REVIEW

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Effectivity of African leaf extract (*Vernonia amygdalina*) in wound healing: a systematic review

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ABSTRACT

Background: The use of natural products, particularly those derived from plants, for nutritional and medical purposes to enhance human performance, including wound healing, has gained more attention in recent years. Prior studies showed the health benefits of African leaf (*Vernonia amygdalina*) as anti-parasitic, anti-malarial, anti-helminthic, antiviral, anticancer, anticoagulant, antithrombotic, analgesic, antipyretic effects, including the wound healing process. However, there are still mixed results regarding its effectiveness. This systematic review aims to elaborate on the effectiveness of African leaf extract in wound healing.

Method: A systematic review using the PRISMA diagram was conducted based on literature searching on three online databases (Google Scholar, Pubmed, and Cochrane Library). An eligibility criteria was applied to the literature search, and the Jadad scoring system was used to assess the study's methodological quality.

Result: We included ten clinical trial studies regarding the role and effectiveness of African leaves in wound healing. Studies come from Indonesia, Malaysia, and Nigeria. The animal models used were Wistar albino rats, rabbits, and mice. The intervention used was African leaf extract as a monotherapy or a combination of African leaf extract with other natural agents. The types used were burn wounds, incision or excision wounds, and diabetic wounds. The outcome measured was the wound healing process marked by re-epithelization, wound healing and closure time, and histopathological evaluation to assess collagen formation, polymorphonuclear leukocyte infiltration, and fibroblast recruitment. Most of the included studies showed positive results of African leaf extract or combination with other agents in wound healing.

Conclusion: African leaf (*Vernonia amygdalina*) showed effectiveness in the wound healing process in terms of facilitating re-epithelization, fastened wound healing time, and significant wound reduction size compared with the control group.

Keywords: *African leaf, Vernonia amygdalina, wound healing*.
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INTRODUCTION

The skin covers a considerable portion of the body's surface. The skin is a barrier, shielding the interior organs from damage, scalding temperatures, and bacterial poisons. There are multiple layers of the skin, including the epidermis, dermis, and subcutaneous tissue layer (hypodermis).[1] An injury or surgical procedure that disrupts the continuity of the tissue results in a wound, which causes tissue damage. Wounds can be classified based on nature, skin layer structure, the healing process, and time.[2] Most wounds are caused by surgical wounds, abrasions, and diabetic ulcers. There is an increased incidence of injuries in Indonesia from 7.5% in 2012 to 8.2% in 2013. The most prevalent injuries were chronic type wounds with DM (66.7%), followed by cancerous wounds (24.6%).[3,4]

The wound healing process consists of three phases, namely the inflammatory phase, the proliferative phase, and the remodeling phase. Wound healing will stop after the scar tissue that is not as strong as the initial tissue is formed.[2] Currently, treating wounds using traditional herbal remedies has been widely developed. Based on a survey by the World Health Organization (WHO), 80% of the population in Asian and African countries use traditional medicine, namely herbal medicine, because it is cheaper and has minimal side effects.[5] One of the traditional treatments that have been widely researched is using African leaves *(Vernonia amygdalina)*. African Leaf *(Vernonia amygdalina)* is a shrub plant originating from the African continent and other parts of Africa, especially Nigeria, Cameroon, and Zimbabwe, as well as countries with tropical climates, including Indonesia. African leaves have many benefits in traditional medicine. In various studies conducted, this African leaf plant has effects and activities such as anti-parasitic, anti-malarial, anti-helminthic, antiviral, anticancer, anticoagulant, antithrombotic, analgesic, antipyretic effects, and also plays a role in accelerating the wound healing process.[6-8]

Based on previous studies, African leaves contain several chemical compounds, namely flavonoids, tannins, saponins, and glycosides. These compounds are anti-inflammatory and antioxidants, which play a role in the wound healing process.[6-8] Prior study results still provide mixed results regarding the effectiveness of African leaves. In addition, until now, no study has summarized findings from previous studies regarding the efficacy of African leaves in the wound healing process. Based on the background above, this systematic review will further discuss the effectiveness of African leaves *(Vernonia amygdalina)* in wound healing.

