



A review of the *in vitro* and *in vivo* anti-inflammatory and wound-healing activities of medicinal plants

[Una revisión de las actividades anti-inflamatorias y cicatrizantes *in vitro* e *in vivo* de las plantas medicinales]

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Abstract

Context: Inflammation is a natural response to injury or infection. However, if prolonged, it leads to further damage and severe conditions like cardiovascular diseases and diabetes mellitus. Medicinal plants, known for their bioactive compounds, such as polyphenols, flavonoids, and anthocyanins, exhibit anti-inflammatory, antioxidant, and low toxicity properties.

Aims: To thoroughly investigate the anti-inflammatory and wound-healing effects of various medicinal plants by analyzing their bioactive compounds and mechanisms of action.

Methods: A systematic search of PubMed (2014–2024) was conducted using “plant AND anti-inflammation AND wound healing.” Studies were screened by PRISMA guidelines; inclusion required original *in vitro* or *in vivo* data on the anti-inflammatory or wound-healing effect of the plant extract.

Results: Of 970 identified articles, 33 met inclusion criteria. These studies were analyzed for plant-derived inhibition of inflammatory mediators and promotion of wound closure via fibroblast migration and collagen synthesis, and 35 plant species were found to have anti-inflammatory and wound-healing activities. The results show that *Curcuma mangga*, *Solanum diploconos*, and *Curcuma longa* are among the most effective plants, demonstrating significant inhibition of nitric oxide (NO) production, reduction of pro-inflammatory cytokines, and acceleration of fibroblast proliferation. In wound healing assays, these plants promoted faster closure and improved collagen deposition, contributing to efficient tissue regeneration. Comparatively, they provided the best results at lower concentrations and shorter healing times than other plants.

Conclusions: *Curcuma mangga*, *Solanum diploconos*, and *Curcuma longa* may serve as promising candidates for further pharmaceutical development for anti-inflammatory and wound-healing pharmaceuticals; nevertheless, skin irritation and toxicity tests will need to be performed to guarantee their safety.

Keywords: adjunctive therapy; antioxidants; curcumin; plant-based therapy; *Zingiberaceae*.

Resumen

Contexto: La inflamación es una respuesta natural a una lesión o infección. Sin embargo, si se prolonga, puede provocar mayores daños y afecciones graves como enfermedades cardiovasculares y diabetes mellitus. Las plantas medicinales, conocidas por sus compuestos bioactivos, como polifenoles, flavonoides y antocianinas, presentan propiedades antiinflamatorias, antioxidantes y de baja toxicidad.

Objetivos: Investigar a fondo los efectos antiinflamatorios y cicatrizantes de diversas plantas medicinales mediante el análisis de sus compuestos bioactivos y mecanismos de acción.

Métodos: Se realizó una búsqueda sistemática en PubMed (2014-2024) utilizando la etiqueta "planta, antiinflamación y cicatrización de heridas". Los estudios se seleccionaron según las directrices PRISMA; la inclusión requirió datos originales *in vitro* o *in vivo* sobre el efecto antiinflamatorio o cicatrizante del extracto de la planta.

Resultados: De los 970 artículos identificados, 33 cumplieron los criterios de inclusión. Estos estudios se analizaron para determinar la inhibición de mediadores inflamatorios derivados de plantas y la promoción del cierre de heridas mediante la migración de fibroblastos y la síntesis de colágeno. Se encontró que 35 especies de plantas poseen actividades antiinflamatorias y cicatrizantes. Los resultados muestran que *Curcuma mangga*, *Solanum diploconos* y *Curcuma longa* se encuentran entre las plantas más eficaces, demostrando una inhibición significativa de la producción de óxido nítrico (NO), una reducción de las citocinas proinflamatorias y una aceleración de la proliferación de fibroblastos. En ensayos de cicatrización de heridas, estas plantas promovieron un cierre más rápido y mejoraron la deposición de colágeno, contribuyendo a una regeneración tisular eficiente. Comparativamente, proporcionaron los mejores resultados a concentraciones más bajas y tiempos de cicatrización más cortos que otras plantas.

Conclusiones: *Curcuma mangga*, *Solanum diploconos* y *Curcuma longa* podrían ser candidatos prometedores para el desarrollo de fármacos antiinflamatorios y cicatrizantes; sin embargo, será necesario realizar pruebas de irritación cutánea y toxicidad para garantizar su seguridad.

Palabras Clave: antioxidantes; curcumina; terapia adyuvante; terapia basada en plantas; *Zingiberaceae*.

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Abbreviations: BDMC: Bisdemethoxycurcumin; DMC: Demethoxycurcumin; GC-MS: Gas Chromatography-Mass Spectrometry; HPLC: High-Performance Liquid Chromatography; HPLC-DAD: High-Performance Liquid Chromatography-Diode Array Detection; HPLC-GC: High-Performance Liquid Chromatography-Gas Chromatography; LC-NMR/MS: Liquid Chromatography-Nuclear Magnetic Resonance/Mass Spectroscopy; NMR: Nuclear Magnetic Resonance; TLC: Thin-Layer Chromatography; UHPLC-ESI-MS/MS: Ultra-High-Performance Liquid Chromatography coupled with Electrospray Ionization Tandem Mass Spectrometry; UV-Vis: Ultraviolet Visible.

INTRODUCTION

Inflammation is the natural response of the body to injury or infection, aiming at protecting damaged tissue and initiating the healing process. When harmful stimuli, such as pathogens, damaged cells, toxic compounds, or bacterial infection, attack the body eventually works to minimize the injury by initiating a series of cellular and molecular events. These mitigation events contribute to the maintenance of tissue homeostasis. Prolonged or dysregulated inflammation contributes to chronic disorders such as cardiovascular disease and diabetes mellitus (Chen et al., 2018). Wound healing is one of the recovery processes of inflammation. There is an established association between acute inflammation and a successful tissue healing process. However, prolonged or excessive inflammation can slow healing and lead to complications, such as excessive scar tissue formation (Soliman and Barreda, 2022). The wound healing process consists of proliferation and remodeling. In the inflammatory stage, neutrophils and macrophages clear the damaged tissue and fight microorganisms that cause infection. In the proliferation stage, fibroblasts form new tissue, while in the remodeling stage, the tissue is strengthened (Bass et al., 2021; Wilkinson and Hardman, 2020). When the cells have repaired the wound and are no longer needed, they are removed by apoptosis. The remodeling stage is when collagen is converted from type III to type I, and the wound fully closes (Bass et al., 2021).

Inflammation can be influenced by factors such as poor diet, low physical activity, psychological stress, and exposure to industrial pollutants, all of which are increasing rapidly in urbanizing regions, particularly in Asian countries. The prevalence of inflammatory diseases in Asia varies by region and disease type (Furman et al., 2019). For example, the incidence of inflammatory bowel disease (IBD) in Indonesia was reported to be approximately 0.77/100,000 people/year, which was lower than in Singapore (1.14/100,000 people/year) or almost the same as Malaysia (0.76/100,000 people/year) (Aniwan et al., 2022). Therefore, safe and effective anti-inflammatory agents are needed to control the inflammatory process.

Edible and medicinal plants were reported for their antioxidant and anti-inflammatory activities, thus becoming an attractive alternative due to their

natural properties and lower toxicity profile compared to synthetic drugs (Nardi et al., 2016; Wahyuni et al., 2022; 2024). Some medicinal plants accelerate wound healing stages through anti-inflammatory mechanisms and stimulation of collagen synthesis, such as polysaccharides and anthraquinones stabilized lysosomal membrane (Paul et al., 2021), flavonoids inhibit protein denaturation and hemolysis (Bouhlali et al., 2016; Djuichou et al., 2019). Antioxidants in medicinal plants play an important role in wound healing, as they reduce oxidative stress that can damage new cells and tissues (Comino-Sanz et al., 2021). For example, *Camellia sinensis* (green tea) contains polyphenols that have been confirmed to have antioxidant and anti-inflammatory properties, helping to reduce inflammation and speed up healing (Chatterjee et al., 2012).

Emerging evidence supports the therapeutic potential of plant-derived bioactives, flavonoids, tannins, and terpenoids, in modulating inflammation and accelerating tissue repair (Roy et al., 2022). However, translation to clinical use requires rigorous toxicity and pharmacokinetic evaluation. Thus, further exploration of medicinal plants may lead to new therapies that are safer, more effective, and sustainable in addressing various health problems related to inflammation and wound healing. Considering this, this review aims to provide insights into medicinal plants with anti-inflammatory and wound-healing activities. The mechanism by which secondary metabolites alleviate diseases is also described. Various studies have demonstrated the potential of plant extracts in anti-inflammatory and wound healing activities; however, findings remain scattered and vary in methodology, plant species, and evaluation parameters. The mechanisms of action and toxicity have also not been systematically summarized.

This systematic review is necessary to integrate the latest evidence, identify the most promising plants, explain the mechanisms of action, and assess their toxicological aspects. Previous reviews have been limited or have not considered safety, so this review is expected to provide a more comprehensive and relevant contribution.

This review aims to identify medicinal plant species with documented anti-inflammatory and wound-healing effects, emphasizing mechanisms of action and comparative efficacy.

MATERIAL AND METHODS

This review was done by following the PRISMA guidelines (Page et al., 2021).

Eligibility and exclusion criteria (PICOS)

All *in vitro* and *in vivo* studies investigating the pharmacological activity and plant-based medications were included. All studies were included regardless of comparison/control group type. Plant parts, solvents, extraction methods, study design, dose, and concentration ranges were all considered eligible in the study. During the article selection process, only articles written in English were considered eligible.

The following list highlights the PICOS criteria used for study inclusion and exclusion in the current review:

- **P (Population):** cell models (*in vitro*) and animal models (*in vivo*) assessing the anti-inflammatory and/or wound-healing activities of plants.
- **I (Intervention):** any plant extracts as a single herb or in combination with other plants.
- **C (Comparison):** any type of comparison (normal control, negative control, and positive control using various non-steroidal anti-inflammatory drugs).
- **O (Outcome):** anti-inflammatory and/or wound-healing activities, mechanisms of action of the plant extracts/phytochemicals,

and safety (acute or subchronic toxicity).

- **S (Study Design):** any form of experimental design, including *in vitro* and *in vivo*.

Information sources

The articles investigating the anti-inflammatory and/or wound-healing activities of plants (*in vitro* and *in vivo* studies) were systematically searched in the PubMed database using the keywords combined with Boolean operators such as "Plant AND Anti-Inflammation AND Wound Healing".

Search strategy

The search was limited to free full-text articles published from 2014 to 2024, and the detailed strategy and results are depicted in Fig. 1. An additional search was conducted on Google, without restricting the year of publication, when required.

Selection process

To identify all relevant studies, the independent screening was performed by three authors on study screening and selection, such as title and abstract screening, and full-text paper. The titles and the abstracts of the articles were further screened for their relevance to the topic of this study. Additional relevant studies were obtained from the citations in the selected articles. Disagreements were then discussed until a consensus was found. A flow diagram (Fig. 1) details the research selection and data collection process.

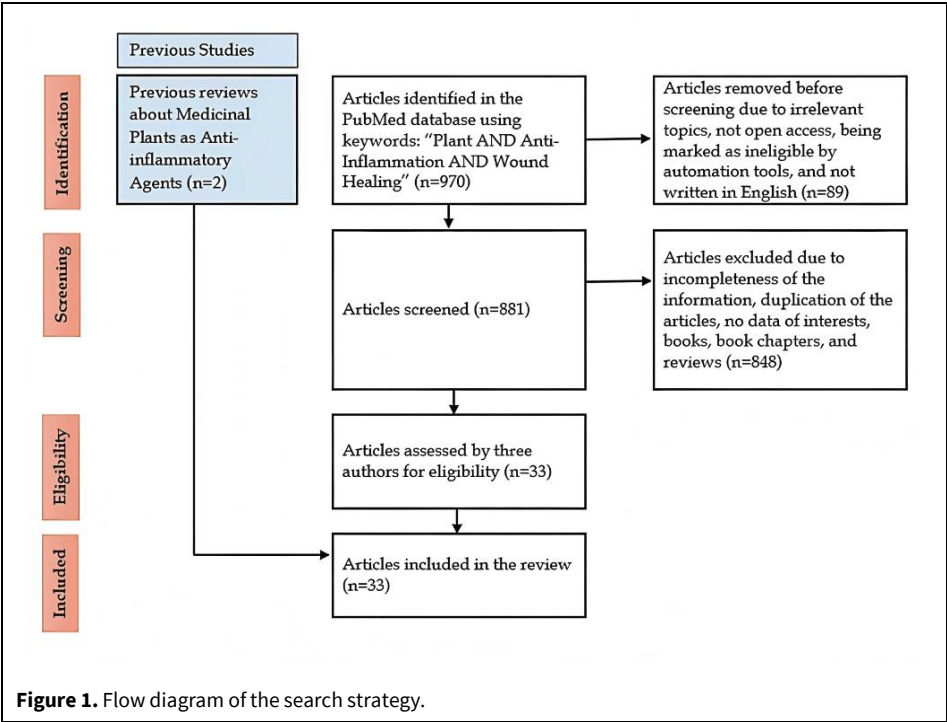


Figure 1. Flow diagram of the search strategy.

Data collection process

Data from included articles were manually retrieved, compiled in tables, and critically appraised in Tables 1 and 2. The results were compared to draw conclusions.

Study of risk of bias assessment

Risk of bias in studies may occur due to different study designs, such as different cells and reagent kits in the *in vitro* studies and different animal models, inducers, and length of study in the *in vivo* studies, and/or incomplete data, among others (Page et al., 2023). Thus, a minimum of two authors thoroughly appraised the studies to achieve the conclusion.

Effect measures

The effect size includes changes in inflammatory biomarker levels (e.g., TNF- α , IL-6, COX-2), epithelialization velocity, and increased tissue regeneration, reported in quantitative terms such as percentage inhibition or healing time. This review included only published *in vitro* and *in vivo* studies with declared ethical approvals.

Synthesis methods

Data synthesis was performed systematically by grouping results based on test model, plant type, and outcome.

Reporting bias assessment

Reporting bias was evaluated by comparing the objectives, methods, and results presented in each study.

Certainty assessment

The certainty of evidence was assessed by considering the risk of bias, the consistency of results across studies, the suitability of the experimental model context to clinical application, and the accuracy and consistency of the reported data.

Summary of measures and synthesis of results

The collected evidence was discussed by all authors to arrive at a critical qualitative synthesis. Disagreements between reviewers were resolved by consensus or third-party arbitration.

RESULTS AND DISCUSSION

Results are summarized in two tables: Table 1 presents *in vitro* and *in vivo* studies of anti-inflammatory and wound healing activities of plants, and Table 2

summarizes the list of plants with anti-inflammatory and wound healing mechanisms.

The mechanism of action of each class of plants that have potential as anti-inflammatory and wound healing agents.

Anti-inflammatory activity

Inhibition of nitric oxide (NO) production

In the development of anti-inflammatory agents, the effectiveness of medicinal plants in inhibiting NO production varies widely depending on the secondary compounds contained in them. *Crassocephalum crepidioides* and *Kaempferia marginata* showed higher effectiveness in inhibiting NO production compared to other plants. *Crassocephalum crepidioides* resulted in NO production inhibition of up to 91.4% at a dose of 125 units (Thao, 2020). This plant contains phenolic compounds and flavonoids that act as anti-inflammatories, strengthening its potential use in inflammation therapy (Adegbola et al., 2017). *Kaempferia marginata* showed the lowest IC₅₀ value of 12.50 $\mu\text{g/mL}$, making it one of the most effective plants (Muthachan and Tewtrakul, 2019). The active compounds are desmethoxycurcumin and curcuminoids, which contribute to inhibiting NO production (Khairy et al., 2023).

Metabolites play a role are flavonoids found in *Crassocephalum crepidioides*, *Dioscorea bulbifera*, and *Euphorbia hirta*. The mechanism of flavonoids inhibits the enzyme NO synthase (NOS), which is responsible for the synthesis of NO from L-arginine. By reducing NOS activity, NO production is reduced, thereby reducing inflammation (Luiking et al., 2010). Another secondary metabolite is curcumin and its derivatives found in *Curcuma mango* and *Kaempferia marginata*. The mechanism of curcumin reduces NOS gene expression and increases antioxidant activity, which helps neutralize free radicals and reduce inflammation (Jakubczyk et al., 2020). Phenolic compounds are secondary metabolites that also play a role, found in *Solanum diploconos* and *Thymus sipyleus*. The mechanism of phenolic compounds such as caffeic acid and rosmarinic acid functions as an NOS inhibitor and reduces the formation of free radicals, which has an impact on reducing NO production (Silva and Lopes, 2020). Terpenoids are found in *Streptocaulon juvenas* and *Euphorbia hirta*. The mechanism of terpenoids can modulate inflammatory signaling pathways, including inhibition of the transcription factor NF- κB , which plays a role in the regulation of NOS expression (Guo et al., 2024).

Table 1. *In vitro* and *in vivo* studies of anti-inflammatory and wound healing activities of plants.

