

Ethnopharmacology and bioactive evidence of medicinal plants for wound healing in Indonesia: A scoping review

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ABSTRACT

Wounds damage the skin, disrupting its normal structure and function. This review discusses medicinal plants commonly used to treat wounds in Indonesia, including their ethnopharmacology, active compounds, and molecular targets that support their bioactive properties. Data were gathered from electronic databases published between 2000 and 2023, such as Web of Science, PubMed, Google Scholar, Scopus, and ScienceDirect. A descriptive analysis was conducted on 94 articles covering ethnopharmacy, phytochemicals, *in vitro* and *in vivo* investigations of the effectiveness of medicinal plants against wound healing. A total of 238 plant species from 60 families have been reported to be used for wound healing in Indonesia. Ursolic acid, curcumin, aloin, emodin, quercetin, kaempferol, luteolin, lantadene, jatrophone, allicin, eugenol, and gingerol are among the chemical components linked to this action that promote wound healing. Herbal medicines can target multiple molecular targets to encourage wound healing, including cytokines interleukin (IL-1, IL-6, IL-10, COX-1, and COX-2), growth factors (tumor necrosis factor-alpha, transforming growth factor-β1, vascular endothelial growth factor), and signaling molecules (reactive oxygen species). Furthermore, we found that herbal medicine targeted mitogenic pathways, such as protein kinase B, phosphoinositide 3-kinase, and smooth muscle actin. Resource monitoring, phytochemical and pharmacological research, and evidence-based drug development can support traditional medicine and facilitate drug discovery, potentially leading to the development of novel drugs for wound care.

INTRODUCTION

Wound healing is a complex response to injury that involves regenerating or reconstructing damaged tissue. It follows a precise and highly regulated sequence of phases: hemostasis, inflammation, proliferation, and remodeling [1]. The healing process is initiated by platelets, which release coagulating chemicals, ultimately leading to the formation of a fibrin clot at the site of injury [2]. The inflammatory phase involves the vigorous mobilization of leukocytes to the site of the wound. During the initial stages of inflammation, interleukin (IL)-6 and IL-1, along

with matrix metalloproteinases (MMPs), play a significant role [3]. The M2 macrophages, which have anti-inflammatory properties, secrete complement components and various growth factors, including vascular endothelial growth factor (VEGF), insulin-like growth factor 1, fibroblast growth factor (FGF), epidermal growth factor, and transforming growth factor (TGF). In addition, they release anti-inflammatory cytokines such as IL-10 during the later stage of inflammation [4,5].

The proliferative phase encompasses the primary regenerative mechanisms that commence on the third day following injury and persist for approximately 2 weeks. The process begins with a rapid increase in the growth and movement of fibroblasts, which then start producing new extracellular matrix (ECM) components such as fibrin, collagen I, collagen III, fibronectin, glycosaminoglycans, proteoglycans, and matrix protein hyaluronan [6]. An essential part of wound

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healing is the angiogenesis process, which entails creating and arranging new blood vessels. Numerous angiogenic stimulators, including platelet-derived growth factor (PDGF), FGF, VEGF, TGF- β , tumor necrosis factor-alpha (TNF- α), angiogenin, and angiopoietin-1, are produced [7]. In the end, epithelialization takes place. Epithelial cells quickly migrate from the borders of the wound to the site of injury [8].

The final stage of wound healing, known as the remodeling phase, usually takes many months or even years to complete. In order to create thicker and more durable collagen fibers, type III collagen is gradually replaced with type I collagen during the progressive transition process. The result is a wholly formed scar with high tensile strength and fewer cells and blood vessels [5,6]. Although acute wounds typically heal naturally, chronic wounds can disrupt this process, leading to persistent inflammation characterized by excessive neutrophil infiltration and prolonged healing times. Managing chronic inflammation is a challenging medical issue that requires substantial health care resources [9].

Plants and plant-based compounds have long been used to treat and manage wounds. Herbal medicines have significantly advanced the treatment of skin wounds, especially in developing countries [3,10]. However, developing plant-derived drugs remains a considerable challenge [11]. Various biopolymers are being investigated to create cost-effective, environmentally friendly, durable, and efficient delivery systems for wound treatment. Natural herbal remedies have become crucial in managing skin disorders and treating infections because of their affordability and the adverse effects of modern medicine [12–14]. Indonesia has over 17,000 islands and a staggering 25,000–30,000 plant species, encompassing a diverse range of 50 natural ecosystems or vegetation types [15]. Indonesia is home to a diverse array of ethnic groups between 300 and 700. This rich ethnic diversity results in various cultures, traditions, and local knowledge systems that vary across different groups and regions. Among these practices, many ethnic Indonesians use natural resources to maintain their health. According to the 2018 Basic Medical Research (*Riskesdas*) data, 31.8% of the Indonesian population continues to rely on traditional medicine for their health care needs [16].

Given the high economic burden of treating and managing wound healing, exploring the scientific potential of medicinal plants from Indonesian regions is crucial. These plants possess properties that can positively impact the environment, quality of life, and the overall economy in both developed and developing countries. This review discusses medicinal plants commonly used to treat wounds in Indonesia, including their ethnopharmacology, active compounds, and molecular targets that support their bioactive properties.

METHODS

Study design

This investigation employed a comprehensive scoping review methodology, integrating the foundational York Framework principles with contemporary systematic review guidelines. The methodological framework synthesized the pioneering approach of Arskey and O'Malley [17], subsequent

refinements by Levac *et al.* [18], and current PRISMA-ScR reporting standards [19]. This structured assessment examined Indonesian ethnomedicinal plants used in wound healing, encompassing both traditional knowledge and scientific evidence. The analytical process followed six sequential phases: research question formulation, literature identification, study selection based on predetermined criteria, systematic data extraction, evidence synthesis, and expert consultation for validation.

Research question

The investigative framework was developed to address the primary research question: “What is the current literature relating to the potential application of medicinal plants for wound healing in Indonesia, and to what extent has research explored the active compounds and their molecular targets?”

Information sources and search strategy

We systematically searched English-language publications from July 4, 2000 to April 30 2023, across multiple electronic databases, including ScienceDirect, PubMed, Google Scholar, Scopus, and Web of Science. Our search was conducted in two stages: preliminary and primary. The preliminary search strategy used comprehensive keywords including: “wound healing” (“plant” or “herb” or “traditional medicine”), “Indonesia,” and “tribe”.

Study selection

Based on this preliminary research, the relevant and frequently used plants for wound healing are discussed. During this primary phase, specific keywords and phrases related to the study's focus were scrutinized, such as “wound healing,” “medicinal plants,” “phytochemicals,” “compounds,” “chemical structures,” “receptors,” and “formulations” to capture the breadth of relevant research. We reviewed primary search results and included ethnopharmacy, phytochemicals, *in vitro* and *in vivo* on wound healing properties. We focused on original publications in English with abstracts available in the databases. The PRISMA flowchart showed the search results and selection process in the present scoping review study (Fig. 1).

Data extraction

Data extraction was performed systematically using a customized Microsoft Excel template to capture comprehensive information on medicinal plants used in Indonesia. The extracted parameters encompassed as follows: (1) demographic characteristics, including tribal affiliation, geographical location, and temporal context; (2) methodological classification (*in vitro* and/or *in vivo* investigations); (3) botanical specifications detailing plant taxonomy, used parts, and preparation methodologies; (4) phytochemical profiles with emphasis on bioactive constituents; (5) molecular mechanisms of action; and (6) therapeutic outcomes (detailed documentation available in Supplementary Tables S2 and S3).

Synthesis

Adhering to the PRISMA-ScR checklist, our rigorous data extraction process ensured a comprehensive and transparent

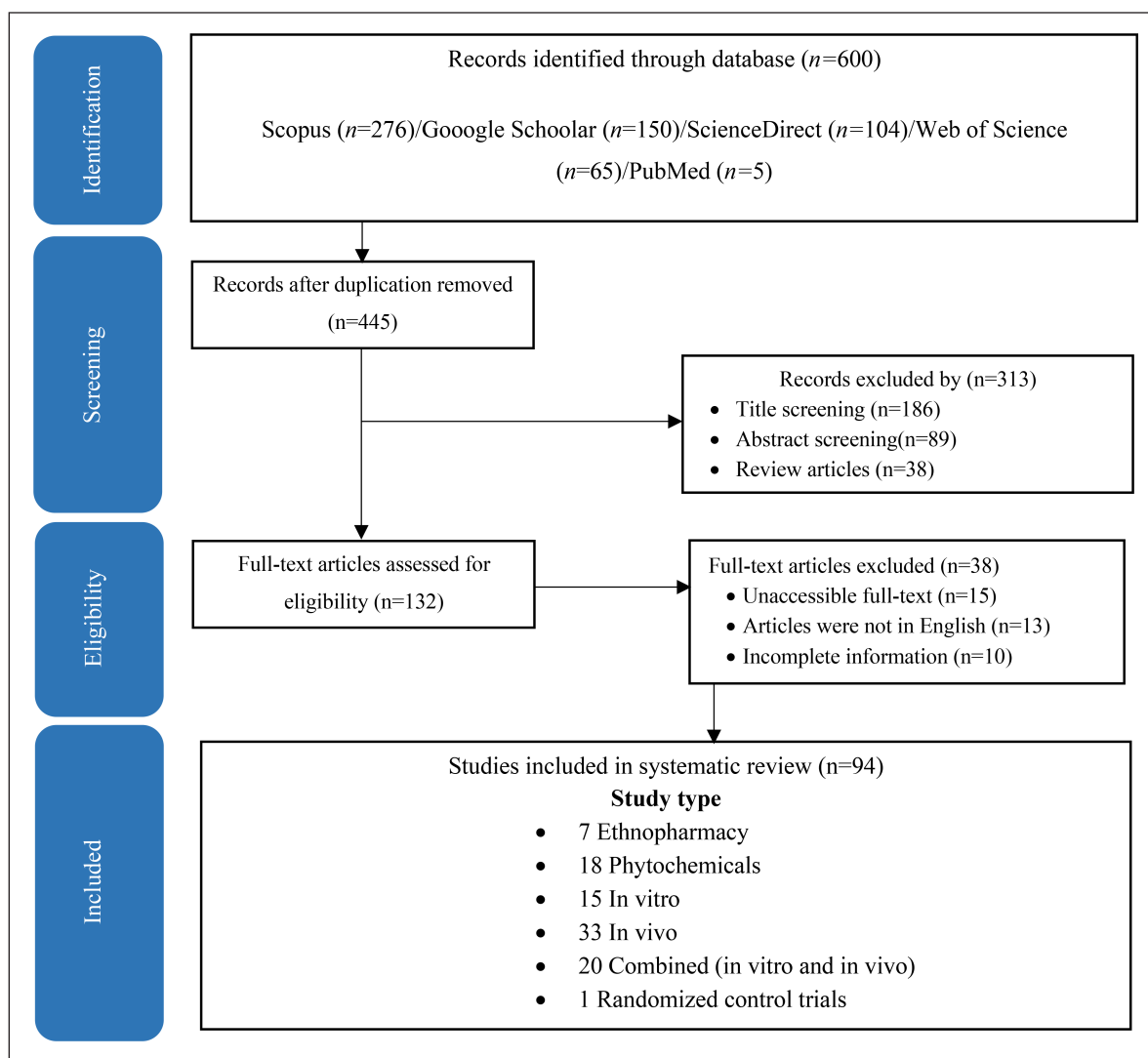


Figure 1. PRISMA flowchart of the included studies.

analysis of the existing evidence landscape, providing a detailed understanding of medicinal plant research in wound healing (detailed documentation available in Supplementary Tables S1).

