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Beyond Traditional Boundaries: A Review on *Calotropis gigantea*'s Efficacy in Wound Healing

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ABSTRACT

Introduction: Wounds result from the disruption of cellular and anatomical continuity in living tissues due to external factors. *Calotropis gigantea*, also known as crown flower or giant milkweed (or "biduri" in Indonesia), is a small tree or shrub with white or purple flowers, widely used in traditional remedies. Its properties, including antimicrobial, cytotoxic, and wound-healing activities, have prompted this literature review to assess its efficacy in wound healing.

Method: A thorough analysis of scientific findings and research conducted in the last 10 years, specifically after January 1, 2014, was undertaken. Data were collected from reputable databases, such as PubMed, Web of Science, and ScienceDirect. After applying publication limitations, three manuscripts were selected as the final outcomes of the review process.

Result: The analysis of multiple studies reveals that *C. gigantea* possesses wound healing properties attributed to phytochemical constituents like flavonoids, tannins, alkaloids, and saponin. These constituents play vital roles in each stage of wound healing, including the inflammatory reaction, proliferation, and remodeling stages. Additionally, *C. gigantea* promotes wound healing, leaving minimal scar residues.

Conclusion: *Calotropis gigantea* has demonstrated its ability to enhance wound healing through various mechanisms, including astringency, antibacterial activity, promotion of homeostasis, facilitation of collagen synthesis, enhancement of re-epithelialization, and stimulation of cell proliferation via its phytochemical constituents. However, due to the scarcity of recent studies, the plant's true efficacy in wound healing remains unclear.

KEYWORDS: *Calotropis gigantea*, biduri, wound healing

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INTRODUCTION

Wounds are defined as a loss or breaking of cellular and anatomic or functional continuity of living tissues caused by external influences such as friction, impact, heat, cold, radiation exposure, and microbes. Healing of a wound is a biological process that is initiated by trauma and often terminated by scar formation. The process of wound healing occurs in different phases such as coagulation, epithelization, granulation, collagenation, and tissue remodeling. Though the wound repair program is remarkably efficient, there are instances such as aging, disease, and magnitude of tissue damage that require intervention to facilitate and/or accelerate the healing process. Natural wound healing remedies commonly used by the public are derived from various herbal plants. The use of herbal plants for medicinal purposes has been practiced since ancient times when synthetic drugs were limited. Besides reducing the side effects associated with synthetic drugs, herbal plants are also safe and affordable, with less to no side effects. [1,2]

Calotropis gigantea, commonly known as crown flower or giant milk weed, or "biduri" in Indonesia, is a minor tree or shurb belongs to family Asclepiadaceae, it is 4-10 cm tall. Its stem is straight, and its waxy flowers are white or purple in colour. The leaves are oval, light green and oppositely oriented. Its stem is smooth and the flower has 5 pointed petals, oval flower buds appear, and it has many branches and the young branches are covered with white, cottony hairs containing milky latex.[3,4] It is a native plant of

India, Malaysia, and China, and distributed in almost all over the world.[4]

Rich in phytochemical, *Calotropis gigantea* is often used for the natural remedy for many diseases. This plant contain glycosides, alkaloids, flavones, tannins and also calotoxin, uschrain, uscharidin and proceroside, as well as cardenolides, flavonoids, terpenes and pregnanes, offering numerous health properties across its every parts. Studies has shown that the leaves and aerial parts of the plant are giving antidiarrheal activity, anti-oxidant activity, anti-microbial activity, cytotoxic activity and wound healing activity, also stem shows hepatotoxic effects. The latex of these plants is also able to be utilized in different conditions as tumors, analgesic, expectorant, piles and asthma.[3,5,6]

With over 80% of the world's population in over 170 of WHO's 194 Member states using traditional medicine currently, utilizing our natural resources has become greatly important.[7] As a country that has abundant natural wealth, it is our privilege to explore and maximize the potential of resources, such as *Calotropis gigantea*. However, despite its promising potential, there is still limited literature available on the efficacy of *Calotropis gigantea*, focusing on wound healing. Therefore, this literature review is conducted to review *Calotropis gigantea's* efficacy in wound healing, providing useful insights regarding the utilization of herbal medicine.