Species, plant origin, year sampled, extraction method, solvent	Analysis of secondary metabolites	Characteristics of the animals and source	Anti-inflammatory test method, results, and statistical analysis	Wound healing test method, results, and statistical analysis	Mechanism and safety	Reference
<i>Achillea asiatica</i> Serg. perennial herbs were collected in Mongolia, in 2017. The herbs were extracted using ethanol, and the solvent was evaporated under reduced pressure.	Six compounds namely, chlorogenic acid, schaftoside, quercetin-3-O-arabinosyl, apigenin-7-O-glucoside, luteolin, and apigenin, were identified using HPLC and LC-NMR/MS.	Sprague-Dawley rats, 7 weeks old, were obtained in Korea. The gender and weight were not described.	<i>In vitro</i> study in RAW264.7 cells and Hs68 fibroblasts. In RAW 264.7 and Hs68 cells, 100 µg/mL <i>Achillea asiatica</i> extract inhibited nitric oxide and PGE₂ production by >50%, indicating robust <i>in vitro</i> anti-inflammatory activity. Luteolin and apigenin isolated from the fraction also significantly reduced the production of these mediators. The ethanol extract of <i>A. asiatica</i> reduced NO and PGE2 release and mRNA expression of inflammatory cytokines in RAW 264.7 macrophages, reflecting anti-inflammatory activity.	<i>In vivo</i> study using linear incision wound model testing in SD rats. The rats were divided into three groups: - Control group (treated with phosphate-buffered saline, PBS). - Positive control (treated with 3% <i>Centella asiatica</i> extract). - Treatment group (treated with 3% <i>Achillea asiatica</i> extract). The treatment significantly increased the wound closure rate starting from 8 days and reduced the wound area by approximately 50%, compared to 60% in the positive control-treated group. Treatment with extract of <i>A. asiatica</i> significantly increased the wound closure rate and improved normal tissue structure reflecting wound healing activity, as shown by histological analysis	The mechanism of toxicity was not described.	(Dorjsembe et al., 2017)
<i>Aloe megalacantha</i> leaf sap (latex) was collected in Ethiopia, in 2018. The extraction method was not described. The latex was dried in open air for 2–4 days, yielding a dark brown powder. Specific evaporation temperature was not described.	Secondary metabolites were not described.	Swiss albino male and female mice, 6–8 weeks old, 25–30 g, were obtained in Ethiopia. Sprague Dawley male and female rats, 3–4 months old, 200–300 g, were obtained in Ethiopia.	<i>In vivo</i> study using inhibition of carrageenan-induced paw edema in rats. The rats were divided into five groups: - Control group: Treated with Tween 80 (2%). - Positive control: Treated with indomethacin (10 mg/kg). - Treatment groups: Treated with 200 mg/kg, 400 mg/kg, and 600 mg/kg of leaf latex. Significant reduction of inflammation was observed at medium latex dose (400 mg/kg) (p<0.01) and high latex dose (600 mg/kg) (p<0.001) compared to the negative control group at 3 hours post carrageenan administration, reflecting anti-inflammatory activity.	<i>In vivo</i> study using excision and incision wound models in mice. The mice were divided into four groups: - Control group: Treated with simple ointment (negative control). - Positive control: Treated with 0.2% (w/v) nitrofurazone. - Treatment groups: Treated with 5% (w/w) and 10% (w/w) latex ointment Significant wound contraction compared to the control group. On day 13, wounds treated with 5% (w/b), 10% (w/b) latex ointment, and standard drug closed significantly by 100%, 99.27%, and 99.42, respectively. The percentage increase in wound-breaking strength of animals treated with 5% (w/b), 10% (w/b) latex ointment, and 0.2% nitrofurazone was 77.81%, 74.47%, and 71.78%, respectively. Both 5% and 10% latex ointments significantly increased wound contraction rates and reduced epithelialization time compared to the control (p<0.05) in the excision model. For the incision model, the latex increased the breaking strength of healed wounds significantly (p<0.001). The study reflects wound healing activity.	The mechanism of toxicity was not described.	(Gebremeskel et al., 2018)

Table 1. *In vitro* and *in vivo* studies of anti-inflammatory and wound healing activities of plants (continued...)

Species, plant origin, year sampled, extraction method, solvent	Analysis of secondary metabolites	Characteristics of the animals and source	Anti-inflammatory test method, results, and statistical analysis	Wound healing test method, results, and statistical analysis	Mechanism and safety	Reference
<i>Aloe trigonantha</i> Leaf sap (made in ointment form) was collected in Ethiopia, the year of the collection was not described. The extraction method and solvent evaporation were not described. The plant gel was dried using a lyophilizer under cold vacuum conditions.	Four compounds, namely, flavonoids, glycosides, phenols, and tannins, were identified using qualitative phytochemical screening tests.	Wistar albino both male and female rats, 6–8 weeks, 200–250 g, were obtained in Ethiopia.	<i>In vivo</i> study using two models using rats: - Xylene-induced ear edema model. - Cotton pellet-induced granuloma model. The rats were divided into five groups for both models: - Negative control: Distilled water (10 mL/kg). - Positive control: Indomethacin (10 mg/kg). - Treatment groups: Doses of 100 mg/kg, 200 mg/kg, and 400 mg/kg of <i>Aloe trigonantha</i> leaf gel. In inhibition of xylene-induced ear edema model, the weight of ear edema was calculated from the difference between the weight of the right ear and the weight of the left ear and then obtained a percentage; Inhibition of inflammation based on concentration, the highest dose (41.5%) showed inhibition of inflammation comparable to indomethacin (42.6%) and showed a significant effect compared to the negative control group ($p<0.05$). The 200 mg/kg dose also significantly inhibited inflammation by inhibiting ear edema ($p<0.05$) compared to the negative control group. In the cotton pellet-induced granuloma model, granuloma formation was reduced in a dose-dependent manner, with 38.6% inhibition at the highest dose. The ointment of <i>A. trigonantha</i> inhibited inflammation by inhibiting ear edema and reduced granuloma formation, reflecting anti-inflammatory activity.	<i>In vivo</i> study using excision and incision wound models in rats. The rats were divided into four groups: - Negative control: Simple ointment (no active ingredient). - Positive control: Nitrofurazone ointment (0.2%). - Treatment groups: 5% (w/w) and 10% (w/w) <i>A. trigonantha</i> gel ointments. Excision and incision wound measurement model testing; the 5% (w/b) ointment-treated group also showed a significant (12.6%) decrease in epithelialization period compared to the control group with the percentage of longer period/number of days required for epithelialization slightly lower than 10%. Tensile strength was significantly increased by approximately 26.5%, 37.6%, and 38.3% ($P<0.05$), respectively, with 5% gel ointment, 10% gel ointment, and 0.2% nitrofurazone ointment. Gel ointment significantly increased wound contraction reduced epithelialization time, and increased tensile strength, reflecting wound healing activity.	The mechanism of toxicity was not described.	(Tazeze et al., 2021)
<i>Argemone mexicana</i> L. fruits were collected in Northwest Ethiopia, in 2022 The fruits were extracted using n-hexane, ethyl acetate, and distilled water with maceration method and the solvent was evaporated at 40°C.	Seven compounds namely, alkaloids, saponins, tannins, glycosides, terpenoids, steroids, and flavonoids, were identified using qualitative phytochemical screening tests.	Wistar albino both male and female rats, 6–8 weeks, 200–250 g, were obtained in Ethiopia.	<i>In vivo</i> study using carrageenan-induced paw edema and cotton pellet-induced granuloma models in rats. The rats were divided into twelve groups for both models: - Negative control: 2% Tween 80. - Positive control: Aspirin (200 mg/kg) and dexamethasone (0.5 mg/kg). - Test Groups: 100, 200, and 400 mg/kg of aqueous (AF); 100, 200, and 400 mg/kg of n-hexane (n-HF); and 100, 200, and 400 mg/kg of ethyl acetate fractions (EAF). The ethyl acetate fraction (EAF) showed the most significant anti-inflammatory activity with a maximum inhibition of paw edema (61.41%; $p<0.01$) and exudate suppression (38.09%; $p<0.01$), at the tested dose of 400 mg/kg. Cotton pellet granuloma mass formation (53.47%; $p<0.01$). The fraction of <i>A. mexicana</i> inhibition paw edema and suppresses exudate, reflecting anti-inflammatory activity.	<i>In vivo</i> study using excision wound model and incision wound model in rats. The rats were divided into eight groups for both models: - Negative control: Simple ointment. - Positive control: Moist-Exposed Burn Ointment (MEBO). - Test groups: 5% and 10% of aqueous (AF); 5% and 10% of n-hexane (n-HF); and 5% and 10% of ethyl acetate fractions (EAF) Significant tensile strength (55%; $p<0.01$) and (81.10%; $p<0.01$) at the tested doses of 5% and 10% w/w ointment which were comparable to burn ointment exposed to moisture. The fraction of <i>A. mexicana</i> reduced the epithelialization period and enhanced tensile strength, reflecting wound healing activity.	The mechanism of toxicity was not described.	(Mengie Ayele et al., 2022)

Table 1. *In vitro* and *in vivo* studies of anti-inflammatory and wound healing activities of plants (continued...)

Species, plant origin, year sampled, extraction method, solvent	Analysis of secondary metabolites	Characteristics of the animals and source	Anti-inflammatory test method, results, and statistical analysis	Wound healing test method, results, and statistical analysis	Mechanism and safety	Reference
<i>Artemisia campestris</i> leaves were collected in Tunisia, in 2015. The leaves were extracted using aqueous extract (water used for maceration) and the solvent was evaporated at 40°C.	Four compounds, namely, tannins, polyphenols, flavonoids, and saponosides, were identified using spectrophotometric methods.	Wistar male rats, the age was not described, 250-270 g. The animal sources were in Tunisia.	<i>In vivo</i> study using inhibition of carrageenan-induced leg edema in rats. The rats were divided into three groups: - Negative control: Sterile saline solution. - Positive control: 150 mg/kg acetylsalicylic acid. - Test group: 200 mg/kg aqueous extract of <i>Artemisia campestris</i>, ACAE). After 3 hours of carrageenan injection, leg edema increased to about 93%, but after 7 hours of treatment, the extract showed edema inhibition of 26%, compared with the value of 3 hours of treatment in the same group. The percentage inhibition of standard anti-inflammatory drugs was (55%, 10 mg/kg bw). Histological analysis revealed a reduced density of inflammatory cells in ACAE-treated tissue, reflecting anti-inflammatory activity.	<i>In vivo</i> study using an excision wound model in rats. The rats were divided into four groups: - Negative control: Sterile saline solution. - Glycerol: Dilution matrix for ACAE. - Positive control: CICAFLORA cream. - Test group: aqueous extract of <i>A. campestris</i>, ACAE. Approximately 50% wound contraction was achieved on days 6, 8, 10, and 12. After 12 days, macroscopic assessment showed that the wound area in the extract-treated group had completely healed. Significant improvement in wound healing progression and oxidative stress damage in wound tissues of rats treated with the extract, compared to controls, reflecting wound healing activity.	The mechanism of toxicity was not described.	(Ghlissi et al., 2016b)
<i>Bergia ammannioides</i> Henye ex Roth herbs were collected in Egypt, in 2011. The herbs were extracted using the fractionation method with N-hexane, chloroform, ethyl acetate, and N-butanol saturated with water, and each fraction was concentrated under reduced pressure to give HxFr (45.5 g), ClFr (0.7 g), EtFr (21.4 g), and BuFr (5.8 g). The solvent was evaporated at 40°C.	Eight compounds, namely, β-sitosterol, lupeol, cycloartenol, quercetin, ellagic acid, kaempferol-3-O-α-L-rhamnoside, and quercetin-3-O-α-L-rhamnoside, were identified using TLC and NMR.	Swiss albino male and female mice, the age was not described, 20-25 g. Sprague-Dawley male rats, the age was not described, 130-150 g. The animals were purchased in Egypt.	<i>In vivo</i> study using xylene-induced ear edema model in mice. The mice were divided into six groups: - Negative control: No treatment or vehicle only. - Positive control: Voltaren gel (diclofenac sodium). - Test groups: Ethanol extract (EtOH), n-hexane fraction (HxFr), ethyl acetate fraction (EtFr), and n-butanol fraction (BuFr) EtOH and its fractions (HxFr and EtFr) inhibited topical edema induced by xylene on mouse ears. On the one hand, HxFr showed the highest inhibitory activity of 64.5% so its main component B-sitosterol was also tested and showed the greatest inhibitory action of 83.8%, BuFr showed very weak activity. <i>Bergia ammannioides</i> inhibited topical edema induced by xylene on mouse ears, reflecting anti-inflammatory activity.	<i>In vivo</i> study using excision wound model in rats. The rats were divided into eleven groups: - Normal group: untreated. - Negative control: Simple ointment. - Test groups: Ointments containing 5% and 10% concentrations of EtOH; ointments containing 5% and 10% concentrations of HxFr; ointments containing 5% and 10% concentrations of EtFr, and ointments containing 5% and 10% concentrations of BuFr. - Positive control: Dermazine cream. Ointments formulated from EtOH, HxFr, and EtFr at 5% and 10% concentrations showed significant activity at P<0.01 relative to the control and other fractions tested. The activity was concentration-dependent. HxFr (10% ointment) showed the most prominent activity at 85.62%. <i>Bergia ammannioides</i> increased collagen synthesis was observed in the treated groups, reflecting wound healing activity.	Mechanism of toxicity was not described.	(Ezzat et al., 2016)

Table 1. *In vitro* and *in vivo* studies of anti-inflammatory and wound healing activities of plants (continued...)

Species, plant origin, year sampled, extraction method, solvent	Analysis of secondary metabolites	Characteristics of the animals and source	Anti-inflammatory test method, results, and statistical analysis	Wound healing test method, results, and statistical analysis	Mechanism and safety	Reference
<i>Clematis simensi</i> leaves were collected in Ethiopia, in 2022. The leaves were extracted using maceration (Made ointment preparation) and the solvent was evaporated at 40°C and later solidified at 37°C in an oven	Five compounds, namely, saponins, tannins, terpenoids, flavonoids, and phenols, were identified using qualitative phytochemical screening tests.	Swiss albino male and female mice, 6–8 weeks, 25–30 g. Wistar male and female rats, 4–6 months, 250–350 g. The animals were purchased in Ethiopia.	<i>In vivo</i> study using inhibition of carrageenan-induced paw edema in rats. The rats were divided into five groups: - Negative control: Distilled water. - Positive control: Sspirin 150 mg/kg. - Three extract groups: 100 mg/kg, 200 mg/kg, and 400 mg/kg doses. Significant differences between the low dose (100 mg/kg) and standard treatment were seen at the 2nd hour (p<0.01). The medium dose (200 mg/kg) and standard treatment showed significant differences at the third and fourth hours (p<0.05), while the higher dose (400 mg/kg) showed no statistically significant differences at all measurement periods. <i>C. simensi</i> at 200 mg/kg and 400 mg/kg significantly reduced paw edema compared to the negative control, reflecting anti-inflammatory activity.	<i>In vivo</i> study using excision and incision wound models in mice. The mice were divided into four groups: - Negative control: Simple ointment base. - Positive control: Nitrofurazone 0.2% w/w. - Two treat groups: 5% and 10% concentrations. For the excision model, both 5% and 10% extract ointments significantly enhanced wound contraction (p<0.001) compared to the negative control, achieving complete wound closure by day 18. For the incision model, tensile strength was significantly improved in the 5% and 10% extract groups (p<0.05) compared to the negative control. <i>C. simensi</i> significantly enhanced wound contraction and improved tensile strength, reflecting wound healing activity.	Acute dermal toxicity tests revealed no signs of irritation, inflammation, or adverse effects on the animals.	(Teshome et al., 2022)
<i>Clerodendrum myricoides</i> leaves were collected in Ethiopia, in 2022. The leaves were extracted using the fractionation method, made ointment with a concentration of 5% and 10% b/w) and macerated in 80% methanol, followed by fractionation with n-hexane and ethyl acetate. The solvent was evaporated at 40°C	Three compounds, namely, flavonoids, alkaloids, and tannins, were identified using qualitative phytochemical screening tests.	Swiss albino male and female mice, 6-8 weeks, 25–30 g. The animal source was in Ethiopia.	<i>In vivo</i> study using inhibition of carrageenan-induced paw edema in mice. The mice were divided into five groups: - Negative control: 2% Tween 80. - Positive control: Indomethacin (10 mg/kg). - Three treatment groups: 100 mg/kg, 200 mg/kg, and 400 mg/kg of the plant extract. Significant reduction in paw edema was observed at doses of 200 mg/kg (p<0.05) and 400 mg/kg (p<0.001), with effects comparable to indomethacin in the later stages of inflammation. The maximum percentage of inflammation inhibition was shown in 4 hours by 400 mg/kg extract (44.44%) and standard (50.90%). Extract of <i>C. myricoides</i> at 200 mg/kg and 400 mg/kg significantly reduced paw edema compared to the negative control, reflecting anti-inflammatory activity.	<i>In vivo</i> study using excision, incision, and burn wound models in mice. The mice were divided into four groups: - Negative control: Simple ointment base. - Positive control: Nitrofurazone ointment (0.2% w/w). - Two treatment groups: 5% and 10% extract ointments. Excision Wound Model: 10% extract ointment showed complete wound contraction by day 16, reducing epithelialization significantly (p<0.001). Incision Model: Tensile strength increased significantly in the 10% extract group (p<0.001) compared to controls. Burn Wound Model: 10% extract ointment significantly shortened epithelialization time (p<0.001), with wound contraction rates comparable to nitrofurazone ointment. Extract of <i>C. myricoides</i> reducing epithelialization, increased tensile strength, and shortened epithelialization time, reflecting wound healing activity.	No adverse effects or signs of inflammation, edema, or erythema were observed in acute dermal toxicity tests at a dose of 2000 mg/kg	(Beyna et al., 2024)

Table 1. *In vitro* and *in vivo* studies of anti-inflammatory and wound healing activities of plants (continued...)