RESULTS

Ethnopharmacology

The PRISMA flowchart (Fig. 1) summarizes the search results and selection process of the present scoping review study. A total of 94 studies about medicinal plants used for wound healing in Indonesia were used in writing this review. This review assessed 238 plant species belonging to 60 families for wound-healing properties using research data from 11 islands and 25 ethnic groups in the Indonesian Archipelago, which can be accessed in Figure 2 [20]. Data from the Aceh Province of Sumatra were collected from three villages: Sebarjadi [21], Sekerak [22], and Labu [23]. In other areas in Sumatra, data were collected from North Sumatra [24,25], Riau's Kampar

Hilir [26], Jambi's Serampas, and Lampung's Way Kambass [27]. Data from Java were obtained from Subang in the western region [28] and Turgo and Mount Merapi in the central region [29,30]. In the eastern region of Java, data were obtained from Pacitan [31], Mount Tengger [32], and Mount Wilis [33].

Data were collected from Dayak Sintang [34] and Mempawah [35] in West Kalimantan and Sukamara in Central Kalimantan [36]. In eastern Indonesia, data were collected from Minasatene in South Sulawesi [37] and Kalii Indra Triba in Central Sulawesi [38]. In the province of Irian Jaya, data were collected from Raja Ampat [39]. In addition, data were obtained from small islands such as South Bangka [40,41], Bali [42,43], Moyo Island in west Nusa Tenggara [44], Narmada and Belu in East Nusa Tenggara [45], Sumenep, Madura [46], and Halmahera in Maluku [47].

As shown in Figure 3a, plants from the Asteraceae family are frequently used in Indonesia for wound healing, including *Acmella uliginosa* (Sw.) Cass, *Ageratum*



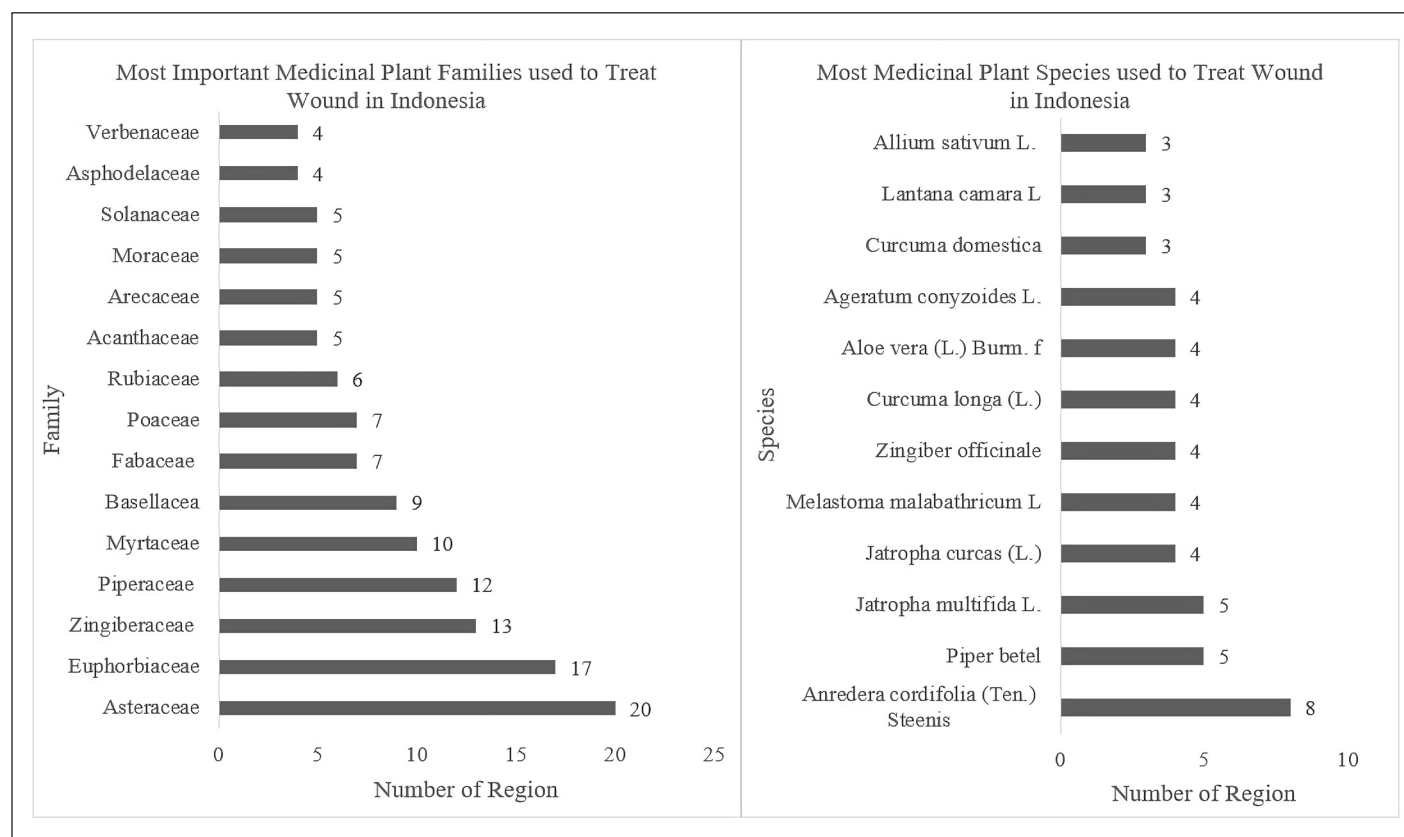


Figure 3. Important medicinal plant families (a) and species used as wound healing in Indonesia (b).

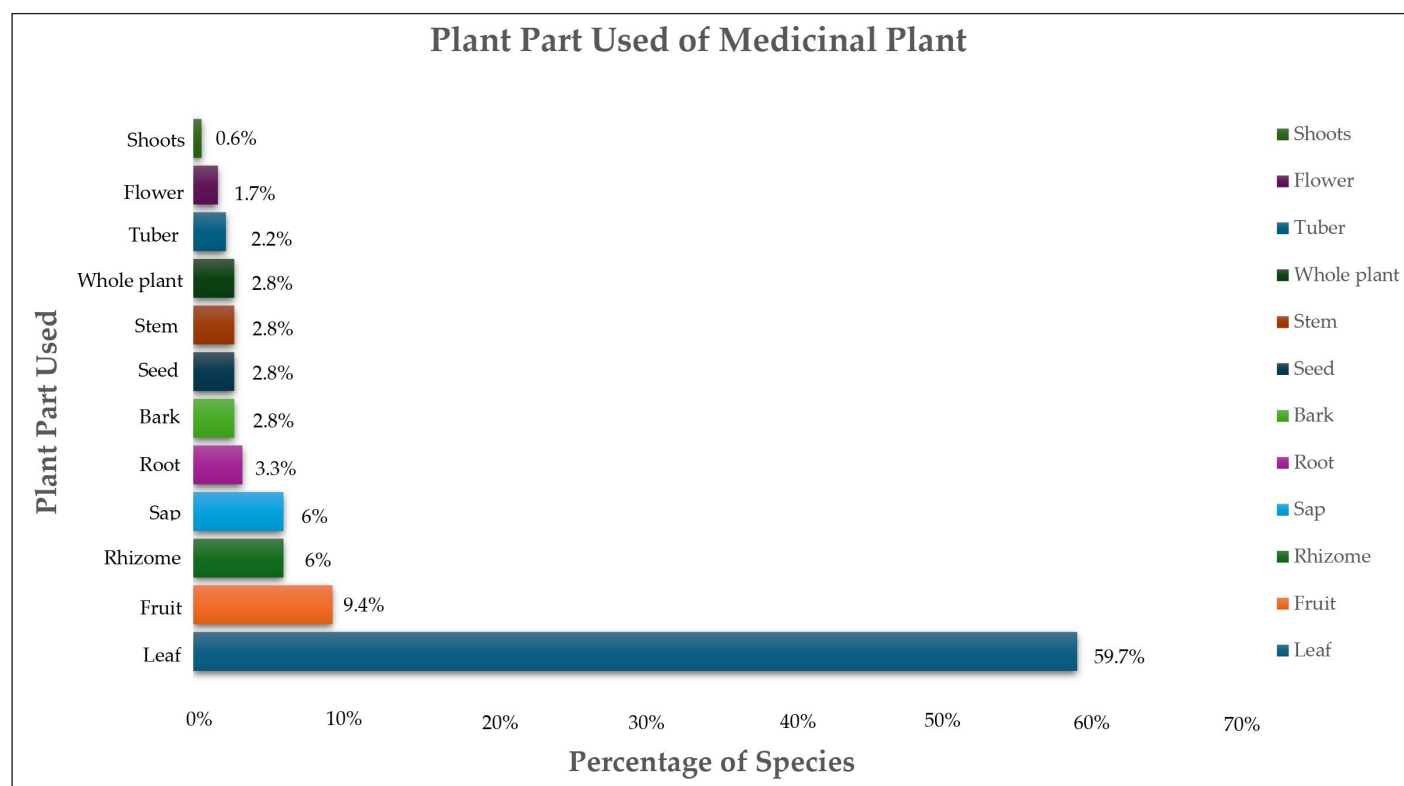


Figure 4. Percentage of medicinal plant parts used for herbal preparation in Indonesia.

conyzoides L., *Bidens pilosa* L., *Bidens biternata* (Lour.), and *Crassocephalum crepidioides* (Benth.) S. moore; additional plant species mentioned were *Chromolaena odorata* (L.), *Conyza sumatrensis* (Retzius), *Erechtites valerianifolius* (Link ex Spreng.), *Eupatorium inulifolium* Kunth, *Eupatorium odoratum*, *Gynura procumbens* (Lour.) Merr, *Synedrella nodiflora* (L.) Gaerth, *Mikania micrantha*, and *Sonchus arvensis* [21,23,33,37,41]. Plants from this botanical family are frequently used for wound healing because they thrive in tropical habitats and have widespread occurrence and therapeutic properties. Consequently, these plants are primarily sought as an alternative to modern, expensive drugs and chemical-based treatments whose adverse effects can be harmful [48].