METHODS

In this Literature Review, we employed an analytical review method, gathering comparative data from databases such as PubMed, Web of Science, and ScienceDirect, with a publication date limitation of the past 10 years, starting from January 1, 2014. The search terms used included: *Calotropis gigantea*, biduri, and wound healing. We meticulously reviewed all retrieved abstracts, studies, and citations. Additionally, we searched the reference sections of selected journals for relevant studies. Initially, we identified 15 findings, which were then narrowed down to 9 publications after applying our limitations. Further screenings led to the selection of a subset of 3 manuscripts. Each reviewed paper was independently assessed by the authors, all of which contained information regarding the efficacy of *Calotropis gigantea* in wound healing.

RESULTS AND DISCUSSION

Calotropis gigantea's Wound Healing Properties

The leaves and aerial parts of *C. gigantea* exhibit various properties that contribute to enhancing wound healing. These parts contain abundant calotropin, alkaloids, flavonoids, tannins, and saponins, each of which plays a distinct role in enhancing wound healing. According to Alafnan et al in 2021, several essential phytochemicals in *C. gigantea*, particularly flavonoids, have been reported for their wound healing activity. Secondary metabolite analysis has revealed the presence of flavonoids, such as tamarixin, which may contribute to the wound healing properties. In our study, flavonoids and terpenoids have been identified to possess astringent and antimicrobial properties, thereby promoting wound healing and epithelization. It is well-established that flavonoids also inhibit lipid peroxidation, not only by preventing or reducing cell necrosis but also by enhancing vascularity and improving the viability of collagen fibrils.[8] Additionally, cytoxin is also reported to be present in *C. gigantea*, playing an important role in wound healing.[9]

Wound healing is a complex process that can generally be divided into three stages: the inflammatory reaction, proliferation, and remodeling. The inflammatory phase begins from the occurrence of the wound until approximately day 3 to day 5. Macroscopic signs of the onset of wound healing can be observed from the stopping of bleeding in the wound area, known as the hemostasis phase.[2]

The presence of calotropin in *C. gigantea's* flowers greatly assists in this stage. Calotropin acts as a procoagulant, aiding in the blood clotting process during wound formation. Additionally, calotropin can hydrolyze blood clots, promoting smoother blood circulation in the wound area, resulting in increased nutrient and oxygen supply to the wound site. It can also reduce inflammation by neutralizing bradykinin and pro-inflammatory eicosanoids to a level where tissue repair and regeneration can commence. *C. gigantea* also contains alkaloids that possess antibacterial properties, which can disrupt the formation of bacterial cell layers, thus preventing infection in the wound area. Moreover, alkaloids also exhibit analgesic and astringent properties, capable of alleviating pain in the wound area. The presence of flavonoids in this plant, which have anti-inflammatory and analgesic properties, can reduce pain and inflammation in the wound area.[2,3,10]

The second phase is the proliferation phase, occurring from day 5 up to day 21. During this phase, significant cellular activity takes place to repair and heal the wound, characterized by cell proliferation. The processes occurring during this phase would include reepithelialization, fibroplasia, wound contraction, and neovascularization or neocapillarization. Fibroblasts play a crucial role in the wound healing process by producing structural protein products utilized during tissue reconstruction. After injury, fibroblasts become activated, migrate from surrounding tissue to the wound area, proliferate, and secrete various substances involved in building new tissue, such as collagen. During the proliferation phase, new cells and blood vessels are formed. A collection of cells and blood vessels in the new tissue is referred to as granulation tissue. By day 7 post-injury, the wound begins to close, a process driven by reepithelialization. The presence of flavonoids, tannins,

saponins, and alkaloids in biduri latex accelerates the occurrence of reepithelialization. Tannins found in this plants possess astringent properties that aid in wound contraction and enhance epithelialization. Saponins increase hydroxyproline, tensile strength, collagen formation, and promote better epithelialization. Alkaloids present in biduri flower extract also play a significant role in wound healing by stimulating proliferation agents and collagen production.[2,10]