Species, plant origin, year sampled, extraction method, solvent	Analysis of secondary metabolites	Characteristics of the animals and source	Anti-inflammatory test method, results, and statistical analysis	Wound healing test method, results, and statistical analysis	Mechanism and safety	Reference
<i>Commiphora guidottii</i> Chiov. ex. Guid essential oils and resins were collected in Ethiopia, in 2010. The oils were extracted using methanol with steam distillation method and the solvent was dried at a temperature not exceeding 40°C	Five compounds, namely, terpenoids, phenolic compounds, flavonoids, steroids, and tannins, were identified using GC-MS to identify essential oil components and TLC for resin fingerprinting.	Wistar albino male and female rats, aged 10–11 weeks, 50–200 g. Swiss albino male and female mice, 9–11 weeks, 26–35 g. The animal source was in Ethiopia.	<i>In vivo</i> study using inhibition of carrageenan-induced paw edema in mice. The mice were divided into five groups: - Control group: Negative, vehicle treated. - Positive control: Indomethacin (10 mg/kg). - Three test groups: Resin administered at doses of 150, 300, and 600 mg/kg The resin showed significant ($p<0.001$) inhibition of edema. The maximum inhibition was observed at the 600 mg/kg dose, with 65.44% inhibition at the fourth hour. Resin <i>C. guidottii</i> inhibited edema, reflecting anti-inflammatory activity.	<i>In vivo</i> study using excision and incision wound models in rats. The rats were divided into four groups: - Negative control: Simple ointment base. - Positive control: Nitrofurazone (0.2%). - Experimental groups: Ointments containing 4% essential oil or 5% resin Both ointments significantly enhanced wound contraction rates and tensile strength compared to the negative control. Period of Epithelization: - Essential oil: 22.42 days. - Resin: 23.50 days. - Negative control: 25.67 days Testing the linear incision wound model, the tensile strength was calculated to obtain the percentage; the tensile strength presentation was 29.42%. Ointments containing essential oil or resin in <i>C. guidottii</i> enhanced wound contraction rates and tensile strength, reflecting wound healing activity.	The resin was safe at doses up to 3000 mg/kg. Mild effects like reduced locomotor activity were observed at higher doses. The LD₅₀ was near 3000 mg/kg	(Gebrehiwot et al., 2015)
<i>Crassocephalum crepidioides</i> (Benth.) herbs were collected in Vietnam, in 2020. The herbs were extracted using ethanol 70% with fractionation method and the solvent was dried in an oven at 40°C.	Phenolics and flavonoids were identified using a UV-visible spectrophotometer.	Albino Swiss male mice, the age and weight were not described. The animal sources were in Vietnam.	<i>In vitro</i> study using Tested on murine macrophage cells (RAW 264.7) stimulated with lipopolysaccharide (LPS), inhibition of nitric oxide (NO) production method. The concentration tested were divided into three groups: 125, 62.5, and 31.25 µg/mL. The anti-inflammatory effect was dose-dependent, with the highest NO production inhibition of 91.4% when cells were treated at a concentration of 125 units of measurement. The ethanol extract of <i>C. crepidioides</i> reduced the NO inflammatory cytokines in RAW 264.7 macrophages and LPS, reflecting anti-inflammatory activity.	<i>In vivo</i> study using excision wound model in mice. The mice were divided into three groups: - Control: Treated with 5% DMSO and Tween 20 mixture. - <i>Crassocephalum crepidioides</i> hydroethanolic extract-treated: Topical application of 10 mg/kg/day and 50 mg/kg/day. The percentage of wound closure in the 50 mg/kg/day treatment was significantly higher than the control group at the initial stage, at 28.0%, while the percentage in the control group was 15.4% after 4 days. <i>C. crepidioides</i> hydroethanolic extract at 50 mg/kg/day reduced epithelialization time by 3.5 days and improved fibroblast density, angiogenesis, and granulation tissue formation, reflecting wound healing activity.	The <i>in vitro</i> cytotoxicity test (MTT assay) showed CCLE was non-toxic up to 125 µg/mL on RAW 264.7 cells	(Thao et al., 2020)

Table 1. *In vitro* and *in vivo* studies of anti-inflammatory and wound healing activities of plants (continued...)

Species, plant origin, year sampled, extraction method, solvent	Analysis of secondary metabolites	Characteristics of the animals and source	Anti-inflammatory test method, results, and statistical analysis	Wound healing test method, results, and statistical analysis	Mechanism and safety	Reference
<i>Curcuma longa</i> L. was collected in Japan, year of collection is not described. The herbs were extracted using ethanol and carboxymethyl cellulose for topical application. Specific evaporation temperature was not described.	Three compounds, namely, curcumin, DMC, and BDMC, were identified using HPLC.	Wistar and Swiss albino male rats, with an average age of 6 weeks. The weight was not described. The animal sources were in Bangladesh.	<i>In vivo</i> study using inhibition of carrageenan-induced paw edema in rats. The mice were divided into four groups: - Control group: Vehicle (corn oil). - Treatment groups: Curcumin, DMC, and BDMC at 100 mg/kg body weight. Carrageenan was injected intraperitoneally to induce paw inflammation, and paw volume was measured at 1, 3, and 6 hours. All three curcuminoids significantly reduced paw edema compared to the control [35%, 37%, and 31% in the curcumin, DMC, and BDMC groups, respectively]. BDMC was more effective than curcumin and DMC in reducing edema. Curcuminoids in <i>C. longa</i> significantly reduced paw edema compared to the control, reflecting anti-inflammatory activity.	<i>In vivo</i> study using circular wound model in rats. The mice were divided into four groups: - Control group: Sodium carboxymethyl cellulose. - Treatment groups: Curcumin (1%), DMC (1%), and BDMC (1%) applied topically. Measurements were taken on days 0, 3, 6, 9, and 12 to calculate wound closure rates. Circular wound measurements (6 mm), wounds were left open and treated with curcumin (1%), DMC (1%), and BDMC (1%); curcumin (95.0%), DMC (93.17%), and BDMC (89.0%), compared to the control group (65.09%) on the ninth day. On day 12, macroscopic evaluation confirmed that the wound areas in all treatment groups were fully closed (100%), except in the control group (88%). ANOVA was applied with $p < 0.05$ indicating significance. All curcuminoids significantly enhanced wound closure rates compared to the control, reflecting wound healing activity.	The mechanism of toxicity was not described.	(Islam et al., 2024)
<i>Curcuma mangga</i> Valetton & Van Zijp rhizome were collected in Thailand, in 2017. The herbs were extracted using ethanol with maceration method and the solvent was evaporated under reduced pressure at 65°C. Cream preparations were made with a concentration of 2%; 5%; 10%.	Four compounds, namely, curcuminoids (curcumin, demethoxycurcumin, bisdemethoxycurcumin). Labdane diterpenes (demethoxycurcumin, and others like 15,16 bisnorlada-8), were identified using HPLC.	Wistar male rats, age, and weight were not described. The animal sources were not described.	<i>In vitro</i> study using inhibition of nitric oxide (NO) production in LPS-stimulated RAW264.7 macrophages. The mice were divided into four groups: - Positive control: Diclofenac gel ($IC_{50} = 54.3 \mu\text{g/mL}$) - Cream containing <i>C. mangga</i> extract at concentrations of 2%, 5%, and 10% w/w The percentage of inhibition was calculated using the IC_{50} value; IC_{50} values for 2% (49.1 ± 0.9), 5% (42.9 ± 1.0), 10% (34.1 ± 2.1) cream preparations, while the positive control was diclofenac gel IC_{50} 54.3 $\mu\text{g/mL}$. Results showed that 10% w/w cream had the highest NO inhibition with IC_{50} values of 34.1 $\mu\text{g/mL}$ (before the heating-cooling test) and 37.9 $\mu\text{g/mL}$ (after the heating-cooling test). The 10% cream contains <i>C. mangga</i> showed the most potent activity, outperforming diclofenac gel, reflecting anti-inflammatory activity.	<i>In vitro</i> study using: - Cell proliferation (MTT assay): Tested on Human Dermal Fibroblast (HDF) cells. - Cell migration (scratch assay): Tested the migration of HDF cells over 36 hours. - Concentrations tested: 1 $\mu\text{g/mL}$ and 3 $\mu\text{g/mL}$ of creams containing <i>C. mangga</i> extract (2%, 5%, 10%). Proliferation of human dermal fibroblast (HDF) cells; HDF cell migration was highest at 36 hours at 80.1%, followed by 2% w/w (78.7%) and 10% w/w (76.4%). After the cooling heating test, it was found that the cream containing 5% w/w extract at 3 $\mu\text{g/mL}$ increased HDF cell migration at 36 hours to 75.2%, followed by 2% (73.5%) and 10% w/w cream (72.8%), respectively when compared to the control group (61.1%). The 5% cream contains <i>C. mangga</i> significantly enhanced HDF cell migration and proliferation, reflecting wound healing activity.	The mechanism of toxicity was not described.	(Srirod and Tewtrakul, 2019)

Table 1. *In vitro* and *in vivo* studies of anti-inflammatory and wound healing activities of plants (continued...)

Species, plant origin, year sampled, extraction method, solvent	Analysis of secondary metabolites	Characteristics of the animals and source	Anti-inflammatory test method, results, and statistical analysis	Wound healing test method, results, and statistical analysis	Mechanism and safety	Reference
<i>Dioscorea bulbifera</i> L rhizome was collected in Thailand, in 2011. The herbs were extracted using ethanol and water with maceration method. Specific evaporation temperature was not described.	Five compounds, namely, quercetin, kaempferol, catechin, myricetin, and 3,5-dimethoxyquercetin, were identified using HPLC.	Human (human dermal fibroblasts (HDFs) and RAW264.7 macrophages). The age and weight were not described. The animal sources were not described.	<i>In vitro</i> study using inhibition of nitric oxide (NO) production in LPS-stimulated RAW264.7 macrophages. Test compounds included myricetin, quercetin, and kaempferol, with IC₅₀ values of 39.0 µM, 56.2 µM, and 46.6 µM, respectively. Positive controls used were NSAIDs like ibuprofen (IC₅₀ = 54.5 µM) and aspirin (IC₅₀ = 43.2 µM). Inhibition of NO production; kaempferol and quercetin had IC₅₀ values of 46.6 and 56.2 µg/mL, respectively. Myricetin demonstrated the most potent inhibitory activity on NO production, surpassing ibuprofen and comparable to aspirin, reflecting anti-inflammatory activity.	<i>In vitro</i> study using wound healing assay with human dermal fibroblast (HDF) cells. Test samples included myricetin, quercetin, and catechin at concentrations of 1–100 µM. Catechin showed the highest activity with complete wound closure (100% migration) within 2 days at 3 µM concentration. Wound healing assay using HDF cells; very strong wound healing effect and promoted marked cell proliferation, resulting in % viability of 107.4-137.6 (n-hexane fraction), 121.1-151.9 (ethyl acetate fraction), 98.0-131.9 (chloroform), 90.9-115.9 (Water) respectively. The catechin compound significantly increased fibroblast migration by 2.4-fold compared to the control after 24 hours. Catechin promoted rapid fibroblast migration and wound closure faster than other compounds, reflecting wound healing activity.	The mechanism of toxicity was not described.	(Chaniad et al., 2020)
<i>Dorema aucheri</i> Boiss herbs were collected in Iraqi Kurdistan, the year of the collection was not described. The herbs were extracted using ammoniac gum from <i>D. aucheri</i> (DAG) was dissolved in 10% Tween 20 for topical treatment. Specific evaporation temperature was not described.	Seven compounds namely, flavonoids, phenolic compounds, and polysaccharides. Additionally, its essential oils contain components such as β-caryophyllene, cuparene, thymol, and carvacrol were identified using GC-MS.	Sprague Dawley rats, both male and female, 7–8 weeks, 180–200 g. The animal sources were in Iraq.	<i>In vivo</i> study was indirectly assessed through its effects on wound healing using a dorsal excision wound model in rats. The mice were divided into four groups: - Negative control: Treated with normal saline solution. - Positive control: Treated with intrasite gel. - Two treat groups: Treated with 250 mg/kg and 500 mg/kg of <i>Dorema aucheri</i> gum. Measurement of inflammatory mediators using ELISA Kit; DAG-treated mice (0.2 mL 500 mg/kg) showed comparable levels of TNF- (62.12 µg/mL). TNF-α and IL-6 levels were significantly decreased, while IL-10 levels were increased in the 500 mg/kg treated group. The topical application of <i>D. aucheri</i> gum significantly downregulated inflammatory cytokines (TNF-α, IL-6, and IL-10) in the treated groups compared to the control group, reflecting anti-inflammatory activity.	<i>In vivo</i> study using excisional wound model testing (a full-thickness excision wound model was created on the dorsal neck of rats). The mice were divided into four groups: - Negative control: Treated with normal saline solution. - Positive control: Treated with intrasite gel. - Two treat groups: Treated with 250 mg/kg and 500 mg/kg of <i>Dorema aucheri</i> gum. 92.58% and 87.80% results were obtained from intrasite gel and DAG-treated rats (0.2 mL 250 mg/kg), respectively. The 500 mg/kg group showed significant acceleration in wound healing compared to the control and 250 mg/kg groups, with a wound closure percentage of 90.85% on day 15. Histological evaluation revealed enhanced collagen deposition, reduced inflammatory cell infiltration, and increased fibroblast proliferation in the DAG-treated groups, reflecting wound healing activity.	Acute toxicity studies revealed no toxic effects at doses of 2 g/kg and 5 g/kg.	(Ahmed et al., 2024)

Table 1. *In vitro* and *in vivo* studies of anti-inflammatory and wound healing activities of plants (continued...)

Species, plant origin, year sampled, extraction method, solvent	Analysis of secondary metabolites	Characteristics of the animals and source	Anti-inflammatory test method, results, and statistical analysis	Wound healing test method, results, and statistical analysis	Mechanism and safety	Reference
<i>Ephedra ciliata</i> herbs were collected in Pakistan, the year of collection was not described. The herbs were extracted using methanol with maceration method (made cream preparation). Specific evaporation temperature was not described.	Four compounds namely, quercetin, gallic acid, p-coumaric acid, and sinapic acid, were identified using HPLC.	Albino both male and female rats, 8–12 weeks, 200–250 g. The animal sources were in Pakistan.	<i>In vivo</i> study using carrageenan-induced paw edema (acute model) and cotton pellet granuloma (chronic model) in rats. The rats were divided into six groups: - Negative control: Saline solution. - Positive control: Indomethacin (10 mg/kg). - Treat groups: Ec.Me-treated groups (50 mg/kg, 100 mg/kg, 200 mg/kg), quercetin (120 mg/kg). Inhibition of carrageenan-induced paw edema; Starting from the 4th hour, treatment with 100 mg/kg showed a significantly better effect compared to the group dosed with 50 mg/kg. The other treatment groups 100 mg/kg extract and 200 mg/kg showed comparable anti-inflammatory effects with no statistical difference (p>0.05) throughout the study. <i>E. ciliata</i> in the carrageenan model reduced paw edema and in the cotton pellet model inhibition of granuloma formation, reflecting anti-inflammatory activity.	<i>In vivo</i> study using excision and burn wound healing models in rats. The rats were divided into six groups: - Negative control: Base cream without Ec.Me. - Positive control: Heparin sodium, 5000 IU. - Treat groups: Ec.Me creams (5%, 10%, 20%), quercetin (20% cream). The cream-treated group and the quercetin-treated group showed comparable healing effects (p>0.05). On day 14, the percentages of wound closure in the controls were 5, 10 and 20%. respectively were 81.4 ± 0.45, 81.1 ± 0.70, 88.7 ± 0.35. The extract promoted wound contraction and re-epithelialization, reflecting wound healing activity.	Ec.Me was found safe up to a single dose of 2000 mg/kg in an acute toxicity study.	(Yaseen et al., 2020)
<i>Euphorbia hirta</i> L. leaves were collected in Bangladesh, in 2015 The leaves were extracted using ethanol 95% with the maceration method and the solvent was evaporated at 78.37°C.	Seven compounds, namely, carbohydrates, saponins, alkaloids, steroids, flavonoids, tannins, and terpenoids, were identified using qualitative phytochemical screening tests.	Swiss albino female rats, the age was not described, 180-200 g. The animal sources were in Bangladesh.	<i>In vivo</i> study using wound healing models in alloxan-induced diabetic rats. The rats were divided into eight groups: - Group I: Normal control (distilled water). - Group II: Diabetic wound control. - Group III: Diabetic wound control + 100 mg/kg/day ethanolic extract (oral). - Group IV: Diabetic wound control + 200 mg/kg/day ethanolic extract (oral). - Group V: Diabetic wound control + 400 mg/kg/day ethanolic extract (oral). - Group VI: 5% povidone iodine ointment. - Group VII: 5% ethanolic extract ointment. - Group VIII: 10% ethanolic extract ointment. The extract at a dose of 100 mg/kg orally, showed minimal amount of granulation tissue, a large number of mononuclear inflammatory cells, and delayed epithelialization, the dose of 200 mg/kg showed a moderate amount of granulation tissue, few mononuclear inflammatory cells, and early epithelialization. Oral administration of ethanolic extract significantly reduced malondialdehyde (MDA) and nitric oxide (NO) levels, reflecting anti-inflammatory activity.	<i>In vivo</i> study using an excision wound model in rats. Treatments included oral administration and topical application of the ethanolic extract at different doses (5% and 10% ointments). Excision wound model testing: The percentage of wound contraction on the 16th day of observation showed that diabetic control was 6.12%. In the orally treated groups, it was found to be 35.92, 44.69 and 61.42% at different doses (100, 200 and 400 mg/kg), topical application of 5 and 10% whole plant extracts resulted in wound contraction percentages of 32.86% and 36.32%, respectively, while that of the standard drug, povidone iodine ointment, was 39.79%. Histopathological studies showed improved granulation tissue formation and reduced inflammation in the treated groups, reflecting wound healing activity.	No skin irritation in the acute toxicity study for topical formulations.	(Tuhin et al., 2017)

Table 1. *In vitro* and *in vivo* studies of anti-inflammatory and wound healing activities of plants (continued...)