Plants in the Euphorbia family were the second most used for wound healing. These plants are often found in cultivated and wild areas and are used for medicinal purposes. Most Indonesians have traditionally used *Anredera cordifolia* and *Curcuma longa* for their wound-healing properties (Fig. 3b). These plants could serve as reliable resources, and several studies have consequently been conducted on these plants to explore their biological activities and phytochemical compositions [49].

Leaves are the most commonly reported plant parts used in herbal medicine preparations in Indonesia (Fig. 4) [34] and are renowned for their suitability and durability in developing medicinal treatments [49,50]. Durability reflects the survival rate of therapeutic plants following harvesting, where taking a reasonable amount of leaf biomass does not harm the

plant, in contrast to harvesting the stem, root, or entire plant, which can endanger the plant [51]. Moreover, many studies have demonstrated that leaves harbor many plant secondary metabolites, such as alkaloids, glycosides, and essential oils, which are responsible for their therapeutic qualities. In addition, leaves serve as the focal point for phytochemical reactions and as storage areas for organic matter [49]. Conversely, using stems or roots leads to the need for more sustainable use of plants, mainly when extracted from their natural habitats [51].

Plant components are subjected to various preparation methods before being used in herbal remedies. The predominant method of preparation involves crushing (49%), followed by drying (14%), powdering (14%), smearing (13%), and decoction (13%). Significant contributors used in the overall manner of preparation were found to be pasta (4%), raw material (4%), oils (2%), expressed juices (1%), and squeezed plant parts (1%) (Fig. 5). Several studies have yielded comparable findings, indicating that decoction is the most prevalent preparation technique [50,52] primarily because of its simplicity, ease of use, and cost-effectiveness. Moreover, additional research has demonstrated that the decoction process can enhance the effectiveness of extracting plant compounds, thereby increasing their bioactivity [53].

Bioactivity evidence

Figure 3b depicts the 11 most used Indonesian plants for wound treatment, some of these species, such as *Allium sativum* L., *Melastoma malabathricum* L., *Piper betle*

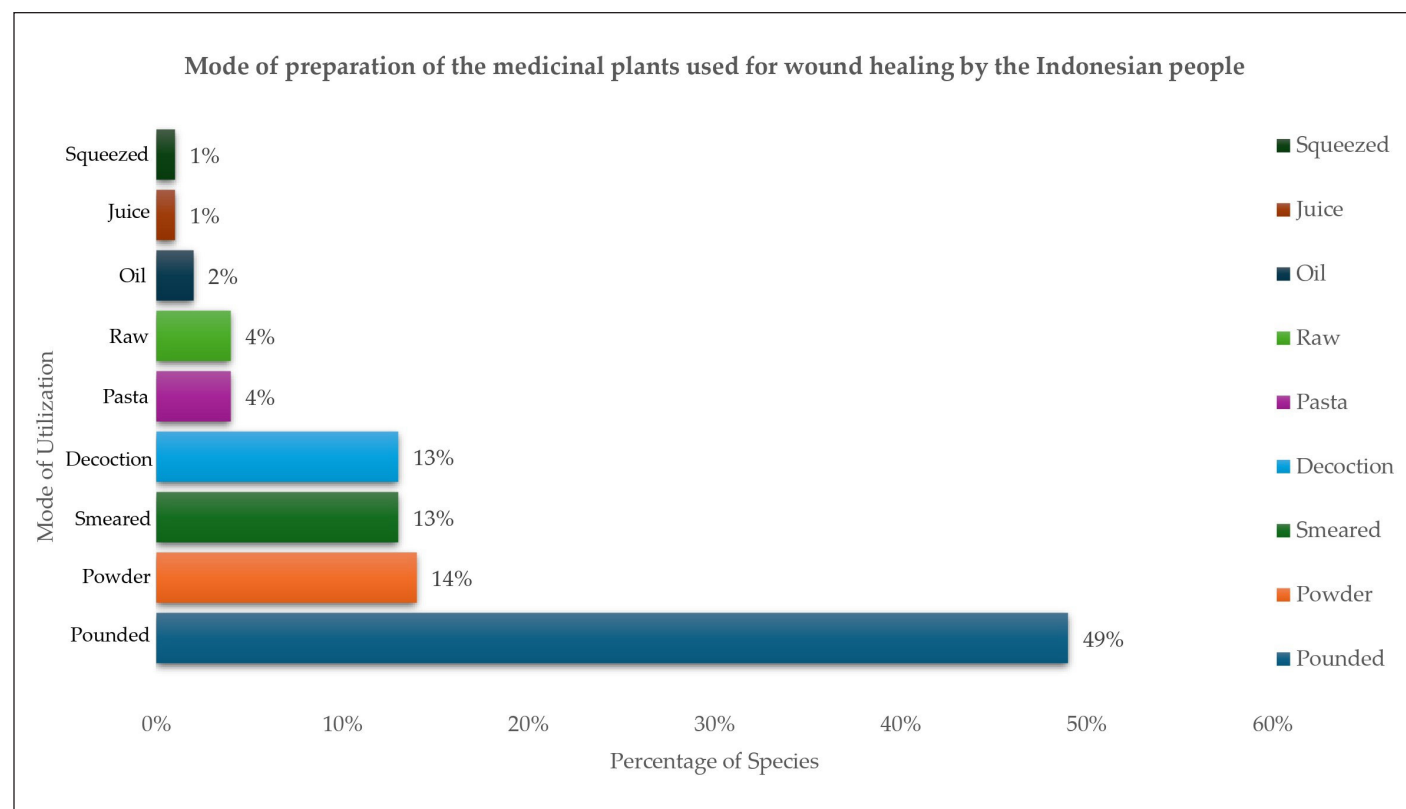


Figure 5. Preparation of herbal drugs for wound healing by the Indonesians.

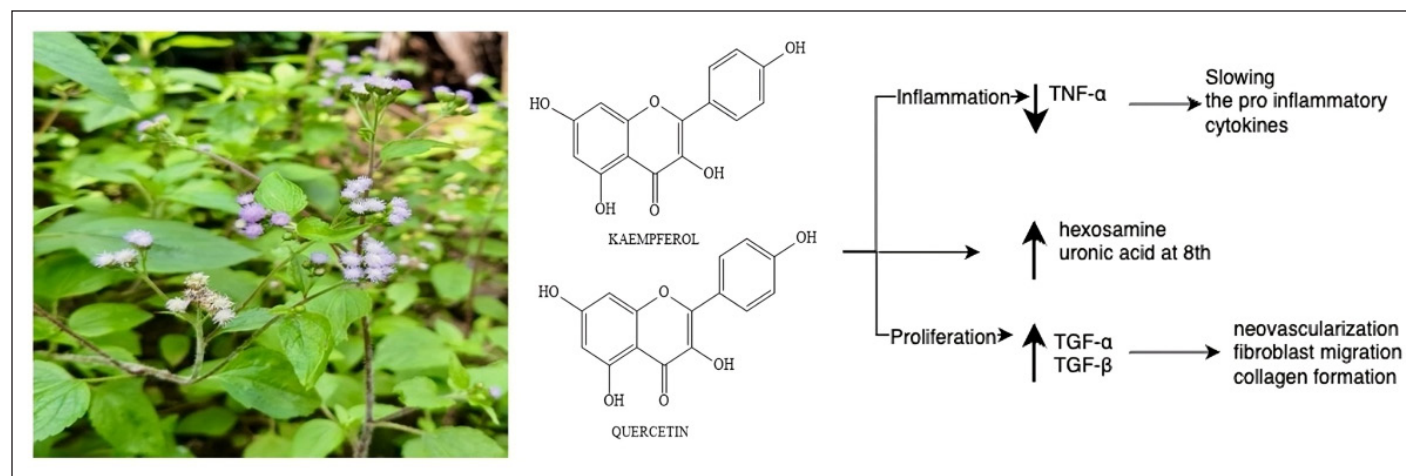


Figure 6. Bioactive and pharmacological target of *A. conyzoides* L on wound healing.

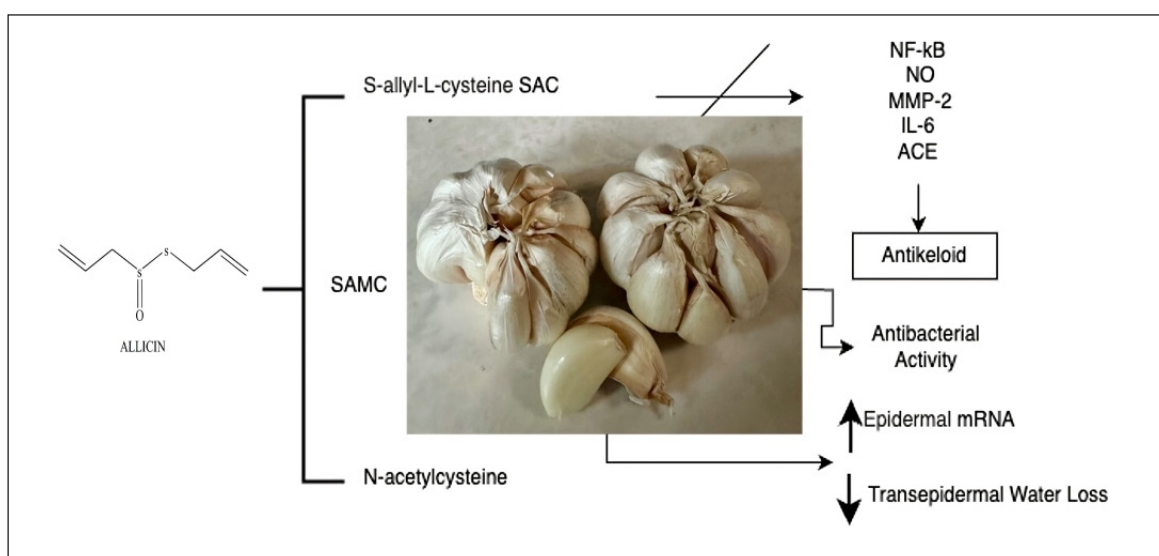


Figure 7. Bioactive and pharmacological target of *A. sativum* L on wound healing.