The final phase in the wound healing process is the maturation phase (remodeling). This phase begins from the third week post-injury and can last for years, depending on the type of wound. Its goal is to refine the formation of new tissue into strong tissue. Fibroblasts start to leave the granulation tissue, the redness diminishes, and fibrin fibers from collagen become more abundant.[2]

C. gigantea flower extract contains flavonoids that play a role in enhancing collagen survival, preventing cell damage, promoting DNA synthesis, and preventing wound infections. Additionally, it also contains alkaloids that stimulate proliferation agents and collagen production, and saponins that increase tensile strength and promote better collagen formation and epithelialization.[2,8]

Observation of Wound Healing Progress Utilizing *C. gigantea* Extract

In 2018, Marphirah conducted a study where 30 mice that were subjected to wounds before and were treated according to 6 categories:

- P1: Application of biduri (*C. gigantea*) flower ointment at a concentration of 5%
- P2: Application of biduri (*C. gigantea*) flower ointment at a concentration of 10%
- P3: Application of biduri (*C. gigantea*) flower ointment at a concentration of 15%
- K+: Application of povidone iodine ointment (positive control)
- K-: Application of empty ointment (negative control)

The application was performed topically covering the entire wound surface, starting immediately after the formation of wound (day 0). Each group received ointment application three times daily, in the morning, afternoon, and evening, with a 4-hour interval between applications. Clinical observations were conducted from day 1 to day 14, assessing wound diameter.[2]

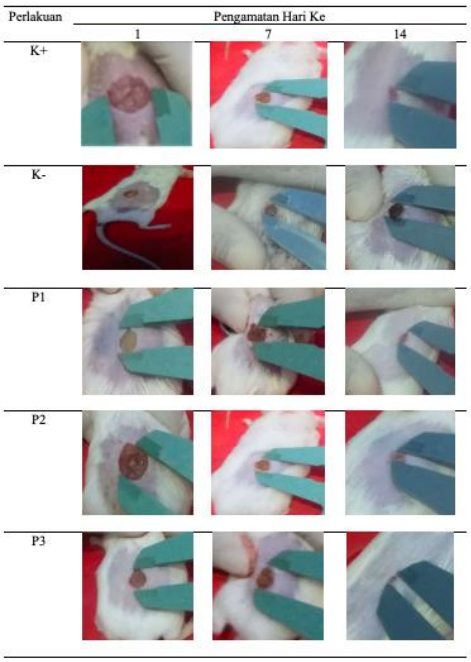

Figure 1. Comparison of Macroscopic Wound Healing Process on Days 1, 7, and 14 in Each Treatment Group.[2]

The results from Figure 1 shows variations in the time required to reduce wound diameter across treatment groups. The treatment with 15% biduri flower extract ointment (P3) was shown to be the fastest reduction in wound diameter, occurring in 6.00 ± 0.63 days. Following this, treatments with 5% (P1) and 10% (P2) *C. gigantea* flower extract ointment showed reduction in wound diameter in 6.83 ± 0.75 days and 6.67 ± 0.52 days, respectively. The positive control (K+) and negative control (K-) exhibited reductions in wound diameter in 6.83 ± 0.75 days and 9.83 ± 0.75 days. It has also been demonstrated that in P3 or 15% *C. gigantea* flower extract ointment, the process of healing significantly became higher, leaving no residual wound marks as it doesn't leave any wound due to the ability of the extract to facilitite fibroblast proliferation whcih makes the wounds close faster.[2]