Species, plant origin, year sampled, extraction method, solvent	Analysis of secondary metabolites	Characteristics of the animals and source	Anti-inflammatory test method, results, and statistical analysis	Wound healing test method, results, and statistical analysis	Mechanism and safety	Reference
<i>Globularia alypum</i> L. leaves were collected in north of Tunisia, in 2015. The leaves were extracted using methanol with the maceration method and the solvent was evaporated at 50°C.	Five compounds, namely, cinnamic acid, linoleic acid, oleic acid, palmitic acid, and stearic acid, were identified using GC-MS.	Wistar male rats, the age was not described, 250–270 g. The animal sources were in Tunisia.	<i>In vivo</i> study using a carrageenan-induced paw edema model in rats. The rats were divided into three groups: - Negative control: Saline solution-treated. - Positive control: Acetylsalicylic acid (AA, 150 mg/kg). - Treat group: <i>G. alypum</i> extract-treated group (200 mg/kg). Inhibition of carrageenan-induced paw edema; After 7 hours of the experiment, the paw size was reduced by 40% in the treated group. <i>G. alypum</i> extract significantly reduced paw edema ($p < 0.01$), reflecting anti-inflammatory activity.	<i>In vivo</i> study using circular burn model testing in rats (a second-degree burn wound model was created on the dorsal skin of rats). The rats were divided into three groups: - Negative control: Saline solution-treated. - Positive control: Cytol <i>Centella</i> cream - Treat group: <i>G. alypum</i> extract-treated group (200 mg/kg). Wound area decreased significantly in the extract group at day 12 ($p < 0.01$), and day 16 ($p < 0.001$) compared to the untreated group. Histopathological examination revealed improved tissue regeneration in the <i>G. alypum</i> extract group compared to controls, reflecting wound healing activity.	<i>G. alypum</i> extract demonstrated no toxic effects in the study. Histological examinations of tissues showed no adverse effects related to <i>Globularia alypum</i> extract treatment	(Ghल्ली et al., 2016a)
<i>Jatropha neopauciflora</i> Pax. latex was collected in Mexico, in 2014. The solvent was not described.	Four compounds, namely, phenols, flavonoids, carbohydrates (mainly fructose), and proteins, were identified using HPLC.	CD1 male, 7 weeks, the weight was not described. Wistar male rats, the age and weight were not described. The animal sources were in Mexico.	<i>In vivo</i> study using a carrageenan-induced paw edema model in rats. The rats were divided into six groups: - Topical administration: Latex (100%). - Oral administration: Latex (250 mg/kg, 500 mg/kg, 750 mg/kg). - Positive controls: Naproxen sodium (25 mg/kg) and dexamethasone (10 mg/kg). Inhibition of carrageenan-induced paw edema; Inhibition of inflammation with latex was only 25%, whereas concentrations of 500 and 750 mg/kg latex administered orally showed similar behavior by reducing inflammation between 65% and 70% and compared to the control (naproxen sodium) there was no significant difference ($p < 0.05$). Oral administration of latex <i>J. neopauciflora</i> reduced inflammation, reflecting anti-inflammatory activity.	<i>In vivo</i> study using tensile strength method. The rats were divided into five groups: - Control group: Gel without latex. - Test groups: Latex treatments at concentrations of 50%, 75%, and 100%. - Positive control: Recoveron (commercial cream). Wound model measurement: In the test of wound healing activity, the three concentrations used (50%, 75% and 100%) showed a wound healing efficacy of 100%, and there was no significant difference between the concentrations used ($p < 0.05$) and the control group that was treated with wound healing therapy. The 100% latex concentration <i>J. neopauciflora</i> resulted in a tensile strength increase comparable to the positive control, reflecting wound healing activity.	The latex was non-toxic to human cervical carcinoma cells and fibroblast cell lines at IC_{50} values of 1250 $\mu\text{g/mL}$ and 1000 $\mu\text{g/mL}$	(Hernandez-Hernandez et al., 2017)
<i>Kaempferia marginata</i> Carey. rhizomes were collected in Thailand, in 2010. The rhizomes were extracted using ethanol with maceration method. Specific evaporation temperature was not described.	Three compounds namely, desmethoxyyangonin, curcuminoids, and diterpenes, were identified using HPLC.	Human dermal fibroblast (HDF) cells and RAW264.7 cells. The age and weight were not described. The animal source was not described.	<i>In vitro</i> study using human dermal fibroblast (HDF) cells and murine macrophage RAW264.7 cells. This study was divided into five groups: - Control group: Untreated cells. - Positive control: Diclofenac gel ($IC_{50} = 64.9 \mu\text{g/mL}$). - Test group: Gel containing <i>K. marginata</i> extract at concentrations of 2.5%, 5.0%, and 10.0% w/w. Inhibition of NO production; gel with 10% w/w concentration showed the highest activity with $IC_{50} = 12.50 \mu\text{g/mL}$ (diclofenac gel, IC_{50} value = $64.90 \mu\text{g/mL}$). The gel <i>K. marginata</i> showed superior NO inhibition compared to diclofenac, reflecting anti-inflammatory activity.	<i>In vitro</i> study using two methods, they are: - Cell proliferation assay: HDF cells were exposed to gel concentrations of 2.5%, 5.0%, and 10.0% w/w for 48 hours. - Cell migration (scratch assay): HDF cells were scratched to simulate a wound, and the migration rate was monitored over three days. Wound healing test using human dermal fibroblast (HDF) cells; wound healing activity with gel (5% w/w) showed the highest % cell viability (134.05%) and the highest percentage result of cell migration at 85.20 using HDF cells. Every concentration (2.5%, 5.0%, and 10.0%) exhibited significantly higher wound healing activity compared to the control, reflecting wound healing activity.	Mechanism of toxicity was not described.	(Muthachan and Tewtrakul, 2019)

Table 1. *In vitro* and *in vivo* studies of anti-inflammatory and wound healing activities of plants (continued...)

Species, plant origin, year sampled, extraction method, solvent	Analysis of secondary metabolites	Characteristics of the animals and source	Anti-inflammatory test method, results, and statistical analysis	Wound healing test method, results, and statistical analysis	Mechanism and safety	Reference
<i>Mangifera indica</i> L. fruit peels were collected in Mexico, the year of collection was not described. The fruit peels were extracted using methanol with the maceration method and the solvent was evaporated in a fume hood until dry	Four compounds, namely, phenol, resorcinol, conjugated resorcinol, and mangiferin, were identified using HPLC-DAD and HPLC-MS	Mice (CD 1) male and Wistar female rats. The age and weight were not described. The animal sources were in Mexico.	<i>In vivo</i> study using histopathological analysis. This study is divided into four groups: - Positive control: Diclofenac. - Treatment: Methanolic extract of mango peel 10% was applied topically at 0.5 mg. - Vehicle control - Control (untreated ear). Histopathological analysis: The group treated with the extract at 10% concentration saw moderate leukocyte infiltrates and less edema, there was no significant difference between the extract and diclofenac groups. The results are expressed as median. Methanolic extract of <i>M. indica</i> peel showed a reduction in edema comparable to diclofenac, with significant anti-inflammatory effects indicated through histological and thickness reduction analyses, reflecting anti-inflammatory activity.	<i>In vivo</i> study using wound contraction. This study is divided into three groups: - Treatment: Methanolic extract of mango peel 10%. - Positive control: Dexpantenol 5%. - Vehicle control. Measurement of wound contraction, the percentage of wound shrinkage was evaluated using the initial wound size (1 cm) at 100%; at 10% extract concentration, it exceeded 50% closure after the fifth day. Tensile strength was significantly better in the methanolic extract of <i>M. indica</i> peel-treated groups compared to the vehicle and dexpantenol, reflecting wound healing activity.	The mechanism of toxicity was not described.	(Espinosa-Espinosa et al., 2022)
<i>Ononis spinosa</i> L., dan <i>Ononis natrix</i> L. herbs were collected in Turkey, in 2011-2012 The herbs were extracted using n-hexane, ethyl acetate, and methanol with maceration method. The solvent was evaporated under reduced pressure at 50°C.	Ten compounds namely, trifolirhizin, ononin, formononetin, and genistein, as well as phenolic acids (gallic acid, caffeate), volatile oils (anethol, carvone, menthol), and terpenes (β-amyrin, α-onocerin). No specific identification tools for metabolites.	Swiss albino male rats, the age was not described, 20-25 g. Sprague-Dawley male rats, the age was not described, 160-180 g. The animal sources were in Turkey.	<i>In vivo</i> study using carrageenan-induced hind paw edema and acetic acid capillary permeability test in rats. The rats were divided into four groups: - Negative control: Untreated animals. - Vehicle control: Base ointment. - Test groups: Treated with plant extracts (e.g., ethyl acetate extract of <i>Ononis spinosa</i> roots). - Positive control: Indomethacin (10 mg/kg). The results of the carrageenan-induced hind paw edema test showed that EtOAc-NR had 30.4% inhibition at 360 min, while EtOAc-SR showed 21.2% inhibition at 180 min, 24.5% inhibition at 270 min, and 27.2% inhibition at 360 min. However, the extracts had no activity against ear edema caused by TPA. Extracts exhibited significant anti-inflammatory effects with inhibition values ranging from 21.2% to 40.4%, reflecting anti-inflammatory activity.	<i>In vivo</i> study using linear incision and circular excision wound models in rats. The rats were divided into four groups: - Negative control: Untreated wounds. - Vehicle control: Base ointment. - Test groups: Treated with ethyl acetate extract of <i>Ononis spinosa</i> roots. - Positive control: Madecassol® (commercial wound-healing ointment). Testing linear incision and circular excision wound models; EtOAc-SR had outstanding wound healing activity with a tensile strength value of 42.6% in the linear incision wound model and a 60.1% reduction in wound area on day 12 in the circular excision wound model. Extract-treated wounds showed contraction and a tensile strength, reflecting wound healing activity.	Mechanism of toxicity was not described.	(Öz et al., 2017)

Table 1. *In vitro* and *in vivo* studies of anti-inflammatory and wound healing activities of plants (continued...)

Species, plant origin, year sampled, extraction method, solvent	Analysis of secondary metabolites	Characteristics of the animals and source	Anti-inflammatory test method, results, and statistical analysis	Wound healing test method, results, and statistical analysis	Mechanism and safety	Reference
<i>Phlomis russeliana</i> (Sims) Lag. herbs were collected in Turkey, in 2015 The herbs were extracted using methanol followed by fractionation with n-hexane, dichloromethane, and ethyl acetate. Specific evaporation temperature was not described.	Two compounds, namely, phytol and 1-heptadecanoic acid, were identified using GC-MS.	Balb-c male mice, the age was not described, 25–28 g. The animal sources were in Turkey.	<i>In vitro</i> study using the inhibition of lipopolysaccharide (LPS)-induced nitric oxide (NO) production in RAW 264.7 cells. This study is divided into five groups: - Treat group: The extract was tested at concentrations of 0.125, 0.25, 0.5 and 1 mg/mL. - Positive control: L-NAME (0.1 mg/mL). Effects of fractions on nitrite production in RAW264.7 cells statistical significance is shown for each compound vs. LPS (*p<0.05; *p<0.01; *p<0.001). Significant reductions in NO production were observed at all tested doses, reflecting anti-inflammatory activity.	<i>In vivo</i> study using excision wound model in mice. - The mice were divided into four groups: - Normal control: Untreated. - Negative control: Blank gel. - Test group: <i>P. russeliana</i> extract gel (the extract gel was applied topically to full-thickness excisional wounds on mice every day for 10 days). - Positive control: Madecassol®. On Day 10, wounds treated with the extract gel showed significant improvements in healing, comparable to the positive control (Madecassol®). Enhanced granulation tissue thickness, angiogenesis, and collagen formation were observed in <i>P. russeliana</i> extract gel, reflecting wound healing activity.	The mechanism of toxicity was not described.	(Okur et al., 2020)
<i>Plumbago zeylanica</i> Linn., <i>Datura stramonium</i> Linn., and <i>Argemone mexicana</i> Linn herbs. The place and year of collection were not described. The herbs were extracted using methanol and the solvent was evaporated at reduced pressure at 50°C Blended to make a polyherbal gel with extract ratio 4:4:2.	Four compounds, namely, polyphenols, flavonoids, alkaloids, and phenolic compounds. No specific identification tools for metabolites.	Wistar albino both male and female rats, the age was not described, 180-200 g. The animal source was in India.	<i>In vivo</i> study using Inhibition of carrageenan-induced paw edema in rats. The rats were divided into six groups: - Normal control: No treatment. - Negative control: Gel base. - Positive control: Diclogel. - Treat group: Polyherbal - Gel (2% and 5%). Significant and maximal anti-inflammatory effect after 180 min of carrageenan injection compared with normal and negative control animals (p<0.0001). This may be due to inadequate histamine and serotonin release. Polyherbal gel demonstrated a significant reduction in paw edema compared to the negative and normal controls, reflecting anti-inflammatory activity.	<i>In vivo</i> study using linear incision and excision wound model testing in rats. This study is divided into five groups: - Normal control: No treatment. - Negative control: Gel base. - Positive control: Povidone iodine. - Treat group: Polyherbal gel (2% and 5%). High rates of wound contraction (p<0.0001), early epithelialization period (p<0.0001) and increased wound healing strength (p<0.0001) were observed in the 2% and 5% polyherbal gel-treated groups when compared to the normal control group and negative control group. Polyherbal gel showed enhanced wound contraction, shortened epithelialization period, and increased tensile strength in the incision model, reflecting wound healing activity.	Mechanism of toxicity was not described.	(Dev et al., 2019)

Table 1. *In vitro* and *in vivo* studies of anti-inflammatory and wound healing activities of plants (continued...)