L., *C. longa* L., and *Zingiber officinale* L., are indigenous to Indonesia and Southeast Asia [54–58]. The others are American natives, *Jatropha multifida* L. (Central and South America) [59], *Jatropha curcas* L. (Mexico to Central America) [60], *A. cordifolia* (Ten.) Steenis. (South America) [61], *Lantana camara* L. (Tropical America) [62], and *A. conyzoides* (Tropical America) [63]. *Aloe vera* (L.) Burm., on the other hand, is indigenous to the Mediterranean [64].

***Ageratum conyzoides* L.**

Ageratum conyzoides L., often known as *bandotan* in Indonesia, is a herbaceous plant that thrives in many subtropical and tropical regions [65]. *Ageratum conyzoides* is an annual herb widely used as a traditional medicine in many countries worldwide. This specific plant has long been acknowledged for its medicinal qualities in treating minor injuries, burns, and infections through anti-inflammatory and hemostatic effects and numerous skin disorders [66]. Debbarma *et al.* [67]

demonstrated that a leaf paste can treat cuts and wounds. The efficacy of petroleum ether, chloroform, methanol, and aqueous extracts of *A. conyzoides* was investigated using excision, incision, and dead space wound models, with methanol and aqueous extracts demonstrating significant wound-healing activity [68]. As shown in Figure 6, *A. conyzoides* extract can enhance cellular proliferation and collagen synthesis. Wounds treated with *A. conyzoides* extract healed faster as shown by higher rates of epithelialization, wound contraction, and histological results. Furthermore, this enhanced hexosamine- and uronic acid-induced levels of collagen synthesis after 8 days of treatment [69].

Plant components such as saponins, phenolics, and flavonoids are believed to accelerate the wound-healing process [68]. The flavonoids in *A. conyzoides* L. leaves, including kaempferol and quercetin, have anti-inflammatory and antioxidant properties beneficial for wound healing. Furthermore, the alkaloid and saponin components of *A.*

conyzoides are involved in wound-healing activity through fibroblast stimulation, anti-inflammatory effects, cell repair, and enhancing skin-cell strength [70]. During the inflammatory phase, *A. conyzoides* inhibits TNF- α production in wounded tissue while activating growth factors and cells to promote healing, slowing the release of proinflammatory cytokines, and increasing the production of anti-inflammatory cytokines. The aqueous extract of *A. conyzoides* enhances the synthesis of growth factors such as TGF- α and TGF- β at the wound site. TGF- α subsequently stimulates neovascularization, fibroblast migration, and collagen formation [71].

Allium sativum L.

Allium sativum L. (garlic) is a common edible and traditional plant used to prevent and treat various diseases and is referred to as bawang putih in Indonesia (Fig. 7). *Allium sativum* is a member of the Liliaceae family and contains a wide range of natural compounds, including organosulfur, amino acids, selenium derivatives, saponins, phenylpropanoids, flavonoids, alkaloids, fatty acids, and sterols [72,73]. *Allium sativum* L. has a substantial antibacterial effect on bacteria that cause skin infections and has broad antibacterial activity against gram-negative and gram-positive bacteria such as *Staphylococcus aureus*, *Escherichia coli*, *Bacillus subtilis*, and *Mycobacterium*, *Pseudomonas*, *Klebsiella*, *Salmonella*, *Proteus*, *Micrococcus*, and *Clostridium* species [73,74]. Allium extract had a lower minimum inhibitory concentration (MIC) than honey. Combined in treating burns, the allium and honey mixture displayed shorter epithelialization and wound contraction times than *A. sativum* extract alone [75].

Organic sulfurs such as S-allyl-L-cysteine (SAC), S-allylmercaptocysteine (SAMC), and N-acetylcysteine are significant bioactive compounds derived from the alliin compound. SAC has anti-inflammatory, antiapoptotic,

and antioxidant properties, whereas SAMC has anticancer properties [76]. Reducing the size of keloids is an aim of wound healing. *Allium sativum* extract has been shown to inhibit the production of nuclear factor-kB (NF-kB), nitric oxide (NO), MMP-2, IL-6, and angiotensin-converting enzyme and, therefore, is a potentially effective keloid treatment [76,77]. In treating full-thickness excisional wounds, an allium ointment was used to reduce wounds twice as effectively as the vehicle, leaving more visually appealing scars [78]. In another study, thiosulfate-enriched *A. sativum* extract upregulated the expression of epidermal mRNA, 3 days after wounding and reduced transepidermal water loss on day 8 [79].

Aloe vera (L.) Burm.f

Aloe vera (L.) Burm. f, also called lidah buaya, is a long-established medicinal plant belonging to the Liliaceae family. Both leaves and gel are frequently employed to treat wounds and are particularly effective in treating skin conditions such as burns, infections, and diabetic dermal wounds by accelerating wound healing due to their antibacterial and antioxidant characteristics. *Aloe vera* is more effective better than regular antibiotics in killing gram-positive bacteria such as *S. aureus*, *S. epidermidis*, and *S. pyogenes* and gram-negative bacteria *P. aeruginosa* associated with skin wounds, burns, and acne [50,52]. *Aloe vera* extracts contain ascorbate, vitamins A, C, and E, phenolic compounds, anthraquinones, and other chemical components that have potent antioxidant properties that effectively decrease lipid oxidation due to their synergistic effect [80].

Moreover, the most prevalent components in *A. vera* gel are aloin, emodin, and β -sitosterol, which are considered to have significant bioactivities in treating wound healing (Fig. 8) [81]. In addition, *A. vera* effects different phases of the wound-healing process [82]. *Aloe vera* gel enhances the proliferation

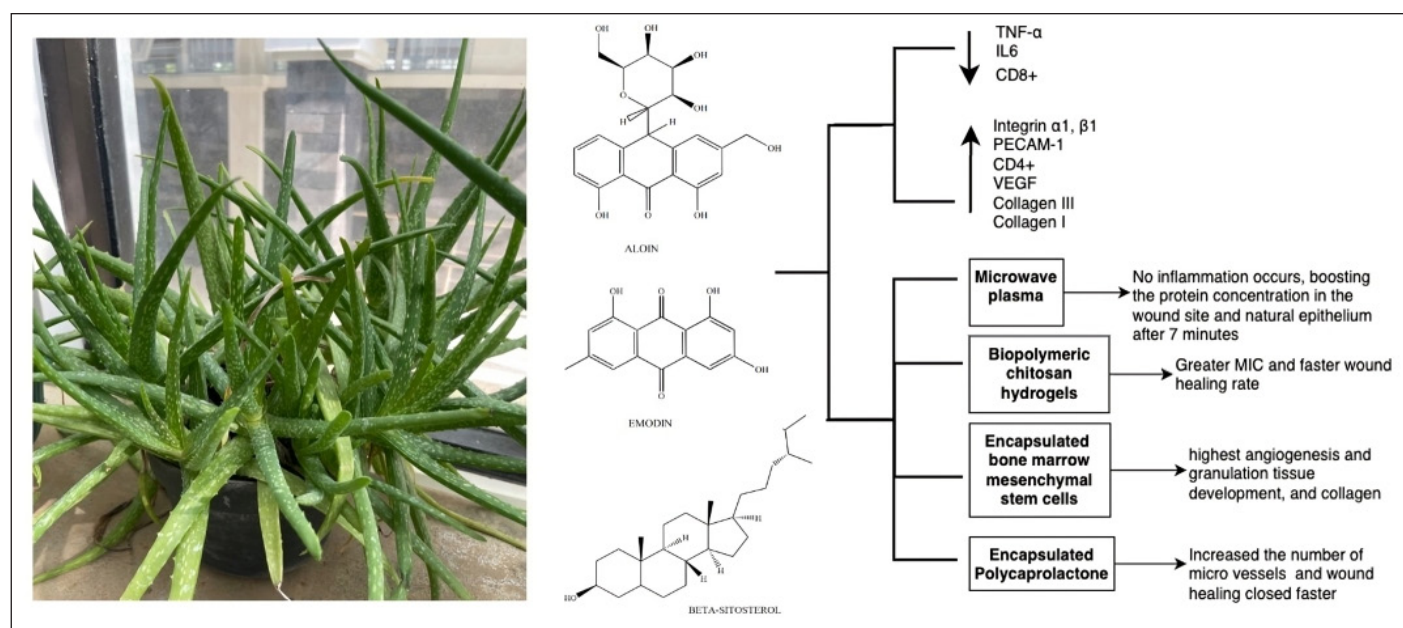


Figure 8. Bioactive and pharmacological target of *A. vera* (L.) Burm. f on wound healing.

and migration of fibroblast cells during inflammation and proliferation and the production of ECM components, such as fibronectin, proteoglycans, and collagen, leading to an accelerated proliferative phase and expedited wound healing. During the remodeling and maturation phase of wound healing, *A. vera* treatment was shown to significantly increase the number of fibrocytes and enhance the density of collagen mass in a more structured manner, which can reduce the size of scar tissue and optimize biomechanical function [83].

In vivo investigations show that *A. vera* cream decreases TNF- α and IL6 levels while increasing the ratio of CD4⁺ and CD8⁺ lymphocytes in the wound region [84]. Numerous studies have created drug-delivery systems (DDSs) for *A. vera* to treat wound healing. Activating *A. vera* with microwave plasma produced a noninflammatory treatment that increased the protein concentration in the wound site and natural epithelium after 7 minutes of exposure in an incision albino mice wound [85]. The combination of *A. vera* and biopolymers chitosan hydrogels produced a high MIC and a rapid rate of wound healing at 3, 7, and 14 days [81,86]. The highest levels of angiogenesis and granulation tissue growth were observed when *A. vera*-encapsulated mesenchymal stem cells from bone marrow were administered to patients with burns. In addition, an increased expression of collagen III and I and VEGF peaked on day 14 of treatment [81]. Furthermore, microvessels increased when a full-thickness excisional wound was treated with *A. vera*-encapsulated polycaprolactone (PCL) gel, producing faster wound healing than that observed with PCL or *A. vera* alone [87].

