exhibited moderate to strong antibacterial activity against *Staphylococcus aureus* and *Bacillus cereus*, increasing with concentration; however, they were ineffective against *Escherichia coli* and *Salmonella typhi*. No significant difference was found between the two extracts.
15	CD68 Expression on Macrophages as Anti-Inflammatory Effect of Tamarillo (Solanum betaceum Cav.) Fruit Peel Ethanol Extract (Study on Carrageenan-Induced Buccal Mucosa of Rats)	Bindaputri JF, Sudiono J (2024)[29]	This study used a carrageenan-induced mouse model to evaluate the anti-inflammatory effects of Tamarillo peel ethanol extract by analysing macrophage activity through CD68 expression via immunohistochemistry. Significant differences between treatment and control groups were confirmed by statistical analysis.	Tamarillo peel ethanol extract demonstrated significant anti-inflammatory effects by increasing CD68 expression in macrophages, promoting inflammation resolution and tissue repair. This effect is likely due to flavonoids and other bioactive compounds, highlighting its potential as a natural alternative to conventional anti-inflammatory agents.

DISCUSSION

Wound healing is a complex and coordinated biological process involving various types of cells and growth factors. One component of this process is the macrophage, which plays a role in the inflammatory phase. Macrophages have a dual role, namely as pro-inflammatory cells that trigger the immune response and as anti-inflammatory cells that support tissue regeneration [20]

In the healing of skin excision wounds, regulating macrophage activity is crucial for achieving optimal healing results. Reundeu leaves have long been used in traditional medicine in various cultures, including those in Southeast Asia, as a wound-healing agent. Bioactive compounds contained in reundeu leaves, such as flavonoids, saponins, triterpenoids, steroids, and polyphenols, are known to have antibacterial and antioxidant properties.[13]

The flavonoid compounds in the extract act as anti-inflammatories that inhibit the phospholipase enzyme, preventing phospholipids in the cell membrane from being converted into arachidonic acid.[25] This inhibits the cyclooxygenase and lipoxygenase pathways, disrupting the synthesis of prostaglandins and leukotrienes.[25] The disruption of prostaglandins and leukotrienes as inflammatory mediators reduces vasodilation of blood vessels, thereby decreasing the number of inflammatory cells and reducing redness during the inflammatory phase.[25] Flavonoid compounds can combat microorganisms [25] Flavonoids form complex compounds with extracellular proteins, thereby damaging bacterial cell membranes.[30]

Flavonoids also have a mechanism for the formation of granulation tissue, which occurs by preventing the formation of Reactive Oxygen Species (ROS). Oxidative stress due to wounds causes an imbalance between Reactive Oxygen Species (ROS) and endogenous antioxidants. Flavonoids have biological activity as antioxidants that can reduce free radicals by donating a hydrogen atom (H +) to free radicals so that they can repair damaged tissue.[30] The mechanism of flavonoids as immunomodulators by increasing the activity of IL-2 (interleukin 2) and lymphocyte proliferation. Activated Th1 (T helper 1) cells will affect SMAF (Specific Macrophage Arming Factor), namely molecules including IFNγ (interferon gamma) that can activate macrophages. If an antigen, such as bacteria, enters the body, T lymphocytes and macrophages work together to kill the bacteria. Macrophages will phagocytose bacteria, and T lymphocytes will differentiate into CD4+ and CD8+ cells. CD4+ cells differentiate into Th1 cells, which then produce the cytokines IFNγ and TNFα and stimulate Natural Killer cells. CD8+ cells also produce the cytokine IFNγ. This cytokine activates macrophages to produce compounds, including nitric oxide (NO), which is helpful for killing bacteria.[31]

Flavonoids and triterpenoids have been shown to possess antibacterial activity. The antibacterial mechanism of flavonoids typically involves disrupting bacterial cells. Flavonoids can

interact with lipid membranes, leading to increased permeability and cell leakage, which can ultimately result in bacterial death. Triterpenoids disrupt membrane integration, inhibit nutrient transport, and cause leakage of cellular components.[32]

Terpenoid and saponin compounds can enhance the body's immune response. Terpenoids can increase the production of IL-2, antibodies, and T cells, while inhibiting nitric oxide (NO) production in endotoxins, which stimulates macrophages. IL-2 can enhance the cytolytic activity of T cells and natural killer (NK) cells, and increase IFN-γ secretion, thereby indirectly activating macrophages. Saponins exhibit antiseptic activity and can also modulate the nonspecific immune system by enhancing phagocytic activity and promoting monocyte proliferation. Saponins have been reported to induce the production of cytokines such as interleukins and interferons, which are thought to have immunostimulatory effects on the body.[33]

In the early phase of wound healing, M1 macrophages dominate and produce pro-inflammatory mediators to clear the wound area of pathogens. However, a transition to anti-inflammatory M2 macrophages is necessary to trigger fibroblast proliferation, angiogenesis, and the formation of new tissue. The active compounds in reundeu leaves have the potential to facilitate the transition from M1 to M2, thereby accelerating tissue regeneration.

Based on its phytochemical content, potential anti-inflammatory mechanisms, and economic benefits, reundeu leaves have great potential as a supporting agent in wound healing therapy following skin excision. Integrating experimental research, clinical trials, and appropriate topical formulations will be key to optimizing the use of this plant in healthcare.

CONCLUSION

Reundeu leaves show potential as a wound healing agent, but further animal and clinical studies are needed to confirm their mechanisms, particularly through histopathological evaluation of macrophage modulation.

CONFLICT OF INTEREST

The authors reported no potential conflict of interest.

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