Species, plant origin, year sampled, extraction method, solvent	Analysis of secondary metabolites	Characteristics of the animals and source	Anti-inflammatory test method, results, and statistical analysis	Wound healing test method, results, and statistical analysis	Mechanism and safety	Reference
<i>Plantago australis</i> leaves were collected in Brazil, in 2014. The leaves were extracted using hydroethanolic solution (30% water and 70% ethanol). The solvent was evaporated at a low temperature (< 40°C) under vacuum.	One compound, namely verbascoside was identified using HPLC.	Wistar male rats, the age was not described, 180 ± 20 g. The animal source was in Brazil.	<i>In vivo</i> study using Inhibition of carrageenan-induced paw edema in rats. The rats were divided into four groups: - Negative control: Saline solution. - Two treat groups: <i>P. australis</i> hydroethanolic extract at 250 mg/kg and 500 mg/kg. - Positive control: 40 mg/kg sodium diclofenac. Pretreatment at a dose of 500 mg/kg inhibited edema by 22.70% after one hour of induction, four hours later (33.20% inhibition after 4 hours), when compared with the control group. In addition, the 250 mg/kg dose inhibited edema by 23.80% and 18.30% after two and four hours, respectively, better than the control group. Pretreatment with <i>P. australis</i> hydroethanolic extract treatment inhibited edema, reflecting anti-inflammatory activity.	Combination of <i>in vitro</i> and <i>in vivo</i>: Scratch Test (HaCaT) and rat wound model. Scratch Test (HaCaT) This study is divided into six groups: - Negative control: Serum-free medium. - Positive control: DMEM + 10% FBS. - Treat group (<i>P. australis</i> hydroethanolic extract): 2.5, 5, 10, and 25 µg/mL. Rat wound model: The rats were divided into three groups: - Negative control: Saline solution. - Treat group: <i>P. australis</i> hydroethanolic extract at 500 mg/kg and 1000 mg/kg. In the Scratch Test (HaCaT), verbascoside and PAHE significantly enhanced cell migration compared to the negative control without toxicity. In the rat wound model, PAHE at 500 and 1000 mg/kg accelerated wound healing, showing higher closure percentages than the control on days 7, 14, and 21. <i>P. australis</i> hydroethanolic extract treatment significantly improved wound closure rates, reflecting wound healing activity.	Mechanism of toxicity was not described.	(Sperotto et al., 2018)
<i>Portulaca pilosa</i> L. herbs were collected in 2015. The place of collection was not described. The herbs were extracted using a hydropropylene glycol solution 70% with percolation method and the solvent was evaporated under reduced pressure at 37 °C.	Nine compounds, namely, gallic acid, flavonoids, mucilage, tannins, reducing sugars, phenols, steroids, diterpenoids, and carotenoids, were identified using HPLC.	Wistar both male and female rats, aged 21 days, weighing between 250–350 g. The animal source was in Brazil.	<i>In vivo</i> study using histopathological analysis in rats. The rats were divided into four groups: - Negative control: Gel vehicle, 150 mg/kg. - Positive control: Fibrinase®, 100 U/kg. - Treat group: <i>P. pilosa</i> gel (10% concentration, 150 mg/kg). - Treat group: <i>P. pilosa</i> extract (150 mg/kg). In quantitative microscopic analysis, the number of inflammatory cells in the wound averaged 4.1 ± 1.88, significantly different from the positive control which averaged 17.8 ± 2.37 cells/field. Significant reduction in inflammatory cells in groups treated with <i>P. pilosa</i> extract, reflecting anti-inflammatory activity.	<i>In vivo</i> study using excision wound model testing in rats. The rats were divided into four groups: - Negative control: Gel vehicle, 150 mg/kg. - Positive control: Fibrinase®, 100 U/kg. - Treat group: <i>P. pilosa</i> gel (10% concentration, 150 mg/kg). - Treat group: <i>P. pilosa</i> extract (150 mg/kg). Significant increase in wound contraction percentage for <i>P. pilosa</i> extract (56%) compared to control (29.42%). Enhanced fibroblast proliferation and angiogenesis were observed. The extract and gel <i>P. pilosa</i> showed significant potential to enhance wound repair, reflecting wound healing activity.	The mechanism of toxicity was not described.	(Barros et al., 2017)

Table 1. *In vitro* and *in vivo* studies of anti-inflammatory and wound healing activities of plants (continued...)

Species, plant origin, year sampled, extraction method, solvent	Analysis of secondary metabolites	Characteristics of the animals and source	Anti-inflammatory test method, results, and statistical analysis	Wound healing test method, results, and statistical analysis	Mechanism and safety	Reference
<i>Rumex abyssinicus</i> J. rhizomes were collected in Ethiopia. Year of collection was not described. The rhizomes were extracted using 80% methanol with maceration method (made ointment preparation) and the solvent was evaporated at 40°C in a ventilated oven until dry.	Five compounds, namely, tannins, saponins, flavonoids, steroids, and anthraquinones. No specific identification tools for metabolites.	Swiss albino both male and female mice, 6–8 weeks, 25–30 g. Wistar both male and female rats, 3–4 months, 200–300 g. The animal source was in Ethiopia.	<i>In vivo</i> study using inhibition of carrageenan-induced leg edema in rats. The rats were divided into five groups: - Negative control: 1% Carboxymethyl cellulose. - Three treat groups: Concentration of extract 250 mg/kg, 500 mg/kg and 750 mg/kg of extract. - Positive control: 10 mg/kg indomethacin. The extract displayed significant dose-dependent inhibition of paw edema, with the highest dose (750 mg/kg) achieving 61.54% inhibition at 4 h. The standard drug (indomethacin) achieved 84.6% inhibition. <i>In vivo</i> experiments confirmed that the extract <i>R. abyssinicus</i> reduced inflammation, reflecting anti-inflammatory activity.	<i>In vivo</i> study using linear incision and excision wound models in rats. The rats were divided into four groups: - Negative control: Ointment base only. - Two treat groups: 5% and 10% hydroalcoholic extract ointment. - Positive control: 0.2% nitrofurazone ointment. Wounds treated with 5% and 10% (w/w) hydroalcoholic extract ointment showed significant wound healing activity in both models, as evidenced by increased wound contraction, shorter epithelialization time, higher tissue breaking strength, and increased hydroxyproline content. Tensile strength was significantly increased by about 36.2%. The <i>R. abyssinicus</i> extract ointment showed faster wound contraction, shorter epithelization time, and higher hydroxyproline content compared to controls, reflecting wound healing activity.	No toxicity or adverse effects were observed at the tested doses during the 14-day observation period.	(Mulisa et al., 2015)
<i>Schinus terebinthifolius</i> Raddi. essential oils were collected in Brazil, in 2010. The essential oils were extracted using hydrodistillation method and the solvent was stored at a temperature of -20°C after extraction.	Three compounds namely, p-cymen-7-ol, 9-epi-(E)-cariophyllene, carvone, and verbenone, were identified using chromatography.	C57BL/6 male mice, 7–8 weeks, 25–30 g. The animal source was in Brazil.	<i>In vivo</i> study using histopathological analysis in mice. The rats were divided into two groups: - Negative group: Lanolin/vaseline base. - Treated group: 10% <i>S. terebinthifolius</i> leaf oil (STRO). The histopathological analysis with the essential oil promoted a reduction in the accumulation of leukocytes and pro-inflammatory cytokines and increased the number of blood vessels and the deposition of collagen fibers significantly, compared with the control group. STRO-treated wounds showed reduced leukocyte accumulation, lower TNF-α, CXCL-1, and CCL-2 levels, and reduced neutrophil and macrophage activity, reflecting anti-inflammatory activity.	<i>In vivo</i> study using wounds treat in mice. The rats were divided into two groups: - Negative group: Lanolin/vaseline base. - Treated group: 10% STRO. Significant improvement in the percentage of wound closure after day 3 post-wounding at approximately 37%. Treated wounds showed increased wound closure, angiogenesis, and collagen deposition, reflecting wound healing activity.	Mechanism of toxicity was not described.	(Estevão et al., 2017)

Table 1. *In vitro* and *in vivo* studies of anti-inflammatory and wound healing activities of plants (continued...)

Species, plant origin, year sampled, extraction method, solvent	Analysis of secondary metabolites	Characteristics of the animals and source	Anti-inflammatory test method, results, and statistical analysis	Wound healing test method, results, and statistical analysis	Mechanism and safety	Reference
<i>Solanum diploconos</i> (Mart.) fruits were collected in 2014. Place of collection was not described. The fruits were extracted using ethanol 95% with maceration method and the solvent was evaporated at a temperature below 50°C.	Three compounds, namely, caffeic acid, ferulic acid, and coumaric acid, were identified using HPLC.	Male Swiss rats and female Wistar rats, the age and weight were not described. The animal source was in Brazil.	<i>In vivo</i> study using Inhibition of nitric oxide (NO) production in rats. The rats were divided into three groups: - Negative control: Vehicle (PBS, 10 mL/kg). - Positive control: Indomethacin (30 mg/kg). - Treat group: <i>Solanum diploconos</i> extract (100 mg/kg). The extract reduced cell counts in the inflammatory exudate (73.5% inhibition) and decreased levels of TNF-α, IL-1β, and IL-6 cytokines. These effects were comparable to indomethacin. Treatment with the extract significantly reduced NO with a maximum inhibition, reflecting anti-inflammatory activity.	<i>In vivo</i> study using scratch test in rats and <i>in vitro</i> study using fibroblast L929 cells. The rats were divided into two groups <i>in vivo</i> test: - Negative control: Base cream. - Treat group: Base cream containing 1% <i>Solanum diploconos</i> extract. The rats were divided into three groups <i>in vitro</i> test: A scratch assay using fibroblast L929 cells treated with 1, 10, or 100 μg/mL of extract. <i>In vivo</i> results: The cream containing 1% extract significantly accelerated wound healing (~35% reduction in wound area). <i>In vitro</i> results: The extract increased fibroblast migration by up to 2.6-fold. Scratch test with 1% <i>S. diploconos</i> extract cream preparation; Increased fibroblast migration at all concentrations tested, <i>S. diploconos</i> cream accelerated skin wound healing compared to the control group (base cream) significantly of the wound area, reflecting wound healing activity.	Mechanism of toxicity was not described.	(Benvenuti et al., 2021)
<i>Streptocaulon juvenas</i> rhizomas were collected in Vietnam. Year of collection was not described. The rhizomas were extracted using ethanol 70% with maceration method and the solvent was condensed using a rotary vacuum evaporator and freeze-dried. The freeze-dried yield was stored at -20°C	Six compounds, namely, glycosides, cardenolides, hemiterpenoids, triterpenoids, terpenoids, and phenylpropanoids. No specific identification tools for metabolites.	Albino Swiss male mice, the age was not described, 25 $\pm$ 2 g. The animal source was in Vietnam.	<i>In vivo</i> study using Inhibition of nitric oxide (NO) production in mice. The mice divided into four groups: - Control group: DMSO 5% and Tween 20% solution. - Treated groups: <i>S. juvenas</i> root ethanolic extract at 10, 50, and 100 mg/kg/day. The extract (125 μg/mL) decreased the amount of NO by 69% compared to the negative control, in life wound histopathology analysis showed that the number of inflammatory cells decreased by 2.3 times in rats treated with the extract. A significant reduction in inflammatory cell density and down-regulation of TNF-α and NF-κB1 expression by 4.7 and 3.7 times, reflecting anti-inflammatory activity.	<i>In vivo</i> study using excision wound model testing in mice. The mice divided into four groups: - Control group: DMSO 5% and Tween 20% solution. - Treated groups: <i>S. juvenas</i> root ethanolic extract at 10, 50, and 100 mg/kg/day. After 12 days, the percentage of wound closure in extract-treated rats was 99.47%, while the percentage of wound closure in control rats was 67.86%. In addition, the average time for complete closure in the extract-treated rats was lower compared to the control rats by about 3 days. Histological evaluation confirmed increased fibroblast and angiogenesis activities, reflecting wound healing activity.	Mechanism of toxicity was not described.	(Nguyen et al., 2017)

Table 1. *In vitro* and *in vivo* studies of anti-inflammatory and wound healing activities of plants (continued...)

Species, plant origin, year sampled, extraction method, solvent	Analysis of secondary metabolites	Characteristics of the animals and source	Anti-inflammatory test method, results, and statistical analysis	Wound healing test method, results, and statistical analysis	Mechanism and safety	Reference
<i>Thymus sipyleus</i> Boiss. aerals were collected in Turkey, in 2013. The aerals were extracted using 96% ethanol, n-hexane, and water (for decoction and infusion). The solvent was evaporated under reduced pressure at 40°C using a rotary vacuum evaporator. The extracts were then lyophilized and stored at -20°C.	Four compounds, namely, phenolic compounds, specifically luteolin-7-O-glucoside, rosmarinic acid, thymol, and carvacrol, were identified using HPLC.	3T3-Swiss albino mice fibroblast cells (<i>in vitro</i>), the age and weight were not described. The study did not use animal models; the research focused on <i>in vitro</i> cellular studies using fibroblasts.	<i>In vitro</i> study using suppression of nitric oxide (NO) and tumor necrosis factor-alpha (TNF-α) production in lipopolysaccharide (LPS)-stimulated macrophages. Decoction and infusion extracts showed the highest inhibition of NO production (50.86% and 47.79%, respectively) and TNF-α production (54.79% and 49.76%, respectively) at 50 µg/mL. The extract showed the highest activity with a percentage inhibition of 50.86%. This decreased in NO production by the extract might protect macrophages from NO damage, reflecting anti-inflammatory activity.	<i>In vivo</i> study using scratch assay This study was divided into six groups: Decoction and infusion extracts were applied at concentrations of 50, 100, and 200 µg/mL to determine their effects on wound closure. Scratch test: the percentage closure of the scratched area was 19.4% in the control cells, while the average closure percentage was 35.74%. Decoction and infusion extracts showed wound closure rates approximately 3.6 and 4.2 times higher than untreated controls. The decoction and infusion extracts <i>T. sipyleus</i> were particularly promoting fibroblast migration and proliferation, supporting their traditional use in wound healing treatments, reflecting wound healing activity.	Mechanism of toxicity was not described.	(Ustuner et al., 2019)
<i>Urtica dioica</i> L., Greece. Place and year of collection was not described. The herbs were extracted using ethyl acetate followed by acetonitrile, and then double-distilled water with Soxhletation method and the solvent was removed from the extract through freeze-drying (lyophilization), and the dry extract was stored at -80°C to prevent chemical degradation	Six compounds namely, saponins, flavonoids, carbohydrates, ketoses, resins, and coumarins, were identified using ¹ H NMR spectroscopy.	Wistar male rats. The age and weight were not described. The animal source was in Greece.	<i>In vitro</i> study using histopathological analysis in rats (red blood cell (RBC) membrane stabilization and inhibition of protein denaturation). RBC stabilization was observed at 30% and 75% at concentrations of 0.2 g/L and 1 g/L, respectively. Protein denaturation inhibition reached 50% at a concentration of 0.42 g/L. Few fibroblasts were observed, and maturation started at deeper sites, while re-epithelialization started at the periphery. It was shown that the inflammatory granulomatous tissue was more mature with fewer chronic inflammatory cells, significantly reduced edema and capillary blood vessels with more mature/flattened endothelial cells could be observed, reflecting anti-inflammatory activity.	<i>In vivo</i> study using linear incision and excision wound models in rats. The rats were divided into three groups: - Positive control group: Madecassol cream. - Two treat groups: Wounds treated with ointments containing 2 mg/g and 4 mg/g of the <i>Urtica dioica</i> extract. Rats were treated with two concentrations of extracts (i.e., 200 and 400 µg per dose). On day 6, the area of Madecassol-treated wounds was reduced by 45 ± 2% and the area treated with the extract was reduced by 80 ± 2.5%, Madecassol-treated wounds healed completely by day 12, while extract-treated wounds healed between days 9 and 10. The extract accelerated wound closure, reduced inflammation, promoted cell proliferation, and increased fibroblast activity, making it a promising natural therapeutic for wound care, reflecting wound healing activity.	Mechanism of toxicity was not described.	(Kasouni et al., 2021)

Table 1. *In vitro* and *in vivo* studies of anti-inflammatory and wound healing activities of plants (continued...)

Species, plant origin, year sampled, extraction method, solvent	Analysis of secondary metabolites	Characteristics of the animals and source	Anti-inflammatory test method, results, and statistical analysis	Wound healing test method, results, and statistical analysis	Mechanism and safety	Reference
<i>Zehneria scabra</i> L. leaves were collected in 2021. Place of collection was not described. The leaves were extracted using 80% methanol for ointment preparation made with maceration method and the solvent was evaporated under reduced pressure at 40°C	Six compounds namely, alkaloids, flavonoids, saponins, tannins, terpenoids, and steroids, were identified using standard phytochemical screening methods.	Swiss albino both male and female mice, 6–8 weeks, 25 ± 5 g. The animal source was in Ethiopia.	<i>In vivo</i> study using carrageenan-induced paw edema model in mice. The mice were divided into five groups: - Negative control: Normal saline solution. - Three treat groups: 100 mg/kg, 200 mg/kg and 400 mg/kg of fraction. - Positive control: 5 mg/kg indomethacin. Anti-inflammatory activity showed statistically significant anti-inflammatory action ($p<0.05$; $p<0.01$; $p<0.001$, respectively) starting at the second hour of observation, resulting in an edema inhibition of 61.5%. At 400 mg/kg, the maximum inhibition of paw edema was observed (52.8%). <i>Z. scabra</i> fractions possess significant anti-inflammatory, reflecting anti-inflammatory activity.	<i>In vivo</i> study using linear incision and excision wound model testing in mice. The mice were divided into six groups: - Negative control: Simple ointment base. - Three treat groups: 5% and 10% ethyl acetate fraction ointment; 5% and 10% aqueous fraction ointment. - Positive control: 0.2% nitrofurazone ointment. Significant wound reduction ($p<0.05$ and $p<0.01$) in the excision wound model. The 10% ethyl acetate and aqueous fraction ointments significantly accelerated wound contraction and reduced the epithelization period compared to the negative control, reflecting wound healing activity.	No toxicity was observed up to 2000 mg/kg. The solvent fractions showed no adverse effects on mice during the 14-day observation period.	(Fisseha et al., 2022)
<i>Ziziphus jujuba</i> Mill. flower blossoms were collected in Romania, in 2022. The flower blossoms were extracted using 70% ethanol (made into ointment with 10% concentration) with reflux method and the solvent was evaporated under reduced pressure.	Three compounds namely, rutin, quercetin, and chlorogenic acid, were identified using UHPLC-ESI-MS/MS.	Wistar male rats, 9 weeks old, 214–259 g. New Zealand male albino rabbits, the age was not describe, 4.55 ± 0.07 kg. The animal source was in Romania.	<i>In vivo</i> study using inhibition of carrageenan-induced paw edema in rats. The rats were divided into three groups: - Treat group: lipophilic ointment containing <i>Z. jujuba</i> extract. - Negative control: Lipophilic base. - Positive control: Indomethacin ointment (40 mg/g). The lipophilic ointment containing <i>Z. jujuba</i> extract reduced paw edema by 42.24% at 4 hours, compared to 58.02% in the control group and 44.33% with Indomethacin ointment. <i>Z. jujuba</i> extract reduced paw edema, reflecting anti-inflammatory activity.	<i>In vivo</i> study using burn model testing in rabbits. The rabbits were divided into four groups: - Treat group: Lipophilic ointment containing <i>Z. jujuba</i> extract. - Negative control: Lipophilic base. - Positive control: Cicatrizin ointment. - Normal control: Untreated. A wound closure rate of 79.07% by day 12, compared to 76.76% in the untreated group and 85.09% in the Cicatrizin-treated group. The <i>in vivo</i> test reduced inflammation and enhanced wound closure rates comparable to reference drugs, reflecting wound healing activity.	Mechanism of toxicity was not described.	(Hovaneț et al., 2022)

Table 2. List of plant species with anti-inflammatory and wound healing mechanisms.