METHODS

Study eligibility

We determined the study eligibility using inclusion criteria as follows: (1) a study regarding the effect of African leaf as a treatment for wound healing, (2) a clinical trial study using an animal model, (3) using African leaf as monotherapy or combination with other agents, (4) original research, and (5) published in full manuscript format in English or Bahasa. We exclude incomplete studies and studies with meta-analysis, systematic review, review, or case report design.

Search strategy and study selection

Literature research was done on three online databases, PubMed, Cochrane Library, and Google Scholar, without a time limit. The keyword we used for study searching was a combination of some keywords with Boolean operators consisting of [("African leaf" OR "*Vernonia amygdalina*") AND ("wound healing" OR "wound treatment")]. The duplicate results were eliminated, and the abstract of the chosen study was checked to see if it applied to the topic of our study. Studies beyond the screening stage are next evaluated using eligibility standards for the full-text manuscript. The analysis and synthesis phase of the process includes studies that satisfy the qualifying requirements. The Recommended Reporting Items for the Systematic Review and Meta-Analysis (PRISMA) flowchart, shown in Figure 1, was used to make all study selections.

Study quality assessment

The study quality assessment was done using the Jadad scoring system. The scoring system consists of five parameters: (A) Study described as randomized (this includes the use of words such as random, randomly, and randomization), (B) Study described as double-blind, (C) Description of withdrawals and dropouts, (D) Method to generate the sequence of randomization described and appropriate (table of random numbers, computer generated, etc.), and (E) Method of double-blinding described and appropriate (identical placebo, active placebo, dummy, etc.). Each question was to be answered with either a yes or a no. Each yes would score a single point, each no zero points; there would be no fractional points. The score will deduct one point if (F) The method to generate the sequence of randomization described and inappropriate or (G) the method of double-blinding described and inappropriate.[9] The study is declared of good quality if it fulfills half of the maximum score (> 3).

Synthesis of the study

The relevant research that complied with the eligibility standards was then used to complete the narrative synthesis. We arrange data from comparable extraction results in accordance with the outcomes we wish to assess at the synthesis analysis step to conclude.

RESULTS

Study characteristics

We retrieved 1,664 studies from three online databases, and 360 duplicated studies were excluded. Thus, 1,304 studies' abstracts were screened, and 1,266 were excluded. Thirty-eight studies were reviewed further for their eligibility criteria. Twenty-eight studies were excluded due to not having a clinical trial, not original research, not using an animal model, not being available in full text, and not being available in English or Bahasa. Therefore, only 10 clinical trials were included in our final analysis, as depicted in Figure 1. The majority of the included studies come from Indonesia; the others come from Malaysia and Nigeria. Three studies used rabbits as animal models, six used Wistar albino rats, and only one used mice (*Mus musculus)* as the study subjects. The type of wounds evaluated in the included studies was burn wound in studies by Ginting *et al.*, Harahap *et al.*, and Lahagina *et al.*[11-13] Five studies used an excision wound on the dorsal parts.[3,4,10,14,15] One study by Ruslim *et al.* evaluated wounds after tooth extraction, and Soji-Omoniwa *et al.* evaluated diabetic wound healing in rats.[16,17] All the detailed study characteristics are presented in Table 1.

Study quality assessment result

Two authors did quality assessments of the study to avoid bias. The assessment was carried out using the Jadad scoring system. Table 2 shows seven studies considered good quality, while the other three had bad quality.

African leaf *(Vernonia amygdalina)* and its phytochemical characteristics

Asteraceae family member Vernonia amygdalina, sometimes known as the bitter plant or African leaf, is one of the six most popular medicinal plants in the *Vernoniae* genus. A 2–5 m-tall shrub or small tree, Vernonia amygdalina, has elliptic-shaped petiolate leaves with a 6 cm circumference. It is a typical crop grown on homesteads and a tree used for fodder. It is frequently used in meals due to its medicinal and nutritional properties. The leaves are removed from their bitter flavor by soaking in multiple water changes or boiling in excessive water and then eaten as a vegetable (macerated leaves in soup), in Nigerian soup (Ogbono soup), or a meal from Cameroon. Tablets from a freeze-dried sample of the V. amygdalina extract have been developed to boost HIV patients' immunity and manage diabetes.[10,15-17]

Vernonia amygdalina contains several active compounds, including flavonoids and terpenoids, which have been extracted from the plant after considering phytochemicals and bioactive components. Vernolide and water-soluble peptides (edotides), two substances derived from V. amygdalina, showed cytotoxicity against cancer cells. African leaves (Vernonia amygdalina) contain flavonoids, tannins, antioxidants, and saponins as active ingredients. Some compounds offer advantages that can aid in the healing of