An *in vitro* study revealed that *A. vera* enhanced TGF- β 1 and b-fibroblast growth factor (bFGF) expression

in mouse embryonic fibroblasts [88]. Adding *A. vera* gel to fibroblasts and endothelial cells also increased the expression of integrin α 1, β 1, and platelet endothelial cell adhesion molecule (PECAM-1) genes [89].

Anredera cordifolia (Ten.) Steenis

Anredera cordifolia (Ten.) Steenis belongs to the genus *Anredera juss.* The plant is commonly referred to as the Madeira vine and, in Indonesia, is known as *binahong* or *pinahong*. *Anredera cordifolia* is commonly and extensively used in traditional wound treatment and healing practices and is readily available due to its cultivation in Indonesia [90]. The flavonoids in *A. cordifolia* leaves exhibit broad-spectrum antibacterial properties, and the plant possesses antioxidant and anti-inflammatory characteristics (Fig. 9) [91].

The leaves of *A. cordifolia* are effective against black-pigmented bacteria, specifically *Porphyromonas gingivalis* and *Prevotella intermedia*, which cause chronic periodontitis [92]. *Anredera cordifolia* leaf-based soap exhibits antibacterial properties against *S. aureus* and *E. coli*. An extensive study conducted in Indonesia on the therapeutic properties of *A. cordifolia* for treating wounds showed that *A. cordifolia* extract and fraction facilitates wound healing by diminishing inflammation, enhancing tissue regeneration, and stimulating collagen and hydroxyproline production in incisions, excisions, burns, and chronic wounds in diabetes patients [93–95]. Binahong leaf extract has also been found to prevent the activation of inflammatory mediators, such as TNF- α , IL-1, and IL-6 [96,97].

Anredera cordifolia contains saponin, tannin, triterpenoid, alkaloid, flavonoid, phenolic, steroid, glycoside,

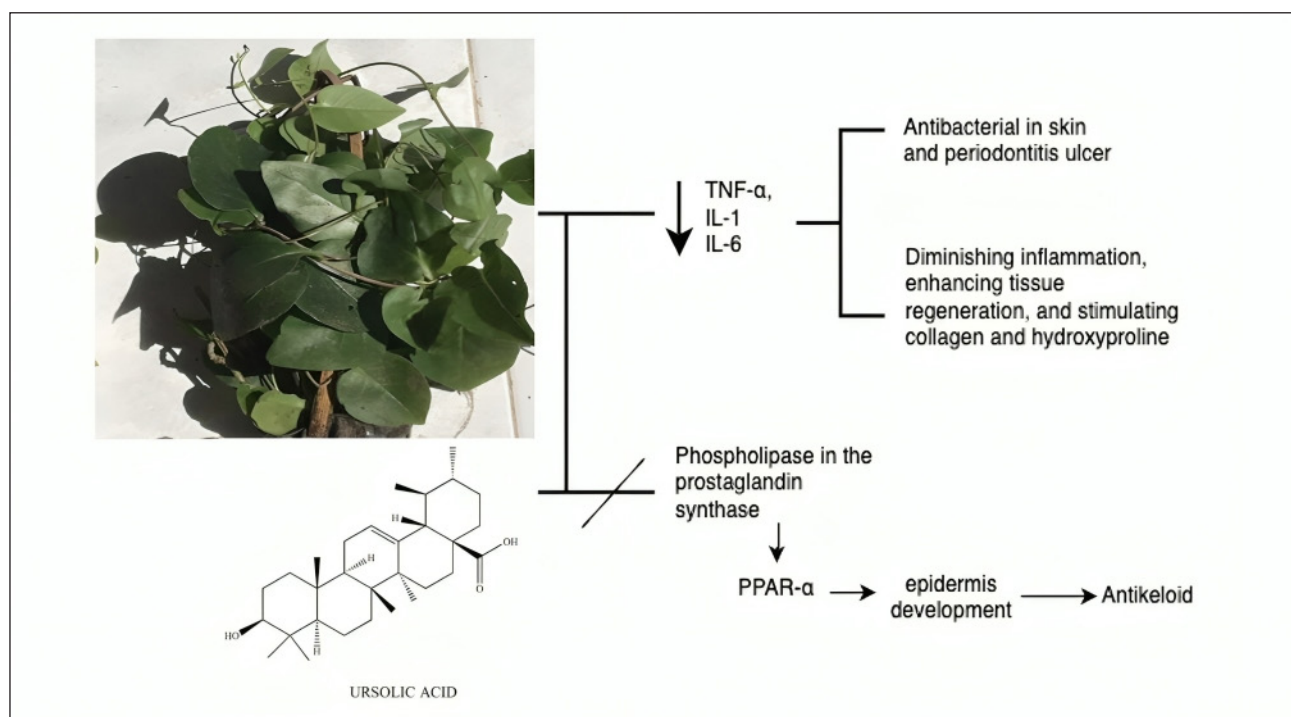


Figure 9. Bioactive and pharmacological target of *A. cordifolia* (Ten.) Steenis on wound healing.

oleanolic acid, protein, β -sitosterol, ursolic acid, and ascorbic acid [93,96,98]. Ursolic acid, used to standardize the ethanolic extract of *A. cordifolia*, is most abundant in the leaves and interferes in wound healing by inhibiting phospholipase in the prostaglandin synthase cascade. Ursolic acid also increases the expression of peroxisome proliferator-activated receptor- α , which drives epidermis development in the second step of the wound-healing process [99].

Curcuma longa L.

Turmeric, in Indonesia, known as *kunyit* (*C. longa* L.), is a rhizomatous perennial herb in the Zingiberaceae family [100,101]. Turmeric has been clinically confirmed to have pharmacological qualities, including antioxidant, anti-inflammatory, and chemoprotective effects (Fig. 10). Turmeric rhizomes contain various bioactive compounds, such as curcumin, turmerone, zingiberene, phellandrene, sabinene, borneol, and cineol, but curcuminoids have received the most attention [102]. The anti-inflammatory, protective, and antioxidant qualities of turmeric offer excellent potential for research on wound healing [103].

Curcumin exhibits radical scavenging activity, as assessed using 1,1-diphenyl-2-picrylhydrazyl (DPPH), 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS), N,N-dimethyl-p-phenylenediamine (DMPD), oxygen radical absorbance capacity (ORAC), and hydrogen peroxide scavenging assays. Turmeric can also chelate ferrous ions, lowering their availability to bacteria. Compared with tocopherol, curcumin more significantly inhibits lipid peroxidation [104,105]. The antimicrobial properties of curcumin are crucial in promoting the rapid healing of wounds [106,107]. Curcumin stops bacteria from growing in several ways, such as preventing the formation of biofilms and attachment of bacteria to host receptors. Curcumin also decreases bacterial virulence

factors and damages bacterial DNA, proteins, cell walls, cell membranes, and other parts of bacterial cells [108].

In an *in vivo* experiment, the topical application of curcumin to a burn site and incision wound stimulated the formation of new blood vessels (angiogenesis), deposition of collagen, formation of granulation tissue, and levels of hydroxyproline to accelerate wound healing in less than 14 days [101,107,109]. A previous study demonstrated that curcumin-coated silver nanoparticles (AgNPs) improved wound healing by enhancing the proliferation of L929 fibroblasts and expediting the restoration of the epithelial layer [106]. Applying a curcumin-loaded chitosan/alginate sponge increased wound contraction by 90% in the first 12 days after injury compared with a wound contraction rate of 74% in the control group [110].

Curcumin affects wound healing in multiple phases. During the inflammatory phase, curcumin may inhibit the NF- κ B transcription factor, remove reactive oxygen species (ROS), inhibit lipid peroxidase, reduce the amount of IL-6 produced by macrophages, and increase the levels of superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) [105,111]. During the proliferation phase, the curcumin-treated wounds showed increased TGF- β levels, which improved fibroblast proliferation and granulation tissue development with increased VEGF, TGF- β 1, and hypoxia-inducible factor (HIF-1 α) expression in neovasculation. The remodeling phase was characterized by the development of sweat glands and hair follicles, a fully regenerated epithelial layer, and higher concentrations of type III collagen than type I collagen after 8 days of treatment [103,111].

Jatropha multifida L.

Asia and Africa are home to extensive cultivation of *J. multifida* L., a member of the Euphorbiaceae family. *Jatropha multifida*, commonly known as jarak tintir, is underused, especially in Indonesia. This plant can react to

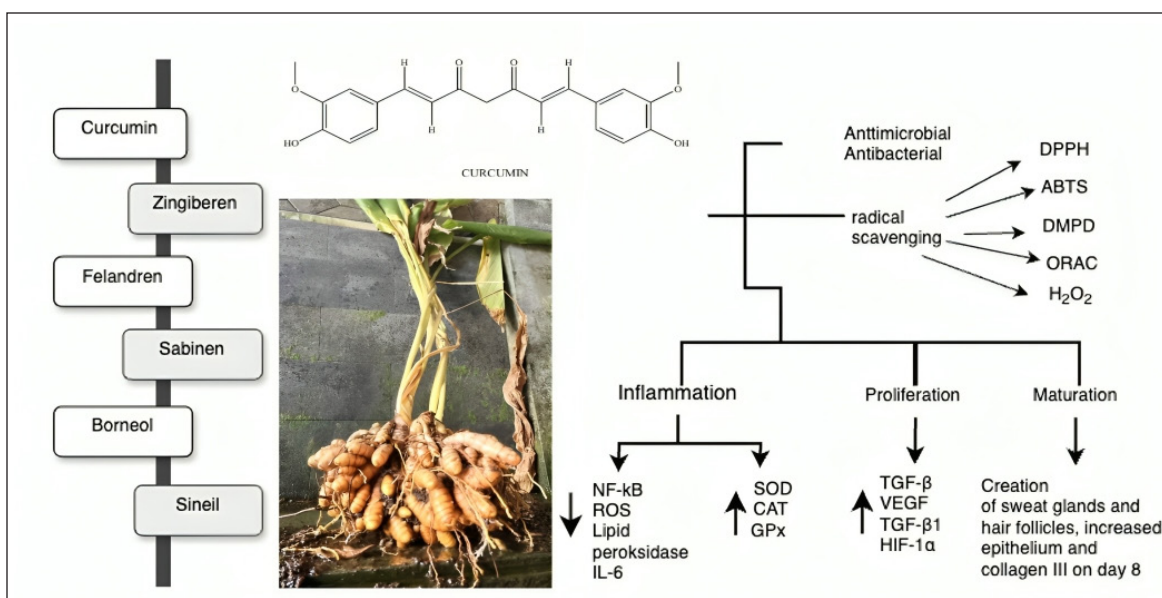


Figure 10. Bioactive and pharmacological target of *C. longa* L on wound healing.