No	Plant	Anti-inflammatory activities	Wound healing activities
1.	<i>Achillea asiatica</i> (family Asteraceae)	Inhibition of nitric oxide (NO) production	Linear incision wound model
2.	<i>Aloe megalacantha</i> Baker (family Asphodelaceae)	Carrageenan-induced paw edema	Linear incision and excision wound models
3.	<i>Aloe trigonantha</i> (family Asphodelaceae)	Xylene-induced ear edema model	Excision and incision wound models
4.	<i>Argemone mexicana</i> (family Papaveraceae)	Carrageenan-induced paw edema	Excision and incision wound models
5.	<i>Artemisia campestris</i> (family Asteraceae)	Carrageenan-induced paw edema	Linear incision and excision wound models
6.	<i>Bergia ammannioides</i> (family Elatinaceae)	Xylene-induced ear edema model	Excisional wound model
7.	<i>Clematis simensis</i> (family Ranunculaceae)	Carrageenan-induced paw edema	Linear incision and excision wound models
8.	<i>Clerodendrum myricoides</i> (family Lamiaceae)	Carrageenan-induced paw edema	Excision, incision, and burn wound models
9.	<i>Commiphora guidottii</i> (family Burseraceae)	Carrageenan-induced paw edema	Linear incision wound model
10.	<i>Crassocephalum crepidioides</i> (family Asteraceae)	Inhibition of NO production	Excision wound model
11.	<i>Curcuma longa</i> (family Zingiberaceae)	Carrageenan-induced paw edema	Circular wound measurement
12.	<i>Curcuma mangga</i> (family Zingiberaceae)	Inhibition of NO production	Proliferation of human dermal fibroblast (HDF) cells
13.	<i>Dioscorea bulbifera</i> (family Dioscoreaceae)	Inhibition of NO production	Wound healing test using HDF cells
14.	<i>Dorema aucheri</i> (family Apiaceae)	levels of TNF-measurement of inflammatory mediators using ELISA	Excisional wound model
15.	<i>Ephedra ciliata</i> (family Ephedraceae)	Carrageenan-induced paw edema	Linear incision and excision wound models
16.	<i>Euphorbia hirta</i> (family Euphorbiaceae)	Inhibition of NO production	Excision wound model
17.	<i>Globularia alypum</i> (family Plantaginaceae)	Carrageenan-induced paw edema	Circular burn model testing
18.	<i>Jatropha neopauciflora</i> (family Euphorbiaceae)	Carrageenan-induced paw edema	Wound model measurement
19.	<i>Kaempferia marginata</i> (family Zingiberaceae)	Inhibition of NO production	Wound healing test using HDF cells
20.	<i>Mangifera indica</i> (family Anacardiaceae)	Histopathological analysis	Measurement of wound contraction
21.	<i>Ononis spinosa</i> (family Fabaceae)	Carrageenan-induced paw edema	Linear incision and circular excision wound models
22.	<i>Phlomis russeliana</i> (family Lamiaceae)	Inhibition of NO production	Excisional wound model
23.	<i>Plantago australis</i> (family Plantaginaceae)	Carrageenan-induced paw edema	Scratch test

Table 2. List of plant species with anti-inflammatory and wound healing mechanisms (continued...)

No	Plant	Anti-inflammatory activities	Wound healing activities
24.	<i>Plumbago zeylanica</i> Linn. (family <i>Plumbaginaceae</i>), <i>Datura stramonium</i> Linn. (family <i>Solanaceae</i>), and <i>Argemone mexicana</i> Linn. (family <i>Papaveraceae</i>)	Carrageenan-induced paw edema	Linear incision and excision wound models
25.	<i>Portulaca pilosa</i> (family <i>Portulacaceae</i>)	Histopathological analysis	Excision wound model
26.	<i>Rumex abyssinicus</i> (family <i>Polygonaceae</i>)	Carrageenan-induced paw edema	Linear incision and excision wound models
27.	<i>Schinus terebinthifolius</i> (family <i>Anacardiaceae</i>)	Histopathological analysis	Linear incision and excision wound models
28.	<i>Solanum diploconos</i> (family <i>Solanaceae</i>)	Inhibition of NO production	Scratch test
29.	<i>Streptocaulon juvenas</i> (family <i>Apocynaceae</i>)	Inhibition of Nitric Oxide (NO) production	Excision wound model
30.	<i>Thymus Sipyleus</i> (family <i>Lamiaceae</i>)	Inhibition of NO production	Scratch test
31.	<i>Urtica dioica</i> (family <i>Urticaceae</i>)	Histopathological analysis	Linear incision and excision wound models
32.	<i>Zehneria scabra</i> (family <i>Cucurbitaceae</i>)	Carrageenan-induced paw edema	Linear incision and circular excision wound models
33.	<i>Ziziphus jujuba</i> (family <i>Rhamnaceae</i>)	Carrageenan-induced paw edema	Burn model testing

From the analysis conducted, *Crassocephalum crepidioides* and *Kaempferia marginata* showed higher effectiveness in inhibiting NO production, supported by metabolite compounds such as flavonoids, curcumin, phenolic compounds, and terpenoids. The mechanism of action of these metabolites involves inhibition of NOS activity and reduction of free radicals, thereby reducing the inflammatory response. Further research is needed to explore the therapeutic potential and specific mechanisms of action of these compounds.

Carrageenan-induced paw edema

In a study on carrageenan-induced edema inhibition, various medicinal plants showed different effectiveness in reducing inflammation. From the analysis conducted, *Argemone mexicana* and *Aloe megalacantha* showed the most significant results in inhibiting edema, with *Argemone mexicana* recording a 61.41% reduction in edema (Mengie Ayele et al., 2022) and *Aloe megalacantha* at a high dose of 600 mg/kg showing a highly significant reduction (p<0.001) within 3 hours of administration (Gebremeskel et al., 2018). Both plants contain secondary compounds that play an important role in anti-inflammatory effects, namely flavonoids, saponins, and tannins (Chagas et al., 2022). Flavonoids are found in *Aloe megalacantha*,

Argemone mexicana, and *Clerodendrum myricoides*. Flavonoids function by inhibiting cyclooxygenase (COX) and lipoxygenase (LOX) enzymes, which are involved in the production of prostaglandins and leukotrienes, reducing the inflammatory response induced by carrageenan (Mukhopadhyay et al., 2023). Tannins are present in *Clematis simensi*, *Curcuma longa*, and *Rumex abyssinicus*. Tannins can bind to proteins and affect cell membrane permeability, reducing exudate and swelling caused by inflammation (Adamczyk et al., 2017). Saponins are found in *Artemisia campestris* and *Globularia alypum*. Saponins have immunomodulatory effects and can reduce inflammatory cell activity by inhibiting the production of NO and inflammatory cytokines, which contributes to the reduction of edema (Jung et al., 2005). Alkaloids are present in *Argemone mexicana* and *Commiphora guidottii*. Alkaloids function as inhibitors of various inflammatory signaling pathways, reducing the release of inflammatory mediators such as histamine and serotonin, which can cause edema (Aryal et al., 2022). Curcumin and its derivatives are found in *Curcuma longa*. Curcumin shows the ability to inhibit the NF-κB pathway and reduce prostaglandin synthesis, which reduces inflammation (Petrone-Garcia et al., 2021). Steroids are present in *Commiphora guidottii* and *Zehneria scabra*. Steroids reduce inflammation by suppressing the

immune response and inhibiting the activation of inflammatory cells (Mukhopadhyay et al., 2023).

Based on the effectiveness shown, *Argemone mexicana* and *Aloe megalacantha* are the most effective plants in inhibiting carrageenan-induced edema. The metabolites that play a major role in this effect are flavonoids, tannins, saponins, and alkaloids, which function by various mechanisms to reduce the production of inflammatory mediators and enhance anti-inflammatory responses. Further research is needed to explore the therapeutic potential of these compounds in the treatment of inflammation.

Xylene-induced ear edema model

In the xylene-induced ear edema model, both plants, *Aloe trigonantha* and *Bergia ammannioides*, showed effectiveness in reducing inflammation, although in different ways and with different success rates. From the available data, *Bergia ammannioides* showed higher effectiveness compared to *Aloe trigonantha*. *Bergia ammannioides* showed edema inhibition of 64.5% with the HxFr fraction and its main component, β -sitosterol, showing the highest inhibitory effect of up to 83.8%. This shows the great potential of *Bergia ammannioides* in overcoming xylene-induced edema (Ezzat et al., 2016). *Aloe trigonantha*, although it showed 41.5% inhibition of inflammation at the highest dose, its effectiveness was still below that of *Bergia ammannioides* and comparable to indomethacin (42.6%). This study suggests that *Aloe trigonantha* also has potential, but not as strong as *B. ammannioides* in this model. Flavonoids are present in *Aloe trigonantha* and *Bergia ammannioides*. Flavonoids function by inhibiting COX and LOX enzymes, which reduce the synthesis of prostaglandins and leukotrienes, two key mediators in the inflammatory process (Mukhopadhyay et al., 2023). By lowering the levels of these mediators, flavonoids reduce edema caused by xylene (Singsai et al., 2020). β -Sitosterol is found in *Bergia ammannioides*. β -Sitosterol is known to have potent anti-inflammatory effects by inhibiting the NF- κ B signaling pathway, which plays a role in the regulation of immune and inflammatory responses. By suppressing NF- κ B activation, β -sitosterol can reduce the production of inflammatory cytokines and mediators that contribute to edema (Sun et al. 2020). Tannins are present in *Aloe trigonantha*. Tannins can bind to proteins and modulate cell membrane permeability, which reduces fluid transudation and exudate in the affected area, helping to reduce swelling and inflammation (Sun et al., 2020). Kaempferol is found in *Bergia ammannioides* (Ezzat et al., 2016). Kaempferol has anti-inflammatory effects that can inhibit NO and cytokine production through inhibition of the NF- κ B pathway and inhibition of COX enzymes, which con-

tributes to the reduction of xylene-induced edema (Ren et al., 2019).

From the analysis conducted, *Bergia ammannioides* showed higher effectiveness compared to *Aloe trigonantha* in inhibiting xylene-induced ear edema. Metabolites involved in this effect include flavonoids, β -sitosterol, and tannins, with the mechanism of action involving inhibition of inflammatory mediators and modification of immune response. Further research is needed to explore the therapeutic potential of these compounds and their specific mechanisms in the treatment of inflammation.

Levels of TNF-measurement of inflammatory mediators using ELISA

In the measurement of inflammatory mediators using ELISA, *Dorema aucheri* showed significant effectiveness in reducing tumor necrosis factor- α (TNF- α) levels in mice treated with DAG (0.2 mL 500 mg/kg), with TNF- α levels recorded at 62.12 μ g/mL (Ahmed et al., 2024). These findings suggest a strong anti-inflammatory potential of *Dorema aucheri*, which may be related to its ability to stimulate wound healing. *Dorema aucheri* is a plant that has shown significant ability to inhibit the production of TNF- α , which is a key mediator in the inflammatory process. Decreasing TNF- α levels may contribute to the reduction of inflammation and accelerate the healing process, making it a promising option in anti-inflammatory medicine (Muth et al., 2023). Flavonoids function as inhibitors of TNF- α production by inhibiting the activation of NF- κ B and mitogen-activated protein kinase (MAPK) pathways, which are involved in the synthesis of inflammatory cytokines. By reducing TNF- α gene expression, flavonoids help reduce inflammatory reactions. Phenolic compounds have strong antioxidant activity, which helps neutralize free radicals and reduce oxidative stress (Muth et al., 2023). By lowering oxidative stress, these compounds can reduce the production of TNF- α and other inflammatory cytokines, thereby reducing overall inflammation (Muth et al., 2023). Polysaccharides can enhance immune responses and play a role in inflammation modulation. They can interact with immune cells and affect the production of cytokines, including TNF- α (Feng et al., 2020). In this way, polysaccharides help relieve inflammation and support the healing process. Essential oils (β -caryophyllene, thymol, carvacrol) are present in *Dorema aucheri* essential oil (Ahmed et al., 2024). These compounds are known to have anti-inflammatory effects by inhibiting inflammatory signaling pathways that trigger TNF- α production. For example, β -caryophyllene can modulate the activity of immune cells, leading to a reduction in the production of inflammatory mediators (Jha et al., 2021).

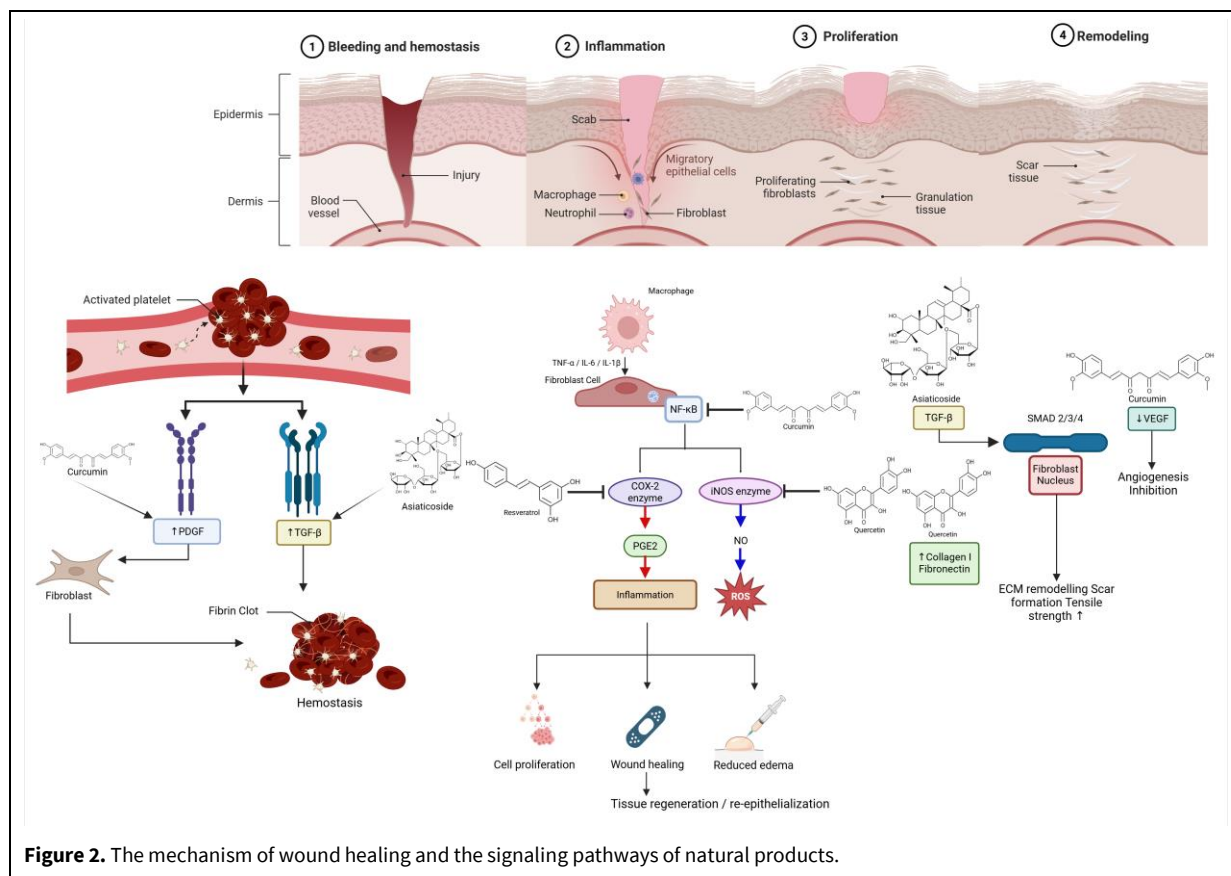


Figure 2. The mechanism of wound healing and the signaling pathways of natural products.