Table 1. Study characteristics

Author	Sample	Wound type	Intervention and treatment group	*V. amygdalina* preparation	Measured outcome	Study result
Builders *et al.*, 2018, Nigeria.[10]	Fifty males and females Wistar albino rats of males weighing about 190-200 grams.	4 cm^2 wound excision on the central trunk part.	I: negative control group (no treatment) II: positive control (cream base) III: *Andrographis paniculate* (AP) cream extract IV: *Vernonia amygdalina* (VA) cream extract V: *Andrographis paniculate*+*Venonia amygdalina* cream extract VI: Silver sulphadiazine cream.	The cream is applied topically once daily for 21 days.	• Wound epithelization • Wound healing time	• Animals treated with AP+VA showed significantly greater healing effects than other groups. • Significant enhanced epithelization time in all the treated animals compared to controls during the 12 days ($P< 0.05$). • The AP+VA group showed significantly greater wound healing time than other groups.
Ginting *et al.*, 2020, Indonesia.[11]	Three rabbits.	Five burn wound areas in each rabbit with 12x20 cm size.	I: positive control (application with Bioplacenton®). II: negative control (without treatment). III: gel with 5% African leaf ethanol extract. IV:7.5% palm oil ethanol extract. V: a combination of 5% African leaf ethanol extract +7.5% palm oil ethanol extract.	The gel is applied topically once daily.	• Diameter of the wound • New tissue formation • Rate of the total healing process.	• Treatment using a combination of African leaf and palm oil ethanol extract has the fastest healing rate (19th day) • The average healing time in the African leaf ethanol extract group is faster than in the negative control and palm oil ethanol extract groups.
Harahap *et al.*, 2020, Indonesia.[12]	Five rabbits weighing 1.5-2 kilograms.	Burn one in the back part of the rabbit with a 2 cm diameter.	I: negative control (gel only). II: positive control (Bioplacenton® gel). III: application of gel combination made from 4% African leaf + 2.5% Bangun leaf extract. IV: application of gel combination made from 8% African leaf + 5% Bangun leaf extract. V: application of gel combination made from 16% African leaf + 10% Bangun leaf extract.	Gel was applied topically twice daily for 11 days.	Wound diameter	The most effective concentration for wound healing was found in the group that received an application of a gel combination made from 16% African leaf + 10% Bangun leaf extract.
Lahagina *et al.*, 2019, Indonesia.[13]	Three rabbits with 2 cm diameter burn wound.	Burn wound with 2 cm diameter.	I: application of Bioplacenton® as the positive control. II: application of hydrocarbon base ointment from 15% ethanol extract of African leaf. III: application of absorption base ointment from 15% ethanol extract of African leaf.	The ointment is applied once daily.	Spread ability test of the ointment and wound healing rate.	• The rabbit in the positive control group died on the 8th day. • The healing rate was faster in the hydrocarbon-based ointment than in the absorption-based ointment (15th vs. 21st day).