In another study by Tanimu et al. in 2024, an experiment was conducted to assess the in vivo wound healing efficacy of different concentrations on C57B6/J wild type mice using a wound closure kinetic assay. Concentrations that demonstrated the fastest wound closure were identified. It was shown that all three plant extracts (B.monnieri, A.indica, and C.gigantea at 15 µg/ml, 20 µg/ml, and 1 µg/ml respectively) achieved complete closure 12 days post wounding. Specifically, with biduri, wound healing was achieved in 12 days, while the control subjects required 14 days for wound healing.[1]

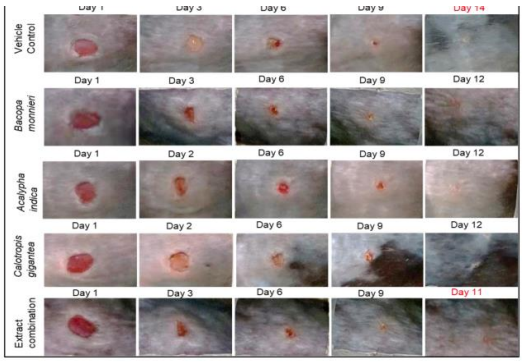

Figure 2. The wound healing progression following the administration of plant extracts and their combination was evaluated on wild type C57B6/J mice. Day 1 marks the initiation of wound creation, after which the rate of wound closure was monitored daily until complete closure. *C. gigantea*'s extract progression is shown on the fourth table.[1]

Histopathological Evaluation of Wound Healing with *C. gigantea*

Based on the results of the histopathological examination of mouse skin tissue during the wound healing process in the positive control (K+), negative control (K-), treatment with 5% biduri flower extract ointment (P1), and observation of *C. gigantea* flower extract ointment 5% (P1) on day 14 post-treatment, stained with H&E at a magnification of 400x, can be observed in Figure 3.

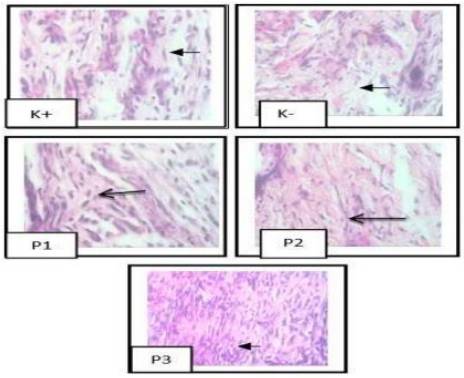

Figure 3. Histopathological Photomicrograph of Mouse Skin on Day 14 of Each Treatment Observation with H&E Staining at 400x Magnification (Arrow Indicates Fibroblasts).[2]

The evidence is shown that the administration of *C. gigantea* flower extract ointment influences the changes in mouse skin tissue during the observed wound healing process, as indicated by the number of fibroblast cells. Observations were based on variations in the degree of degenerative and congestive lesions found. In the positive control group treated with Betadine ointment (K+), a minimal amount of degenerative and congestive lesions was observed in the wound tissue. In the negative control group (K-), a higher number of lesions was observed compared to the positive control (K+). In the application of 5% *C. gigantea* flower extract ointment (P1), variations in degenerative and congestive lesions were also observed. Degenerative and congestive lesions found in the *C. gigantea* flower extract ointment treatment decreased with increasing ointment dosage. With the application of 10% *C. gigantea* flower extract ointment (P2), fewer degenerative and congestive lesions were observed. Moreover, with the application of 15% b*C. gigantea* flower extract ointment (P5), degenerative lesions were further reduced. This may be related to the role of *C. gigantea* flower extract ointment in repairing tissue damage in wounds.[2]

The results indicate that the highest number of fibroblasts was found in the treatment group receiving 15% *C. gigantea* flower extract ointment (P3), with a count of 5.66 ± 0.57. This was followed by the positive control (K+), treatment P2, P1, and negative control (K-) with counts of 5.34 ± 0.97, 5.22 ± 0.72, and 3.88 ± 0.62.[2]

LIMITATIONS

The efficacy of *C. gigantea* as wound healing properties cannot be conclusively demonstrated due to a lack of recent studies. Many of the studies pertaining to the utilization of *C. gigantea* for wound healing properties fall beyond the specified year limitation criteria, thereby hindering a clear assessment of its effectiveness.