From the analysis conducted, *Dorema aucheri* showed significant effectiveness in reducing TNF- α levels, which was attributed to active metabolites such as flavonoids, phenolic compounds, polysaccharides, and essential oils. The mechanisms of action of these metabolites include inhibition of inflammatory signaling pathways and reduction of oxidative stress, which contribute to the reduction of inflammatory reactions. Further research is needed to explore the therapeutic potential of these compounds and their specific mechanisms in the treatment of inflammation.

Histopathological analysis

From the analysis conducted, *Schinus terebinthifolius* showed the most significant results in enhancing the healing process, followed by *Portulaca pilosa*. Flavonoids are found in *Portulaca pilosa* and *Urtica dioica* (Barros et al., 2017; Kasouni et al., 2021). p-Cymen-7-ol and essential oil components are found in *Schinus terebinthifolius* (Kasouni et al., 2021). These compounds are known to have anti-inflammatory effects by inhibiting inflammatory signaling pathways and promoting angiogenesis and collagen deposition. This contributes to tissue repair and wound healing. Saponins and carbohydrates are present in *Urtica dioica*. Saponins have immunomodulatory properties that

can reduce inflammatory reactions and help accelerate the healing process (Pishgahzadeh et al., 2019).

Based on the analysis conducted, *Schinus terebinthifolius* showed the highest effectiveness in reducing inflammation and supporting wound healing, followed by *Portulaca pilosa*. Metabolites that play a major role in these effects include flavonoids, phenols, p-cymen-7-ol, and saponins, with mechanisms that include inhibition of inflammatory mediators, increased angiogenesis, and reduced oxidative stress. Further research is needed to explore the therapeutic potential of these compounds in the treatment of inflammation.

Wound healing

Fig. 2 shows a summary of the healing mechanism of action of some plant-derived compounds that have been discussed in this systematic review.

Linear incision wound model

In the linear incision wound model, the two plants, *Achillea asiatica* and *Commiphora guidottii*, showed different effectiveness in supporting wound healing. From the analysis conducted, *Achillea asiatica* showed more effective results in increasing the rate of wound closure than *Commiphora guidottii*. *Achillea asiatica* showed a significant increase in the rate of wound closure, with a reduction in wound area of

about 50% in 8 days (Dorjsembe et al., 2017). *Commiphora guidottii* has a strength of 29.42%, showing potential in promoting wound healing (Gebrehiwot et al., 2015). Flavonoids are found in *Achillea asiatica*. Flavonoids such as quercetin and apigenin work by inhibiting inflammatory signaling pathways and promoting angiogenesis, which is important for the wound healing process (Huang et al., 2024). Chlorogenic acid is found in *Achillea asiatica* (Dorjsembe et al., 2017). Chlorogenic acid has anti-inflammatory and antioxidant effects. This compound can reduce the production of inflammatory cytokines and help speed up the healing process by increasing tissue regeneration (Hwang et al., 2014). Terpenoids are found in *Commiphora guidottii* (Gebrehiwot et al., 2015). Terpenoids are known to have strong anti-inflammatory effects. They can modulate inflammatory signaling pathways and reduce the accumulation of inflammatory mediators, which helps in the wound healing process (Del Prado-Audelo et al., 2021). Phenolic compounds are found in *Commiphora guidottii* (Gebrehiwot et al., 2015). Phenolic compounds function as antioxidants and reduce oxidative stress, which contributes to the reduction of inflammation and accelerates the wound healing process (Rajashekar, 2023).

From the analysis conducted, *Achillea asiatica* showed higher effectiveness in supporting wound healing compared to *Commiphora guidottii*. Metabolites involved in this effect include flavonoids, chlorogenic acid, terpenoids, and phenolic compounds, with mechanisms of action that include inhibition of inflammatory mediators, enhancement of angiogenesis, and reduction of oxidative stress. Further research is needed to explore the therapeutic potential of these compounds in wound treatment.

Linear incision and excision wound models

In the incisional and excisional wound models, several plants showed variations in effectiveness in supporting the wound healing process. From the analysis conducted, *Aloe megalacantha* and *Urtica dioica* showed the most promising results, with *Aloe megalacantha* being the most effective, followed by *Urtica dioica*. *Aloe megalacantha* showed a significant degree of wound contraction, with 100% wound healing on day 13 for treatment with 5% and 10% latex ointment (Gebremeskel et al., 2018). *Urtica dioica*, although not as effective as *Aloe megalacantha*, this plant showed wound contraction of $80 \pm 2.5\%$ on day 6 (Kasouni et al., 2021). *Clematis simensis* showed a good wound contraction rate of 96.28% on application of 10% ointment on day 14 (Teshome et al., 2022). *Rumex abyssinicus* showed significant wound healing activity, with an increase in tensile strength of about 36.2% (Mulisa et al., 2015). Flavonoids are found in all these

plants. Flavonoids inhibit COX and LOX enzymes, which reduce the production of prostaglandins and leukotrienes, thereby reducing inflammation and promoting wound healing. Flavonoids also function as antioxidants that protect cells from damage (Mukhopadhyay et al., 2023). Tannins are found in *Artemisia campestris*, *Rumex abyssinicus*, and *Commiphora guidottii*. Tannins can bind to proteins, reduce cell permeability, and reduce fluid accumulation in tissues, which is important in reducing edema and accelerating healing (Adamczyk et al., 2017). Saponins are found in *Urtica dioica*, *Rumex abyssinicus*, and *Clematis simensis*. Saponins increase immune activity and have anti-inflammatory properties that can reduce the number of inflammatory cells, accelerate wound healing by modulating immune responses (Chen et al., 2023).

From the analysis conducted, *Aloe megalacantha* showed the highest effectiveness in supporting wound healing, followed by *Urtica dioica* and *Clematis simensis*. Metabolites involved in this effect included flavonoids, tannins, saponins, and terpenoids, with mechanisms including inhibition of inflammatory mediators, enhancement of angiogenesis, and protection of cells from oxidative damage. Further research is needed to explore the therapeutic potential of these compounds in wound treatment.

Excision and incision wound models

The use of *Aloe trigonantha* and *Argemone mexicana* on excisional and incisional wound models showed significant improvement in the wound healing process. In a related study, application of a 5% *Aloe trigonantha*-containing ointment resulted in a 12.6% decrease in epithelialization period compared to the control group, while wound tensile strength increased by 26.5%, 37.6%, and 38.3% at gel concentrations of 5%, 10%, and 0.2% nitrofurazone, respectively. *Argemone mexicana*, on the other hand, showed a higher increase in tensile strength, by 55% and 81.10% at 5% and 10% ointment concentrations ($p < 0.01$), suggesting greater effectiveness in strengthening new tissue structures in excisional and incisional wounds (Mengie Ayele et al., 2022). Secondary metabolites present in these two plants, such as flavonoids, glycosides, phenols, tannins, alkaloids, saponins, terpenoids, and steroids, have specific roles in accelerating the wound healing process. Flavonoids, which are found in both plants, have antioxidant properties that are important in reducing inflammation, aiding in the formation of new tissue, as well as lowering the risk of infection (Bouyahya et al., 2021). Glycosides and phenols, which are also contained in *Aloe trigonantha*, contribute to cellular regeneration as well as the formation of a strong tissue layer (Mengie Ayele et al.,

2022). In addition to flavonoids and glycosides, *Argemone mexicana* contains alkaloids, saponins, terpenoids, and steroids that provide additional benefits to wound healing (Mengie Ayele et al., 2022).

Overall, *Argemone mexicana* showed higher effectiveness in increasing tensile strength in wound tissues compared to *Aloe trigonantha*, mainly due to its alkaloid and saponin contents that provide additional antimicrobial benefits and better absorption. These two plants, with their diverse secondary metabolite profiles, show great potential in wound healing applications in excision and incision models, making them strong candidates for the development of effective wound healing ointments.

Excisional wound model

The effectiveness of wound healing in the excision model using plants such as *Bergia ammannioides*, *Crassocephalum crepidioides*, *Dorema aucheri*, *Euphorbia hirta*, *Phlomis russeliana*, *Portulaca pilosa*, and *Streptocaulon juvenas* showed significant results, with variations in activity based on the concentration and type of secondary metabolites contained in each plant. The secondary metabolites found in this study, such as flavonoids, phenolics, tannins, alkaloids, terpenoids, polysaccharides, as well as compounds such as β -sitosterol and phytol, have an important role in accelerating the wound healing process. The flavonoids and phenolics found in abundance in this plant function as powerful antioxidants that reduce oxidative stress in the wound area, promote tissue regeneration, and accelerate wound contraction (Pietta, 2000). Tannins and flavonoids also contribute to tissue strengthening through astringent activity, which makes wounds heal faster and are resistant to infection. Components such as β -sitosterol, lupeol, and saponins act as anti-inflammatory and antimicrobial agents, helping to reduce swelling and prevent infection in open wounds (Sun et al., 2020). These anti-inflammatory effects reduce excessive inflammatory cell migration, thus allowing faster epithelialization. In addition, saponins help increase the permeability of cell membranes, which improves the absorption of nutrients and drugs in the wound area (Sudji et al., 2015). The polysaccharide content also functions as a humectant that maintains moisture in the wound area, supporting faster wound contraction and accelerating the epithelialization process (Xue et al., 2022). Compounds such as gallic acid and mucilage in *Portulaca pilosa* exhibit astringent effects, strengthen new tissue structures, and support wound contraction well (Hadidi et al., 2024). Notable results in the excisional wound model were obtained with the application of metabolites in certain concentrations, as shown in *Streptocaulon juvenas*, which achieved almost 99.47%

wound closure in 12 days, compared to only 67.86% in the control group (Nguyen et al., 2017).

The use of these plants with different metabolite profiles contributes significantly to wound healing, especially through their antioxidant, anti-inflammatory, and antimicrobial activities. The flavonoids, tannins, saponins, and alkaloids work synergistically to promote new tissue strength, accelerate epithelialization, and provide antimicrobial protection essential for faster and more effective wound healing.

Excision, incision, and burn wound models

Research on excision, incision, and burn wound models showed that the use of *Clerodendrum myricoides* extract had significant effectiveness in accelerating the epithelialization period, with a decrease of 27.55% at 10% compared to the control group, while 0.2% nitrofurazone ointment decreased epithelialization by 24.38% (Beyna et al., 2024). These results indicate that higher concentrations of plant extracts provide better results in wound healing. The secondary metabolites found in *Clerodendrum myricoides*-flavonoids, alkaloids, and tannins-have significant roles in supporting wound healing. Flavonoids, as powerful antioxidants, help reduce oxidative stress on the wound area, inhibit free radicals, and support new tissue formation (Subramanian et al., 2023). This antioxidant activity reduces cell damage and accelerates skin regeneration. The alkaloids in *Clerodendrum myricoides* act as effective anti-inflammatory and antimicrobial agents, which are essential for preventing infection in open wounds. The anti-inflammatory mechanism of alkaloids works by inhibiting the production of inflammatory mediators, thereby reducing swelling and pain (Filho et al., 2006). In addition, the antimicrobial properties of alkaloids help suppress bacterial growth in the wound area, which speeds up the healing process and reduces the risk of infectious complications (Vitale et al., 2022). Tannins have an important role in accelerating tissue contraction and strengthening new tissue structures. Tannins' mechanism as an astringent helps to reduce fluid exudation from wounds, promote the formation of granulation tissue, and strengthen newly formed tissue (Soares et al., 2020). These effects contribute to increased wound tensile strength and accelerate the wound closure process, especially in excisional and incisional wound models.

Overall, *Clerodendrum myricoides* extract showed high effectiveness in wound healing in excision, incision, and burn models, mainly through the combination of antioxidant activity of flavonoids, anti-inflammatory and antimicrobial activity of alkaloids, and astringent effect of tannins. The flavonoid content provides protection against oxidative stress, while the

alkaloids prevent infection, and the tannins support tissue contraction and strengthening, making this plant a potential candidate for the development of wound-healing topical drugs.

Circular wound measurement

In a study, using a circular wound model, *Curcuma longa* with a 6 mm diameter demonstrated high effectiveness in wound healing. The use of curcumin (1%), demethoxycurcumin (DMC, 1%), and bisdemethoxycurcumin (BDMC, 1%) resulted in 100% wound closure, while the control group was only 88% (Islam et al., 2024). This demonstrates the effectiveness of curcumin and its derivatives in accelerating wound healing. Curcumin, demethoxycurcumin (DMC), and bisdemethoxycurcumin (BDMC) in *Curcuma longa* have important roles in wound healing through their strong antioxidant and anti-inflammatory properties (Kumari et al., 2022). Curcumin, as an antioxidant, reduces free radical-induced cell damage in the wound area, thus helping to accelerate tissue regeneration and the formation of new cells. In addition, curcumin inhibits inflammation through the inhibition of pro-inflammatory enzymes such as COX-2, which reduces swelling and pain in the wound area (Yen et al., 2018). Curcumin plays a role in increasing the production of type III collagen, which is important for tissue contraction and strengthening during the healing process (Yahya et al., 2020).

Overall, curcumin, DMC, and BDMC in *Curcuma longa* showed high effectiveness in circular wound healing by utilizing their strong antioxidant and anti-inflammatory activities. Curcumin acts as an antioxidant agent that prevents cell damage, while DMC and BDMC provide additional protection through inflammation reduction and infection prevention. The combination of these three metabolites supports new tissue formation and faster epithelialization, making *Curcuma longa* a strong candidate for wound care.

Proliferation of human dermal fibroblast (HDF) cells

In an HDF cell proliferation study, *Curcuma mango* extract showed significant ability to increase cell migration, which is an important indicator in the wound healing process. Tests showed that HDF cell migration reached 80.1% after 36 hours with the use of 5% by weight extract, followed by 2% (78.7%) and 10% (76.4%) concentration creams. After heating and cooling tests, the 5% concentration extract at a dose of 3 µg/mL still showed an increase in cell migration of 75.2% compared to the control (61.1%), demonstrating the effectiveness of curcuminoids and labdane diterpenes in supporting the healing process (Patiola et al., 2023). Curcuminoids, such as curcumin, demethoxycurcumin, and bisdemethoxycurcumin, play a major

role in accelerating HDF cell migration and proliferation (Cianfruglia et al., 2019). Curcuminoids are known to have strong antioxidant activity, which helps reduce oxidative stress in fibroblast cells, protects against free radical damage, and supports tissue repair (Alabdali et al., 2021). By reducing oxidation in the wound area, curcuminoids allow fibroblast cells to more easily proliferate and migrate to the damaged area, accelerating the proliferation phase in wound healing (Fei et al., 2024). Labdane diterpenes, including demethoxycurcumin and other compounds such as 15,16 bisnorlaba-8, support fibroblast cell migration through anti-inflammatory mechanisms and inhibition of inflammatory mediators (Pertino et al., 2013). Curcuminoids and labdane diterpenes also support granulation tissue formation, which is important for optimal wound healing. Curcumin and its derivatives are known to increase collagen production and regulate the life cycle of fibroblast cells, ensuring that new cells can develop properly in the wound area (Sharma and Sharma, 2017).

Curcuma mango extract, through its curcuminoids and labdane diterpenes content, was shown to be effective in enhancing the migration and proliferation of human dermal fibroblast cells, with significant results at an extract concentration of 5% by weight (Yahya et al., 2020). Curcuminoids provide antioxidant protection and support collagen formation, while labdane diterpenes reduce inflammation and support granulation tissue formation. This combination makes *Curcuma mango* a potential candidate for wound treatment and repair of damaged skin tissue.

Wound healing test using human dermal fibroblast (HDF) cells

In a wound healing assay using HDF cells, *Dioscorea bulbifera* and *Kaempferia marginata* showed high effectiveness in increasing HDF cell viability and migration. N-hexane fraction of *Dioscorea bulbifera* showed cell viability between 107.4-137.6%, while ethyl acetate fraction achieved the highest viability between 121.1-151.9% (Chaniad et al., 2020). Meanwhile, *Kaempferia marginata* gel extract (5% w/w) produced the highest cell viability at 134.05% with cell migration of 85.20% (Muthachan and Tewtrakul, 2019). This suggests that the metabolite content in these two plants is very effective in supporting wound healing. Catechin, which is one of the main metabolites in *Dioscorea bulbifera*, was shown to increase fibroblast migration by 2.4 times compared to the control after 24 hours (Chaniad et al., 2020). Catechin functions as a powerful antioxidant that protects cells from oxidative damage, thus supporting fibroblast cell proliferation and migration necessary for wound healing (Kumari et al., 2022). In *Kaempferia*

marginata, curcuminoids and diterpenes play an important role in supporting fibroblast migration and proliferation activities. Curcuminoids are known to have anti-inflammatory effects that reduce the production of inflammatory mediators, such as TNF- α and IL-6, which promote faster tissue regeneration in the wound area (Rinkunaite et al., 2021). Diterpenes in *Kaempferia marginata* also function as inflammation inhibitors, support a stable cell environment, and accelerate the epithelialization phase, which is important for rapid wound closure and reduced risk of infection (Islam et al., 2020). Quercetin, kaempferol, and myricetin in *Dioscorea bulbifera* also contribute to increased HDF cell viability and proliferation. Quercetin and kaempferol are known to stimulate collagen production, which strengthens new tissue and increases the tensile strength of wounds (Shahbaz et al., 2023). In addition, curcuminoids in *Kaempferia marginata* support epithelial cell migration and granulation tissue formation, thus accelerating healing (Ma et al., 2024). This increase in cell viability is an important indication of the effectiveness of both plants in accelerating wound healing.