Author	Sample	Wound type	Intervention and treatment group	*V. amygdalina* preparation	Measured outcome	Study result
Mustikasari *et al.*, 2020, Indonesia.[14]	Twenty-five mice *(Mus musculus)* were divided into 5 groups.	Incision wound on the dorsal part.	I: negative control group II: positive control group III: 9% African leaf extract IV: 11% African leaf extract V: 13% African leaf extract	The gel is applied topically twice daily until 10 days.	• Epithelial thickness	• The lowest average of epithelization thickness was found in the negative control group. • The positive control group, groups 3 (9%) and 4 (11%), had a moderate epithelialization thickness. • Group 5 (13%) had the highest epithelialization thickness.
Nafiu *et al.*, 2016, Malaysia.[15]	Seventy-five female albino rats weighing 150-200 grams.	A circular excision wound (10 mm diameter) at the dorsolateral region.	I: negative control group (deionized water). II: treated with pure Unilorin honey. III: Treat with fresh, undiluted *V. amygdalina* leaf juice.	20 µL undiluted juice applied topically twice daily.	• Evaluation of wound closure. • Percentage of wound size reduction. • Percent relative wound healing efficiency • Histological evaluation.	• Honey and V. amygdalina reduced the wound sizes significantly ($p< 0.05$) compared to NC. (33.46 ± 0.37% and 30.50 ± 0.28%) compared to NC. • The average time for CWC was significantly ($p<0.05$) reduced in the honey and V. amygdalina treated groups (11.0±0.00 d and V. amygdalina (11.2 ± 0.45 d vs. 13.4 ± 0.90 d). • Histopathology evaluation showed PMNL infiltration and fibroblast recruitment were significantly ($p< 0.05$) increased in honey and V. amygdalina-treated groups compared to NC.
Putrianirma *et al.*, 2019, Indonesia.[3]	Twenty male albino rats weighing 150-200 grams.	A 2 cm incision subcutaneous wound on the dorsal region.	I: treated with Vaseline II: treated with povidone-iodine III: treated with 16.8% African leaf extract ointment. IV: 28% African leaf extract ointment. V: 39.2% African leaf extract ointment.	The ointment was applied topically twice daily for 14 days.	Histopathological examination using a score of reepithelization rate.	• Treatment with African leaf extract *(Vernonia amygdalina)* did not show a significant re-epithelialization rate from the control treatment groups. • The 16.8% African leaf extract ointment group had the best average re-epithelialization score compared to the control and other treatment groups.

Author	Sample	Wound type	Intervention and treatment group	*V. amygdalina* preparation	Measured outcome	Study result
Rachmanita *et al.*, 2019, Indonesia.[4]	Twenty male albino rats weighing 150-200 grams.	A 2 cm incision subcutaneous wound on the dorsal region.	I: treated with ointment base. II: treated with povidone-iodine ointment. III: treated with 16.8% African leaf extract ointment. IV: 28% African leaf extract ointment. V: 39.2% African leaf extract ointment.	The ointment was applied topically twice daily for 14 days.	Histopathological examination using collagen density score.	• The 16.8% African leaf extract ointment group had the highest collagen density score compared with the control and other treatment groups.
Ruslim *et al.*, 2017, Indonesia.[16]	Thirty 2-4 months male Wistar rats.	Wound due to tooth extraction.	I: positive control using povidone-iodine. II: negative control using pure water. III: 1% African leaf extract. IV: 3% African leaf extract. V: 5% African leaf extract. VI: 7% African leaf extract.	Liquid extract was applied topically for 21 days.	Evaluation of socket closure marked by thin mucosal layer, maximal shrinkage on the wound area, and absence of red dots in the wound area.	• The fastest socket closure was observed in the 5% and 7% African leaf extract groups. • The biggest reduction in socket wound size was also observed in the 5% and 7% African leaf extract groups.
Soji-Omoniwa *et al.*, 2022, Nigeria.[17]	Thirty-six albino rats.	A diabetic wound on the dorsal part.	I: Control (non-diabetic) II: Control (diabetic) III: administered metformin IV: 10 ml Cod liver oil + 100 grams VA leaves V: 20 ml Cod liver oil + 200 grams VA leaves VI: 30 ml Cod liver oil + 300 grams VA leaves	Oral feeding ad libitum for 14 days.	Wound contraction rate and fasting blood glucose concentration.	• A significant increase ($p<0.05$) in the wound contraction rate of IV, V, and VI groups compared to the diabetic control group on the 7th and 14th day. • A significant decrease ($p<0.05$) in blood glucose levels in the IV, V, and VI groups compared to the diabetic control group.

Abbreviation: AP= *Andrographis paniculate*; CWC=complete wound closure; NC=negative control, PMNL=polymorphonuclear leukocytes; VA=*Vernonia amygdalina*

wounds. Strong antioxidants known as flavonoids can lower lipid peroxidation, which aids in the re-epithelialization and antibacterial processes. Flavonoids with lower lipid peroxidase levels are more vascular, less prone to necrosis, and have higher collagen fiber viability. Saponins improve the fibroblast TGF- receptor's capacity to bind to TGF. Fibroblasts require TGF to synthesize collagen, flavonoids, saponins, and tannins, which are believed to play a role in the healing of wounds. Tannins are both antibacterial and epithelialization-promoting. Vascular endothelial growth factor transcription and translation are considered to be regulated by tannins.[8,10,15-17] The picture of African leaf plants can be seen in Figure 2.