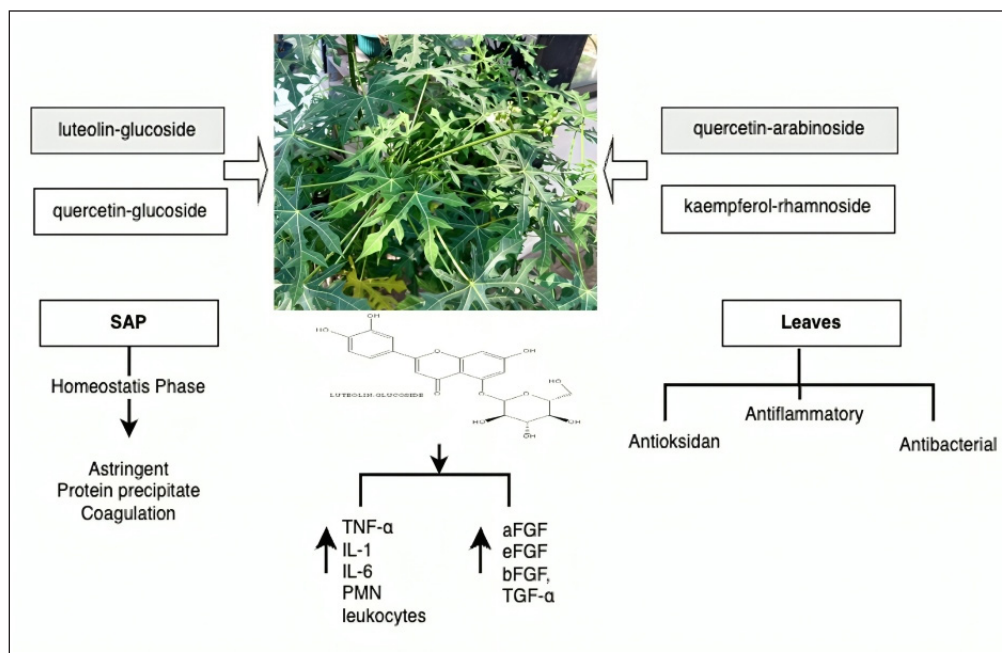


Figure 11. Bioactive and pharmacological target of *J. multifida* L on wound healing.

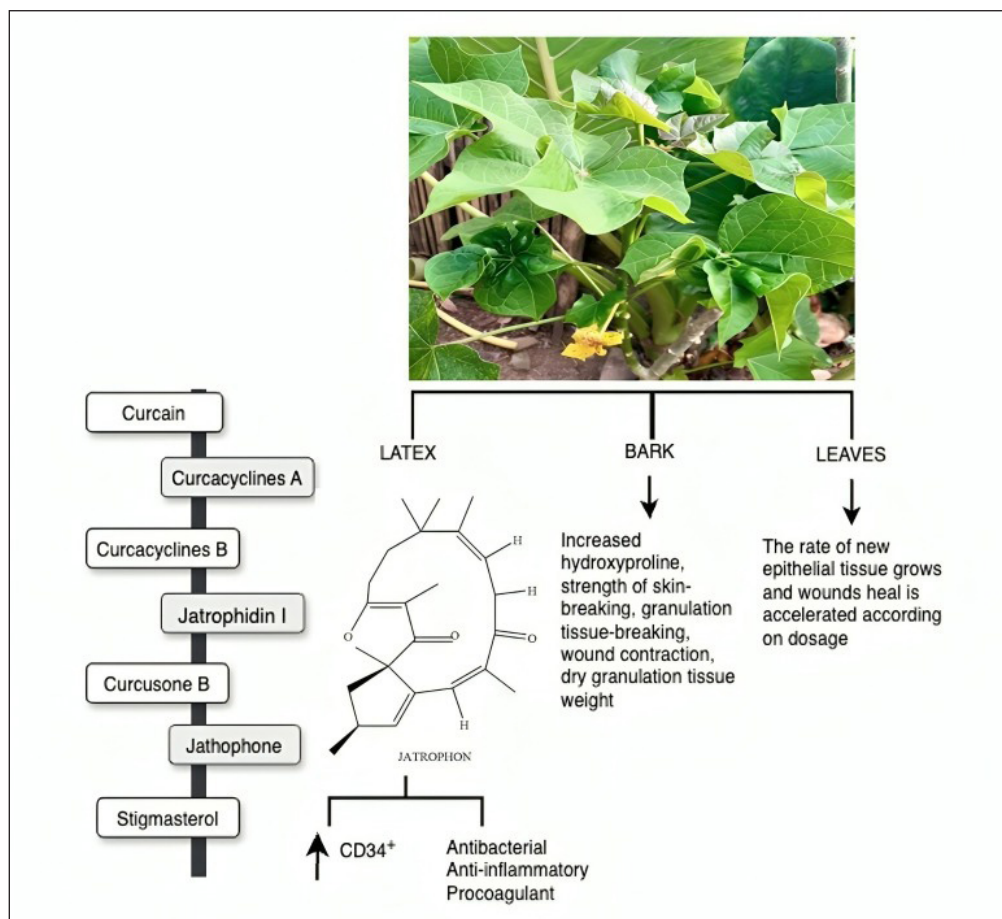


Figure 12. Bioactive and pharmacological target of *J. curcas* on wound healing.

climatic conditions, adjust to agroecological environments, and has accumulated various genetic variants. *Jatropha multifida* has multiple therapeutic properties, including antimicrobial, antifungal, antibacterial, hypoallergenic, cytotoxic, and antihypertensive activities and can be used as a medication to combat infections and promote wound healing (Fig. 11) [112].

In a previous study, *J. multifida* sap healed traumatic ulcers in rats when the sap was applied using an iota carrageenan poly (vinyl alcohol) hydrogel film, considerably enhancing wound healing, resulting in a 98% healing rate by day 10 of treatment [113]. *Jatropha multifida* sap also influenced the hemostasis phase by precipitating proteins through its astringent ability and affecting the cascade response of coagulation in the wound-healing process [114]. *Jatropha multifida* leaf extracts exhibit antioxidant, anti-inflammatory activities, and antibacterial activity. The mentioned activity is attributable to chemicals that were identified via liquid chromatography-mass spectrometry–electrospray ionization analysis and include luteolin glucoside, quercetin glucoside, quercetin arabinoside, and kaempferol rhamnoside. Interestingly, luteolin rhamnoside was the most abundant constituent in the *J. multifida* leaf extracts, with a concentration of 19.73 mg/gv [115].

Several authors have reported that luteolin in *J. multifida* extracts can regulate the production of proinflammatory cytokines, such as TNF- α , IL-1, and IL-6 [115,116]. The *J. multifida*–induced wound healing has also been reported to increase the levels of acidic fibroblast growth factor, epidermal fibroblast growth factor, bFGF, TGF- α , and TGF- β and reduce those of polymorphonuclear leukocytes [115,117,118].

***Jatropha curcas* L.**

Jatropha curcas L., known as Jarak Pagar in Indonesia, is a highly adaptable plant with potential for medicinal uses. More than 170 officially identified species are included in the *Jatropha* genus [119]. *Jatropha curcas* is a small, dense shrub or diminutive tree that grows to 3–5 m but can reach 10 m under ideal conditions and flourishes at 15°C–40°C [120]. Sesquiterpenoids, triterpenes, alkaloids, flavonoids, phenolics, phytosterols, coumarins, neolignan, and lignans are among the many compounds found in *J. curcas* [121].

The phytochemical components of *J. curcas* exhibit numerous pharmacological activities, such as anti-inflammatory, antibacterial, antioxidant, anticancer, antiviral, antidiabetic, analgesic, hepatoprotective, anticoagulant, antifertility, and wound-healing properties (Fig. 12). All parts of *J. curcas* have been used for both traditional medicine and veterinary uses. The leaves, barks, and latexes are used to treat wounds, refractory ulcers, septic gums, and as a styptic in cuts and bruises [122,123].

Applying an ointment containing a methanolic extract from the bark of *J. curcas* produced an increase in total protein and collagen content at the wound site, as shown by the hydroxyproline content of granulation tissues [122]. Furthermore, the extract enhanced wound contraction, granulation tissue formation, skin integrity, and the weight of dry granulation tissue, all of which contributed to improved healing processes [124]. Esimone *et al.* [125] assessed the effectiveness of a herbal ointment containing a methanolic

extract derived from *J. curcas* leaves. Adding the extract to an ointment accelerated wound healing and reduced the time required to develop new epithelial tissue.

Curcain, curcacycline A and B, and jatrophidin I are the most common isolated compounds found in *J. curcas* latex [126,127], along with curcusone B, jatrophone (diterpene), and stigmaterol (triterpene) [128]. These compounds have therapeutic qualities that are useful for wound healing, such as anticancer, antioxidant, antibacterial, antiviral, antinematode, anti-inflammatory, procoagulant, and anticoagulant effects [126]. *In vitro* studies have shown that the *J. curcas* latex spray improved wound healing in human keratinocyte (HaCaT) and human fibroblast (BJ) cell lines as assessed using the scratch test. Indeed, wound healing was faster in formula-treated cells than with the positive control; moreover, the *J. curcas* spray and the biomarker compound, namely curcilyn, have similar antioxidant and wound-healing activities. Balqis *et al.* [123] observed a notable increase in the quantity of circulating CD34⁺ cells with a *J. curcas* treatment than that in the positive control at day 7 in their investigation of the angiogenesis activity of *J. curcas* latex in cream.

***Lantana camara* L.**

Lantana camara (Verbenaceae family), often known as red/ wild sage, grows at 2,000 m and is a dominant and invasive plant in temperate, tropical, and subtropical climates. *Lantana camara* is now found in more than 60 countries in Central and South America, Asia, Africa, and Australia. *Lantana camara*, or *tembelekan* in Indonesia [129], is employed in herbal medicine to relieve skin itching, as an antiseptic for wounds, and externally to treat leprosy and scabies [130]. Place freshly crushed fruits and leaves directly into the affected area to treat wounds. Indigenous tribes have also traditionally used the fresh leaves of *L. camara* for measles [131].