CONCLUSION

In conclusion, *Calotropis gigantea*, with its plethora of phytochemical constituents like flavonoids, tannins, alkaloids, and saponins, demonstrates significant potential in wound healing through various mechanisms such as astringency, antibacterial activity, promoting homeostasis, facilitating collagen synthesis, enhancing re-epithelialization, and stimulating cell proliferation. Despite its acknowledged therapeutic capabilities, there is a noticeable scarcity of contemporary research dedicated to exploring the wound healing efficacy and effectivity of *C. gigantea* extract specifically. It is imperative that further detailed investigations and experimental studies be conducted to fully evaluate its effectiveness in medicinal value. By doing so, we can unlock the potential of *C. gigantea* extract as a cornerstone in herbal medicine for wound care, substantiating its traditional uses with scientific validation and potentially introducing a reliable, effective herbal remedy into the mainstream wound healing management beyond its traditional boundaries and into the scientific world.

REFERENCES

I. Tanimu, H., K, R. Z., Jamora, C., Karthik, P., & Bindhu, O. S. (2024, January 1). Dermal wound healing contribution of aqueous extracts of Acalypha indica, *Calotropis gigantea*, Bacopa

monnier and their combination. https://doi.org/10.1101/2024.01.18.576335

II. Marphirah, M (2019). Pemberian Salep Ekstrak Bunga Biduri (*Calotropis gigantea*) untuk Penyembuhan Luka pada Mencit (Mus musculus) Secara Klinis dan Histopatologis. *BIOTIK: Jurnal Ilmiah Biologi Teknologi dan …*, jurnal.ar-raniry.ac.id, https://jurnal.ar-raniry.ac.id/index.php/biotik/article/view/5637/0

III. Danapur, V., Gopinath, S., & Annapurna, G. (2023). Standardization and Biological Activity of *Calotropis gigantea*. Journal of Pharmacognosy and Natural Products, 9, 247.

IV. Mandal, S. (2023). *Calotropis gigantea*: A brief study on phytochemical and pharmacological profile. Asian Journal of Pharmaceutical Research, 13(1), 34-0. https://doi.org/10.52711/2231-5691.2023.00006

V. Ningsih, D. S., Celik, I., Abas, A. H., Bachtiar, B. M., Kemala, P., Idroes, G. M., & Maulydia, N. B. (2023). A review of the ethno-dentistry activities of *Calotropis gigantea*. Malacca Pharmaceutics, 1(1). https://doi.org/10.60084/mp.v1i1.31

VI. Ahmad, W. (2020). Preliminary phytochemical, antimicrobial, and photochemical study of *Calotropis gigantea* leaf extract. Current Chemistry Letters, 9(3), 105-112.

VII. World Health Organization. Integrating traditional medicine. Retrieved from https://www.who.int/southeastasia/news/feature-stories/detail/integrating-traditional-medicine

VIII. Ahmed, A., Swathi, S., Hammad, S., Umair, K., Abdulwahab, A., Yasmeen, S., Asnawi, Z. A., Akber, A. S., S., A. A., Nafees, A., & Sirajudheen, A. (2021). Evaluation of the phytochemical, antioxidant, enzyme inhibition, and wound healing potential of *Calotropis gigantea* (L.) Dryand: A source of a bioactive medicinal product. *Frontiers in Pharmacology, 12. https://doi.org/10.3389/fphar.2021.701369

IX. Griana, T. P. (2019). Potensi Tanaman Pegagan (Centella asiatica (L.) Urban) dan Widuri (*Calotropis gigantea* (L.)) sebagai Imunomodulator. Journal of Food and Science.

X. Eroschenko, V. P. (2013). DiFiore's atlas of histology with functional correlations. Wolters Kluwer.