Intervention

As stated in Table 1, all included studies divided the sample into control and treatment or intervention groups. The control groups consist of negative and positive control groups. The negative control groups were given no placebo treatment or received a placebo treatment using pure water, deionized water, ointment base, or gel only. In comparison, the positive control groups received standard or usual wound treatment, such as the application of Bioplacenton® or povidone-iodine on the wound area. Five studies used intervention using African leaf extract only with several different concentrations.[3,4,13,14,16] The other study by Builders *et al.* did intervention compared African leaf cream extract with *Andrographis paniculate* cream extract.[10] Study by Ginting *et al.* did an intervention using African leaf and palm oil ethanol extract.[11] A study by Harahap *et al.* did an intervention using an application of a gel combination made from African leaf and Bangun leaf extract.[12] One study by Nafiu *et al.* compared fresh undiluted *V. amygdalina* leaf juice and pure Unilorin honey.[15] The previous study by Soji-Omoniwa *et al.* administered the intervention groups with several concentrations of African leaf and Cod liver oil.[17] The African leaf preparations used in the included study were cream, gel, ointment, oral feeding, and liquid extract. Nine of the included studies used African leaves applied topically in wound areas

Table 2. Quality assessment of the study

Study	A	B	C	D	E	F	G	Total point
Builders *et al.*	1	1	1	1	1	-	-	5
Ginting *et al.*	0	0	1	0	1	-	-	2
Harahap *et al.*	0	1	0	0	1	-	-	2
Lahagina *et al.*	0	0	0	0	0	-	-	0
Mustikasari *et al.*	0	1	1	1	1	-	-	4
Nafiu *et al.*	1	1	1	1	1	-	-	5
Putrianirma *et al.*	1	1	1	1	1	-	-	5
Rachmanita *et al.*	0	1	1	0	1	-	-	3
Ruslim *et al.*	0	1	1	0	1	-	-	3
Soji-Omoniwa *et al.*	1	1	1	1	1	-	-	5

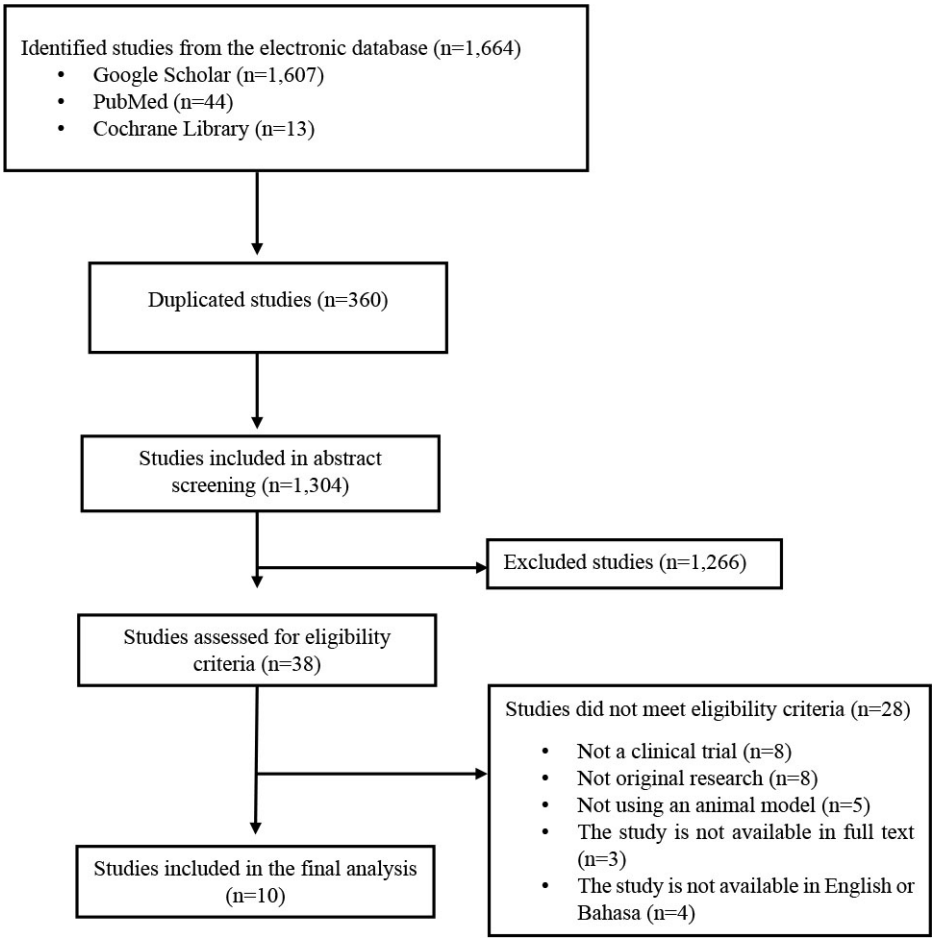

Figure 1. The PRISMA diagram depicting the selection process of studies included in this study.