The finely crushed leaves of *L. camara* are used directly on the skin as a compress to heal cuts, wounds, and swelling in a specific area. An alternative method involves using powdered leaves and coconut oil to treat skin conditions, whereas the whole plant is usually used for herbal treatments (Fig. 13) [132]. Applying the *L. camara* extract significantly accelerated wound contraction (98%), encouraged collagen synthesis, and shortened the average healing time. *Lantana camara* was also shown to demonstrate potential as a medication in healing skin injuries, as shown by the effective repair of excision wounds in laboratory animals [130,133]. *Lantana camara* contains triterpenes lantadene A, reduced lantadene A, and lantadene B, which have antibacterial activity against *S. aureus* and *Salmonella typhi*. The antibacterial activity of the extract could explain its wound-healing activity in terms of decreasing the wound area in the excision wound model [130]. *In vitro* studies, molecular docking, and ADMET prediction demonstrated that the terpenes in *L. camara* decrease ROS, NO, and COX-2 levels, which are essential in reducing inflammation during the wound-healing phase [134].

***Melastoma malabathricum* L.**

Melastoma malabathricum L. (Melastomataceae) is an indigenous plant species found in tropical and subtropical

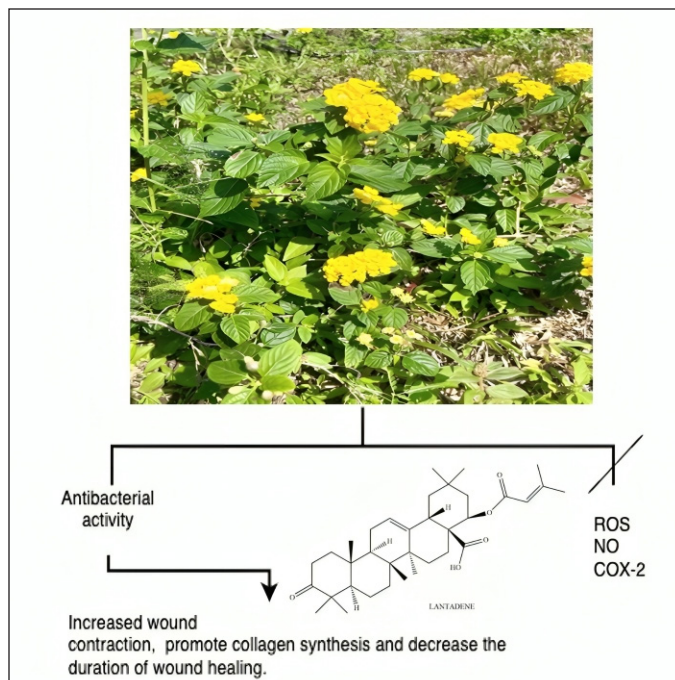


Figure 13. Bioactive and pharmacological target of *L. camara* on wound healing.

regions called Senduduk in Indonesia. The *Melastoma* genus contains approximately 4,000 species of this plant that are globally distributed. The Southeast Asian region has 22 species, two subspecies, and three variants under the *Melastoma* genus. Various uses of *M. malabathricum* have been recorded in traditional medicine, although clinical trials are lacking [56]. In Malay, Indian, and Indonesian traditional medicines, various plant components, such as leaves, roots, and barks, are used for treating illnesses and conditions such as diarrhea, dysentery, leucorrhea, hemorrhoids, cuts and wounds, postpartum infections, toothache, stomachache, flatulence, sore legs, and thrush [135,136].

Melastoma malabathricum, as shown in Figure 14, contains phytochemical compounds such as flavonoids, flavan-3-ols, triterpenes, tannins, anthocyanins, saponins, alkaloids, steroids, glycosides, phenolics, ursolic acid, malvidin-3,5-diglucoside, β -sitosterol, and β -sitosterol-3- α -D-glucopyranoside [56]. The administration of *M. malabathricum* flower and fruit extract showed antibacterial and wound-healing activity due to the high quercetin content, which has a high antibacterial and wound-healing effect [137]. Anbu Jeba Sunilson *et al.* [138] investigated the wound-healing characteristics of *M. malabathricum* leaf ointment extract in excision and incision wound models in rats. *Melastoma malabathricum* improved wound contraction in excision wounds, promoting rapid closure, increasing wound strength, and facilitating tissue regeneration in 18 ± 2 days, whereas incision wounds showed significantly improved tensile strength after 10 days.

A combination of *M. malabathricum* and *Psidium guajava* leaf extract decreased blood glucose levels and

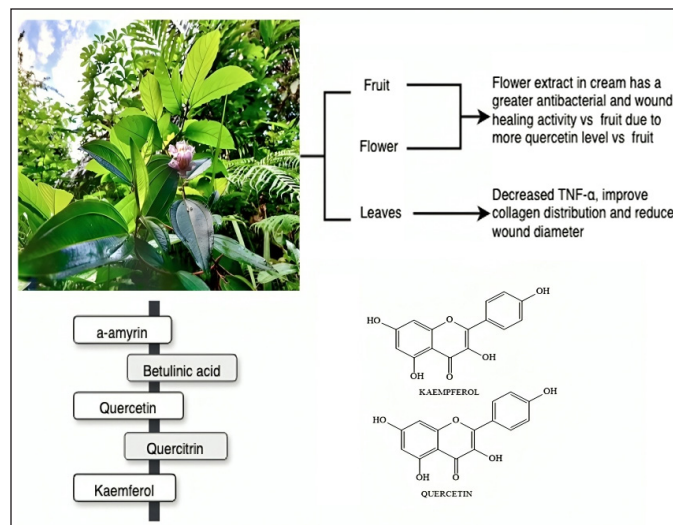


Figure 14. Bioactive and pharmacological target of *M. malabathricum* L. on wound healing.

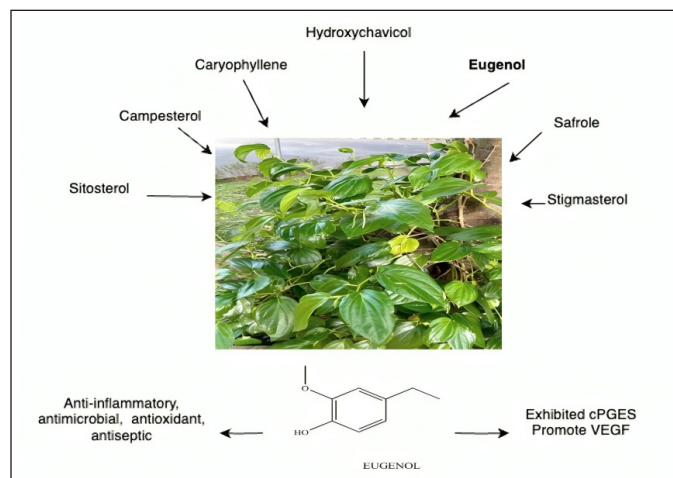


Figure 15. Bioactive and pharmacological target of *P. betle* L. on wound healing.

wound area in rat feet [139]. Forming these extracts into a gel reduced TNF- α levels, wound width, and enhanced collagen distribution [140]. The inhibitory effects of *M. malabathricum* compounds on platelet-activating factor receptor binding with rabbit platelets revealed that a-amyrin and betulinic acid had considerable inhibitory effects of 67.3% and 64.3%, respectively. Furthermore, quercetin and quercitrin appeared to have moderate inhibitory action, with 57.% and 45.4% inhibition percentages, respectively [141].

Thin-layer chromatography was used to analyze extracts of *M. malabathricum* from various geographical regions in Indonesia, and it showed that the predominant ingredients were phenolic compounds, such as quercetin, quercitrin, and kaempferol. An acetone extract included several tannins, including strictinin and casuarinin. Quercetin and quercitrin were revealed as possible antioxidant agents, while kaempferol

was found to have wound-healing effects for diabetes excisional and nondiabetic incisional wounds [142].

Piper betle L

Piper betle L., known as Sirih in Indonesia, is a widely recognized perennial trailing plant in the Piperaceae family. Indigenous to central and eastern Peninsular Malaysia, it is distributed across East Africa and many tropical Asian countries. *Piper betle* has been extensively studied for its diverse phytochemical constituents, exhibiting significant biological activity. The essential oil extracted from betel leaves primarily contains phenols and terpenes. Preliminary phytochemical analysis of aqueous and methanol extracts from betel leaves has identified the presence of alkaloids, flavonoids, tannins, sterols, phenols, glycosides, saponins, and terpenoids [143].

The phytochemical compounds present in *P. betle* (Fig. 15) have various pharmacological activities, such as anticancer, antitumor, and antiproliferative effects, as well as analgesic, anti-inflammatory, antinociceptive, antidepressant, anti-anxiety, anticholinesterase, anti-Alzheimer, hepatoprotective, antioxidant, immunomodulatory, cardioprotective, and wound-healing properties [143]. Limited documentation is available on the wound-healing effects of *P. betle*. Several studies have reported that extracts of *P. betle* stimulate the growth of fibroblasts, reduce the activity of 11β hydroxysteroid dehydrogenase-1, enhance collagen production, prevent the formation of ROS, and encourage the proliferation of NIH-3T3 cells [144,145]. An ethanolic extract of *P. betle* leaves was shown to contain hydroxychavicol, eugenol, safrole, caryophyllene, caryophyllene oxide, silicone oil, campestral, stigmasterol, vitamin E, and sitosterol, with the significant component being eugenol, which is responsible for the flavor and aroma of the leaves [146]. Essential oils obtained from plants are frequently applied to treat wounds.

Eugenol is recognized for having antimicrobial properties due to its distinctive anti-inflammatory, antimicrobial, antifungal, antioxidant, antiseptic, and antiallergic characteristics [147]. Combining eugenol-loaded nanogel and PCL/C nanofiber-enhanced wound healing [148]. Eugenol-loaded cellulose–chitosan hydrogels promote fibroblast cell motility. *In vitro* scratch tests showed that this treatment lowered cPGES expression, limiting cell inflammatory responses and enhancing VEGF expression, which is responsible for a cascade of events involving angiogenesis and wound-healing processes [149].

Zingiber officinale L.