Overall, *Dioscorea bulbifera* and *Kaempferia marginata* showed high effectiveness in wound healing through enhancing fibroblast cell migration and viability. Catechin, quercetin, and kaempferol in *Dioscorea bulbifera* play important roles in enhancing cell proliferation and migration, while curcuminoids and diterpenes in *Kaempferia marginata* support anti-inflammatory and tissue regeneration activities. This combination of metabolites makes these two plants strong candidates in the formulation of effective wound-healing topical agents.

Circular burn model testing

In the circular burn model test, *Globularia alypum* showed high effectiveness in accelerating wound healing, with significantly reduced wound areas on days 12 ($p < 0.01$) and 16 ($p < 0.001$) compared to the untreated group (Ghissi et al., 2016a). This suggests that secondary metabolites such as cinnamic acid, linoleic acid, oleic acid, palmitic acid, and stearic acid play a key role in accelerating the wound healing process. Cinnamic acid acts as an effective anti-inflammatory agent, reducing inflammation around the wound and supporting a faster healing process (Haghighi et al., 2024). The antioxidant properties of cinnamic acid also help to reduce oxidative stress, which can damage cells around wounds, thereby promoting the proliferation of new skin cells and accelerating tissue regeneration. Linoleic acid and oleic acid play an important role in accelerating the formation of new tissue in the burn area (Jara et al., 2020). Oleic acid, as an emollient, provides an addi-

tional protective effect that allows cell regeneration to proceed more smoothly (Deng et al., 2023). These two fatty acids work together to strengthen the skin barrier and support faster formation of granulation tissue. Palmitic and stearic acids help in accelerating wound closure by promoting cell migration and proliferation. These two fatty acids function as emollient agents that help smooth damaged skin surfaces, facilitate regeneration, and strengthen the new skin barrier. In addition, they help prevent infection in burn wounds by creating a protective layer on the skin surface, which reduces the risk of bacterial contamination during the healing process (Weimann et al., 2018).

Globularia alypum is effective in healing burn wounds thanks to secondary metabolites such as cinnamic acid, linoleic acid, oleic acid, palmitic acid, and stearic acid. Cinnamic acid shows anti-inflammatory and antioxidant activities, while linoleic and oleic acids preserve moisture and support new tissue formation. Palmitic and stearic acid help in accelerating migration and strengthening the skin barrier, making *Globularia alypum* a potent and potential burn wound healing agent.

Wound model measurement

In wound healing activity testing, *Jatropha neopauciflora* showed 100% wound healing effectiveness at all concentrations tested (50%, 75%, and 100%), with no significant difference between concentrations ($p < 0.05$) when compared to the control group undergoing wound healing therapy (Michalak, 2023). This effectiveness indicates that secondary metabolites such as phenols, flavonoids, carbohydrates (mainly fructose), and proteins play a major role in supporting the healing process. The phenols in *Jatropha neopauciflora* act as powerful antioxidants, protecting cells around the wound from oxidative damage that can slow healing (Tayyeb et al., 2024). By reducing oxidative stress, phenols help accelerate skin cell regeneration and support the formation of healthy new tissue. Phenol also has antimicrobial properties, which help protect the wound from infections that can slow down the healing process (Sabbineni, 2016). The flavonoids in this plant exert anti-inflammatory effects that reduce inflammation around the wound, accelerate the proliferation phase, and aid in the formation of granulation tissue. The anti-inflammatory properties of these flavonoids inhibit the activity of pro-inflammatory enzymes such as COX-2, which helps accelerate the migration and proliferation of fibroblast cells in the wound area, thus speeding up the epithelialization process (Ysrafil et al., 2023).

Jatropha neopauciflora is effective in wound healing thanks to a combination of phenols, flavonoids, fructose, and proteins. Phenols provide antioxidant and

antimicrobial protection, flavonoids act as anti-inflammatories that accelerate epithelialization, and fructose and proteins support energy requirements and collagen formation. This combination of metabolites makes *Jatropha neopauciflora* a potential agent for accelerating natural wound healing.

Measurement of wound contraction

In the *Mangifera indica* wound contraction measurement test, the use of 10% concentration extract showed high effectiveness by achieving more than 50% wound closure on the fifth day. This suggests that secondary metabolites such as phenols, resorcinol, conjugated resorcinol, and mangiferin play an important role in the wound healing process. The phenols in *Mangifera indica* function as powerful antioxidants, protecting cells around the wound from oxidative damage that can slow down tissue regeneration. The antioxidant activity of phenols helps reduce free radicals in the wound area, accelerates new tissue formation, and prevents oxidative stress. In addition, phenols have antimicrobial properties, which help keep the wound free from infection, allowing the healing process to proceed more quickly and effectively (Kaltalioglu et al., 2020). Resorcinol and conjugated resorcinol also play a role in supporting cell regeneration and new tissue formation. Resorcinol is known to have antiseptic and astringent properties, which strengthen the tissue in the wound area and help the wound contract faster. With its astringent properties, resorcinol attracts the tissues around the wound to coalesce, which supports the natural wound closure process. Conjugated resorcinol enhances the effectiveness of resorcinol in accelerating wound contraction and strengthening the newly formed tissue structure (Shpichka et al., 2019). Mangiferin is the main bioactive compound in *Mangifera indica* that has potent anti-inflammatory properties. Mangiferin works by inhibiting pro-inflammatory enzymes such as COX-2, which reduces inflammation in the wound area and supports the proliferation phase (Shpichka et al., 2019). In addition, mangiferin promotes fibroblast cell migration and proliferation, accelerates granulation tissue formation, and supports the epithelialization process, all of which are important in accelerating wound contraction.

Overall, *Mangifera indica* showed high effectiveness in wound healing through its metabolites phenol, resorcinol, conjugated resorcinol and mangiferin. Phenol acts as an antioxidant and antimicrobial, resorcinol accelerates wound contraction and strengthens new tissue, while mangiferin works as an anti-inflammatory that accelerates cell proliferation. This combination of metabolites makes *Mangifera indica* a

potential natural agent to effectively accelerate wound healing.

Linear incision and circular excision wound models

In linear incision and circular excision wound models, *Ononis spinosa* and *Zehneria scabra* showed high effectiveness in wound healing. *Ononis spinosa* ethyl acetate extract (EtOAc-SR) resulted in a 42.6% increase in tensile strength in the incision wound model and a 60.1% reduction in wound area on day 12 in the excision wound model (Öz et al., 2017). Meanwhile, *Zehneria scabra* showed significant wound reduction ($p < 0.05$ and $p < 0.01$) in the excisional wound model, with statistically significant shorter epithelialization time ($p < 0.001$) than the control (El-Sherbeni and Negm, 2023). Flavonoids in *Ononis spinosa* inhibit pro-inflammatory enzymes such as COX-2, which is important in reducing swelling and promoting fibroblast cell migration (Ju et al., 2022). Volatile oils such as anethol, carvone, and menthol in *Ononis spinosa* contribute to wound healing by providing antiseptic and soothing effects, which help reduce infection in open wounds (Bouyahya et al., 2021). *Zehneria scabra* contains alkaloids, saponins, and steroids that accelerate epithelialization and cell regeneration. Alkaloids in this plant act as antimicrobials that help prevent wound infection, while saponins increase cell membrane permeability, support nutrient and drug uptake in the wound area, and accelerate fibroblast cell migration (Bouyahya et al., 2021). Steroids act as anti-inflammatories that help reduce inflammation around the wound and support the rapid and robust formation of new tissue (Williams, 2018). Flavonoids and tannins in *Zehneria scabra* also provide an astringent effect that supports wound contraction and reduces fluid exudation from the wound area, which helps the wound close faster (Budiawan et al., 2023). The anti-inflammatory properties of the flavonoids in this plant also reduce inflammation, accelerate the proliferation process, and support faster formation of granulation tissue (Zulkefli et al., 2023).

Overall, *Ononis spinosa* and *Zehneria scabra* showed high effectiveness in wound healing through a combination of flavonoids, phenolics, volatile oils, terpenes, alkaloids, saponins, and steroids. Flavonoids and phenolic acids in *Ononis spinosa* provide antioxidant and anti-inflammatory protection, volatile oils and terpenes increase tissue strength, while alkaloids, saponins, and steroids in *Zehneria scabra* support epithelialization and prevent infection. This combination of metabolites makes these two plants potential agents in the treatment of wounds.

Scratch test

In the scratch test, *Plantago australis*, *Solanum diploconos*, and *Thymus sipyleus* showed effectiveness in stimulating wound healing by increasing fibroblast cell migration and closing the wound area faster than the control group. Verbascoside, a major metabolite in *Plantago australis*, functions as a powerful antioxidant that protects cells from free radical damage around the wound (Sperotto et al., 2018). In *Solanum diploconos*, phenolic compounds such as caffeic acid, ferulic acid, and coumaric acid support faster fibroblast cell migration in the wound area. Caffeic acid and ferulic acid have anti-inflammatory effects that help reduce inflammation around the wound, as well as increase antioxidant activity that promotes new tissue regeneration (Genaro-Mattos et al., 2015). Coumaric acid also functions as an antioxidant agent that accelerates wound contraction and aids in the formation of granulation tissue, which is important for strengthening skin structure during healing (Shen et al., 2019). Secondary metabolites in *Thymus sipyleus*, including luteolin-7-O-glucoside, rosmarinic acid, thymol, and carvacrol, have important roles in wound healing through anti-inflammatory and antimicrobial activities. Thymol and carvacrol also have antiseptic properties that protect the wound from bacterial infection, accelerate wound closure, and strengthen the new tissue formed (Costa et al., 2019).

Overall, *Plantago australis*, *Solanum diploconos*, and *Thymus sipyleus* showed high effectiveness in wound healing through metabolites such as verbascoside, phenolic compounds (caffeic, ferulic, coumaric acids), luteolin-7-O-glucoside, rosmarinic acid, thymol, and carvacrol.

Burn model testing

In the burn wound model test, *Ziziphus jujuba* showed high effectiveness in accelerating burn wound healing, with a wound healing percentage reaching 79.07% compared to the first day of treatment, in a burn area of 20 mm (Nguyen et al., 2024). Full recovery occurred within 18 days, indicating that secondary metabolites such as rutin, quercetin, and chlorogenic acid play an important role in the healing process. Rutin, one of the main flavonoids in *Ziziphus jujuba*, acts as a powerful antioxidant that helps reduce oxidative stress in the wound area. This antioxidant activity protects cells around the wound from free radical damage and supports fibroblast cell proliferation and epithelialization, thereby accelerating the healing process. In addition, rutin has an anti-inflammatory effect that helps reduce inflammation, allowing new tissue to form faster and wounds to close more effectively (Hassanpour and Doroudi, 2023). Quercetin, another flavonoid found in *Ziziphus*

jujuba, also functions as an antioxidant and anti-inflammatory that accelerates wound healing. Quercetin inhibits pro-inflammatory enzymes such as COX-2, which helps reduce swelling and pain in burns. In addition, its antioxidant activity increases fibroblast cell proliferation and collagen formation, which are important in strengthening new tissue and accelerating the wound healing process (Cizmarova et al., 2023). Chlorogenic acid plays an important role in supporting cell migration and regeneration during the wound healing process. As an antioxidant, chlorogenic acid protects damaged tissue from oxidative damage and promotes epithelial cell migration to the wound area, which accelerates the formation of granulation tissue. Chlorogenic acid's antimicrobial properties also help protect wounds from infection, allowing the healing process to proceed more smoothly and effectively (Al-Ghanayem et al., 2024).

Overall, *Ziziphus jujuba* shows high effectiveness in healing burns through a combination of metabolites such as rutin, quercetin, and chlorogenic acid. Rutin and quercetin act as antioxidants and anti-inflammatories that support tissue regeneration, while chlorogenic acid accelerates cell migration and prevents infection. This combination of metabolites makes *Ziziphus jujuba* an effective agent for natural burn healing.

Most effective plants for anti-inflammatory and wound healing effects

The three most effective plants for anti-inflammatory and wound healing effects in this study are *Curcuma mangga*, *Solanum diploconos*, and *Curcuma longa*. *Curcuma mangga*, with its primary component curcuminoids, demonstrates excellent anti-inflammatory activity through the inhibition of NO production, a key mediator in the inflammatory response (Srirod and Tewtrakul, 2019). A cream with 10% *Curcuma mangga* extract proved more effective than diclofenac gel, a standard anti-inflammatory drug. In wound healing, this cream accelerated fibroblast migration by 80% within 36 hours, promoting faster tissue regeneration and recovery (Benvenuti et al., 2021; Srirod and Tewtrakul, 2019).

Meanwhile, *Solanum diploconos*, with compounds such as caffeic acid and lutein, effectively reduces inflammatory mediators like TNF- α and NO, showing a 63.5% reduction in NO (Benvenuti et al., 2021). Its anti-inflammatory effects are enhanced by increasing the phagocytosis of dead neutrophils by macrophages, speeding up inflammation resolution. In wound healing tests, a 1% *Solanum diploconos* cream accelerated skin wound healing by approximately 35%, promoting fibroblast migration and faster wound closure (Benvenuti et al., 2021).

Curcuma longa, rich in curcumin, DMC, and BDMC, also exhibits strong anti-inflammatory properties. In the carrageenan-induced paw edema model, the group treated with BDMC showed the most significant reduction in swelling compared to the control group (Islam et al., 2024). In wound healing tests, a 1% topical application of *Curcuma longa* significantly increased wound closure rates, with complete closure by day 12, compared to only 88% in the control group (Islam et al., 2024). Compared to other plants such as *Zehneria scabra* or *Portulaca pilosa*, although these also show notable anti-inflammatory and wound healing effects, they often require higher concentrations or longer timeframes to achieve similar results (Fisseha et al., 2022). For instance, *Zehneria scabra* at a 10% concentration showed 52.8% edema inhibition, but both *Curcuma longa* and *Curcuma mangga* delivered stronger effects at lower concentrations. Additionally, *Portulaca pilosa* took longer to achieve 56% wound contraction, whereas *Curcuma mangga* and *Curcuma longa* promoted faster wound closure (Fisseha et al., 2022; Islam et al., 2024; Srirod and Tewtrakul, 2019).

Overall, *Curcuma mangga*, *Solanum diploconos*, and *Curcuma longa* stand out due to their stronger anti-inflammatory effects and their ability to accelerate wound healing with lower concentrations and shorter healing times compared to other plants. Further studies should include clinical trials and mechanistic evaluations using human tissue models to validate the therapeutic claims of these plants.

CONCLUSION

Based on currently reported *in vitro* and *in vivo* studies, 35 plant species were found to exhibit the potential as anti-inflammatory and wound healing agents, including *Achillea asiatica*, *Aloe megalacantha*, *Aloe trigonantha*, *Argemone mexicana*, *Artemisia campestris*, *Bergia ammannioides*, *Clematis simensis*, *Clerodendrum myricoides*, *Commiphora guidottii*, *Crassocephalum crepidioides*, *Curcuma longa*, *Curcuma mangga*, *Dioscorea bulbifera*, *Dorema aucheri*, *Ephedra ciliata*, *Euphorbia hirta*, *Globularia alypum*, *Jatropha neopauciflora*, *Kaempferia marginata*, *Mangifera indica*, *Ononis spinosa*, *Phlomis russeliana*, *Plantago australis*, Polyherbs (*Plumbago zeylanica*, *Datura stramonium*, and *Argemone mexicana*), *Portulaca pilosa*, *Rumex abyssinicus*, *Schinus terebinthifolius*, *Solanum diploconos*, *Streptocaulon juvenas*, *Thymus sipyleus*, *Urtica dioica*, *Zehneria scabra* and *Ziziphus jujuba*. The 35 species were declared potential candidates from the results of the anti-inflammatory and wound healing tests, showing significant results based on the statistical analysis that had been carried out.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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AUTHOR CONTRIBUTION:

Contribution	Rubiyanti R	Levita J	Abdul Wahab SM	Susilawati Y
Concepts or ideas	x	x	x	x
Design		x		x
Definition of intellectual content	x	x		x
Literature search	x	x		
Experimental studies	x	x		
Data acquisition	x	x	x	x
Data analysis	x	x	x	x
Statistical analysis				
Manuscript preparation	x	x		
Manuscript editing	x	x		
Manuscript review	x	x	x	x

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