with treatment duration ranging from 10-21 days. One study by Soji-Omoniwa *et al.* did intervention to the animal subject through ad libitum oral feeding for 14 days.[17]

Outcome measured

Several outcomes are measured in the included studies to evaluate the effectiveness of the African leaf *(Vernonia amygdalina)* in wound healing. Wound healing was marked by the epithelization rate, epithelial thickness, and new tissue formation. A study by Ginting *et al.* and Harahap *et al.* measured the wound diameter day by day after intervention.[10,11] Wound closure or healing rate was observed in almost all included studies. Three studies by Nafiu *et al.*, Putrianirma *et al.*, and Rachmanita *et al.* did a histopathological evaluation of the wound healing process. A study by Nafiu *et al.* evaluated the PMNL infiltration and fibroblast recruitment, Putrianirma et al. evaluated the re-epithelization rate histopathologically, while Rachmanita *et al.* evaluated the collagen formation using collagen density score.[3,4,15] Ruslim *et al.* measure the wound healing process by assessing socket closure marked by a thin mucosal layer, maximal shrinkage on the wound area, and the absence of red dots in the wound area.[16]

Effectivity of African leaf *(Vernonia amygdalina)* for wound healing

From the ten included studies, the majority showed a significant effect of African leaf application in the wound healing process. Only one study did not show a significant re-epithelialization rate from the intervention compared with the control treatment groups. Based on the re-epithelization rate, a study by Builders *et al.* showed that the group treated with African leaf *(Vernonia amygdalina)* cream extract significantly enhanced the epithelization time on the 12th day compared with the control group.[10] Study by Mustikasari *et al.* found the highest epithelization thickness in the group that received 13% African leaf extract.[14] While a study by Putrianirma *et al.* found the 16.8% African leaf extract ointment group had the best average re-epithelialization score compared with the 28% African leaf extract ointment, the 39.2% African leaf extract ointment, and the control groups.[3] However, these findings were not significant. If we compared the effectivity based on the ointment based, a study by Lahagina *et al.* found the healing rate was faster in the hydrocarbon base ointment than the absorption base ointment (15th vs. 21st day).[13] Histopathology evaluation in Nafiu *et al.* showed PMNL infiltration and fibroblast recruitment were significantly ($p<0.05$) increased in honey and V. amygdalina-treated groups compared to the negative control group.[15] Based on the collagen formation, a study by Rachmanita *et al.* found that the 16.8% African leaf extract ointment group had the highest collagen density score compared with the 28% African leaf extract ointment, the 39.2% African leaf

Figure 2. *African leaf (Vernonia amygdalina) plants.*[8]

extract ointment, and the control groups.[4] In a study by Ruslim *et al.*, wound healing characterized by socket closure was faster with higher doses of African leaf extract. 5% and 7% African leaf extracts have the fastest socket closure.[16] Study by Soji-Omoniwa *et al.* found that a combination of Cod liver oil and 100 grams, 200 grams, and 300 grams of African leaves showed a significant increase ($p<0.05$) in the wound contraction rate compared to the diabetic control group in the 7th dan 14th day and a significant decrease ($p<0.05$) of blood glucose level compared to the diabetic control group.[17]

DISCUSSION

This systematic review discusses the effectiveness of the African leaf *(Vernonia amygdalina)* in wound healing. Wound healing is an intricate series of actions involving numerous cellular and molecular systems. The four phases of the processes—hemostasis, inflammation, proliferation or re-epithelialization, and remodeling—are all carefully regulated and overlap each other. As a result, up to 80% of the original skin's tensile strength is recovered at the end of the process. These steps correspond to the restoration of the skin's barrier function, the destruction and removal of any invasive pathogens and foreign debris, the restoration of the local vasculature and tissues, and finally, the remodeling of the wound site to resemble the intact uninjured tissue. Healing agents can help the healing wound process.[1,2] The use of herbal material, such as African leaf *(Vernonia amygdalina),* is one of the traditional approaches in wound management that is comfortable to patients and has many beneficial effects. African leaf (*Vernonia amygdalina)* has a variety of medical uses.[6-8]