Zingiber officinale (ginger) is a spice, herb, and edible plant known as Jahe in Indonesia. *Zingiber officinale* is an herbaceous perennial represented by over 70 species endemic to Southeast Asia and develops tall (1 m) annual pseudostems (false stems composed of coiled leaves) with narrow leaf blades. Flowers with pale yellow petals and purple margins emerge directly from the rhizome on independent stalks in the inflorescences [150]. The rhizome of *Z. officinale* contains zingerone, gingerols, shogaol, flavonoids, diterpenoid, and sesquiterpenoids, of which zingerone, shogaol, and gingerols are the most potent substances with gingerols and shogaol considered to be responsible for the anti-inflammatory properties of ginger (Fig. 16). The main pharmacologically active compound found in ginger is 6-gingerol [151,152].

Ginger extract has inhibitory effects on lipid peroxidation and enhances the intracellular functions of antioxidant enzymes, including SOD, CAT, and GPX. The ginger extract also improved the plasma antioxidant capacity and decreased lipid peroxidation in diabetic rats [153]. Ginger extract influences cell migration and heat tolerance in mouse fibroblast cells, phosphorylate protein kinase B

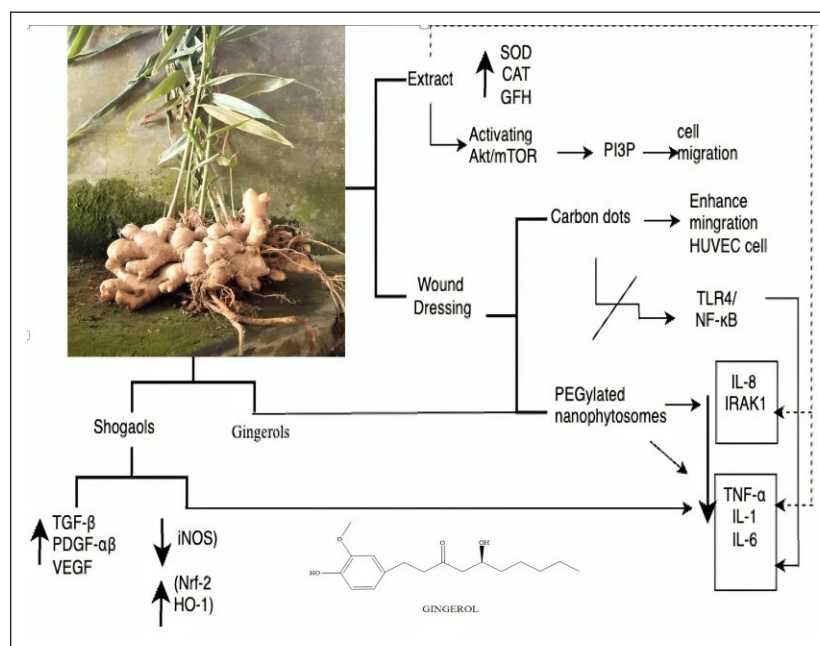


Figure 16. Bioactive and pharmacological target of *Z. officinale* on wound healing.

(AKT) and mTOR, and activates the Akt/mTOR-signaling pathway. Ginger extract also increased phosphatidylinositol 3-phosphate levels in cells, which regulated cell morphology and stimulated cell migration [154]. Ginger extract-loaded hydrogel films significantly increased fibroblast proliferation, granulation tissue formation, collagen remodeling, and reepithelialization after 16 days of treatment [155].

To improve the practical use of ginger extract for clinical application, this has been incorporated into various DDSs. *Zingiber officinale* carbon dots can prevent the overexpression of proinflammatory mediators such as TNF- α , IL-1 β , IL-6, and NO by blocking the phosphorylation pathway of TLR4/NF- κ B in RAW264.7 cells, as well as increasing the migratory capacity of HUVEC cells [156]. The crude extract and 6-gingerol, as well as PEGylated nanophytosomes loaded with 6-gingerol, had a significant effect on downregulating TNF- α , IL-1 β , IL-6, IL-8, and IRAK1 inflammation factors in MDA-MB-231 breast cancer cell lines cells. In addition, they improved the ability of human periodontal fibroblast cells to heal wounds [152].

Additional *in vitro* research has shown that an active compound in ginger, 10-shogaol, stimulated the proliferation of human dermal fibroblasts and normal epidermal keratinocytes and increased the production of TGF- β , PDGF- $\alpha\beta$, and VEGF growth factors in both cell lines; furthermore, in 12–24 hours, the fibroblasts and keratinocytes moved more quickly than in the vehicle control group in the wound-healing assay [139,157]. Poly(lactic-co-glycolic acid) PLGA/PLA-polyethylene glycol-folic acid-PEG-FA nanoparticles loaded with 6-shogaol (NPs-PEG-FA/6-shogaol) accelerated wound repair of colitis in DDS-treated mice, by regulating the expression levels of proinflammatory TNF- α , IL-6, IL-1 β , and iNOS and anti-inflammatory Nrf-2 and HO-1 factors [158].

Herbal active compounds and molecular targets on wound healing

Research on wound healing now primarily addresses chronic or severe wounds, such as diabetic ulcers, burns, deep wounds, and infected wounds, which require extended time and substantial costs for healing. Several bioactive studies have explored the wound-healing potential of eleven medicinal plants traditionally used in Indonesia. These studies have investigated crude extracts, fractionations, and active compounds in various formulations, including simple ointments, nanoparticle formulations, AgNPs, electrospun nanofibers, and hydrogel films.

Although *in vitro* or *in vivo* tests have yielded experimental data for each listed plant, not every mechanism of action has been confirmed. Nevertheless, well-characterized compounds that have been demonstrated to have properties that promote wound healing include luteolin, quercetin, kaempferol [71,115], allicin [76], aloin, emodin, and b-sitosterol [82], ursolic acid [99], a-amyrin, betulinic, quercetin, quercitrin [141], curcumin [103], curcain, curcacycline A and B, jatrophidin, curcusone B, jatrophone, stigmasterol [126–128], lantadene [130] eugenol [147], and gingerols and shogaol [151,152].

Usually, each wound heals by a process that includes hemostasis, inflammation, proliferation, maturation, and remodeling. Plants used in traditional medicine share many of the same biological targets and pathways critical in the mammalian wound-healing cascade. The inflammation and proliferation phases are essential components of wound healing. Medicinal plants can target mitogenic pathways such as AKT, phosphoinositide 3-kinase, and smooth muscle actin (SMA) [102], as well as the proinflammatory NF- κ B pathway [152], which involves caspases, ILs, TNF- α , TGF- β 1, and cyclins [88,159]. The angiogenesis pathway includes VEGF, the ECM synthesis includes MMPs, and differentiation pathways include α -SMA [92,98].

Full-thickness, burn, diabetic, and infection wounds are wound models representing chronic wounds characterized by high levels of proinflammatory mediators and infection. Targets in inflammatory phases have been discovered, including CD8⁺ lymphocytes, ROS, IL-1, TNF- α , IL-6, IL-10, COX-1, and COX-2, and cells that function inside the wound tissue, such as macrophages-1, neutrophils, and platelets [160]. The content of herbal antioxidants can reduce the duration of the inflammatory phase in chronic wounds. Furthermore, antibacterial activities to the most common bacteria found in skin wound infections, such as *S. aureus*, help synergize the wound-healing activity in this phase [107,161].

Antioxidants from flavonoids and terpenes suppress the action of proteases and ROS formed from the accumulation of neutrophils in the wound area. They also protect SOD, CAT, and GPx from oxidative damage [162]. At the transition from the inflammatory phase to the proliferation phase, T lymphocytes, particularly CD4⁺ cells, play a crucial role in wound healing by secreting lymphokines that stimulate fibroblasts, which act as anti-inflammatory agents, and activate factors in major histocompatibility complex class II [84].

Angiogenesis occurs in the proliferation phase to compensate for vascular injury and accelerate the healing of wounds. CD31, also known as PECAM-1 and integrin 11, plays a role in endothelial cell migration and angiogenesis [84]. Together with growth factors such as VEGF, TGF-1, EFG, and HIF-1 α , CD31 is involved in fibroblast proliferation and the formation of new blood vessels via angiogenesis [105,111,155]. Integrins have also been identified as essential in reepithelialization by enhancing keratinocyte proliferation and governing cell migration via the ECM.

Fibroblasts play a vital role in wound healing by preventing fibrin clot formation, producing the ECM, and building collagen structures. The migration and proliferation of fibroblasts in the wound area significantly impact the rate of wound healing. Collagen produced by fibroblasts binds the wound and influences the reepithelialization process, ultimately facilitating wound closure. During the final remodeling phase, collagen III is degraded and replaced by collagen I, whereas the epithelium is formed to complete the wound closure [8].

Strenght and limitations of the study

The ethnopharmacology and bioevidence of several medicinal plants in Indonesia for treating wound healing were clarified by this scoping review. This is the first and most recent

scoping review regarding the active ingredient and molecular target of herbal plants used to treat wounds in Indonesia. In addition, it showed that most locals know the benefits of medicinal plants and commonly use traditional methods to treat wounds. It is important to note several limitations when presenting the review's findings. The limitation is that while *in vitro* and *in vivo* studies have provided experimental data for each plant, the mechanisms of action for many of these plants remain unconfirmed. In addition, there are few clinical studies to support the findings from *in vitro* and *in vivo* preclinical investigations; third, there is a lack of toxicity and safety studies to confirm the efficacy of these treatments. Furthermore, most research omitted information about the formulation's composition, standardization, and preparation methods.

CONCLUSION

The incidence of skin injuries continues to increase globally, leading to substantial annual financial costs. In response, we assessed Indonesia's pharmacopeia and traditional medicine for plants recognized for their medicinal properties. Each botanical investigated contains chemical compounds linked to various pharmacological effects, including antimicrobial, anti-inflammatory, and antioxidant properties. *In vitro* and *in vivo* studies have demonstrated that medicinal plant extracts and their purified active components hold significant potential as wound-healing treatments due to their safety, diverse modes of action, and antibacterial activity. Novel wound-dressing formulations offer several advantages over standard dressings, addressing limitations of natural materials such as solubility and restricted activity at the wound site. Further studies should focus on elucidating the mechanisms of action of the most promising natural substances, particularly their effects on cell-surface receptors, to enhance their bioavailability and minimize adverse effects in wound healing.

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AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

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CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

All data generated and analyzed are included in this research article.

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SUPPLEMENTARY MATERIAL

The supplementary material can be accessed at the link here: [https://japsonline.com/admin/php/uploads/4530_pdf.pdf]