The study included in this systematic review did wound infliction through the form of burn wounds, incision or excision wounds, and diabetic wounds. Study results showed that African leaf extract showed significant positive results in facilitating wound healing. The phytochemicals of African leaf extract contain several bioactive ingredients, such as flavonoids, alkaloids, terpenes, saponins, and sesquiterpenes. Steroids, coumarins, phenolic acids, lignans, xanthones, and anthraquinone have also been found in African leaves. Its antibacterial, anti-inflammatory, and antioxidant effects are what make it famous. The presence of flavonoids, vernodalol, and tannins in African leaf extract was credited with the plant's antioxidant, antibacterial, and anti-inflammatory activities, respectively.[6-8,18]

During the early phase of wound healing, African leaf extracts markedly reduced initial wound size by 30%, which is comparable to other natural agents such as honey (33% wound size reduction), as stated in the study by Nafiu *et al.* from day 6 to 12 post wounding, African leaf extract also showed comparably effect in increasing the healing rate compared with negative control.[15] This shows that African leaf extract influenced wound healing at the early phase and enhanced healing cascades at all phases of wound healing. The anti-inflammatory effect is also exhibited by African leaf extract. In a study by Soji-Omoniwa *et al.*, the group that received African leaf extract showed downregulated expression of iNOS, COX-2, and NF-κB.[17] The generation of NO also decreased in parallel with the down-regulation of iNOS expression due to iNOS activity inhibition. NO is a potent free radical gas communicating certain physiological reactions by serving as a messenger molecule. It creates a cytotoxic wound environment, is poisonous to bacteria, is a powerful vasodilator, improves vascular permeability, and may prevent platelet aggregation. It has been demonstrated that abnormally high NO levels in the wound environment negatively affect wound healing, resulting in poorer wound healing.[18,19]

On the other hand, COX-2 plays a key role as an inflammatory response mediator. It works by generating prostaglandins, which regulate a variety of features of the subsequent inflammation, such as the stimulation of vascular permeability and the infiltration and activation of inflammatory cells. African leaf extract has anti-inflammatory properties and the ability to suppress COX-2 expression. Release of IL1-1, IL-6, and TNF- during the healing process causes COX-2 to be expressed, which catalyzes the conversion of arachidonic acid into prostaglandins, prostacyclins, and thromboxanes. Vasoconstriction is required for hemostasis and is brought on by prostaglandins E and I, which also increase vascular permeability and stimulate inflammatory cells. Prostacyclin and thromboxane A2 also produce vasoconstriction. Africa leaf can thereby promote wound healing in an experimental animal model by reducing inflammation and COX-2 expression.[20,21]

Wound contraction, which typically begins five days after damage, is the last symptom of the proliferation phase. With the help of newly migratory fibroblasts, the connective tissue matrix is created during the dynamic process of wound contraction. As myofibroblasts, which

are responsible for tensile force to draw the wound margins toward the wound center, differentiate, the size of the wound gradually decreases. Giving African leaf extract sped up this process by encouraging the creation and deposition of collagen and other extracellular matrix components.[2,4,20] The limitation of this systematic review is that not all of the included studies assessed the side effects of African leaf *(Vernonia amygdalina)* or its combination with other agents when applied as topical wound therapy. Only one study by Builders *et al.* assessed the intervention side effect through a skin irritation test. They found no erythema or edema formed on the skin of the rats when each of the cream samples was applied.

CONCLUSION

Based on the results of our systematic review, we can conclude that the African leaf *(Vernonia amygdalina)* is an herb plant with natural ingredients that showed positive results in the wound healing process. It can help wound healing by facilitating re-epithelization and formation of new tissue, fastened wound healing time, and significant wound reduction size compared with the control group.

CONFLICT OF INTEREST

The authors declare that there is no competing interest regarding the manuscript.

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AUTHOR CONTRIBUTION

All authors contributed to the study from the conceptual framework, data gathering, and analysis until the study's results were interpreted upon publication.

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