



Effects of *Aloe vera* Based Intervention on Fibroblast Activity and Wound Healing Mechanisms: A Systematic Review

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Received: July 2026; Revised: August 2026; Accepted: September 2026; Published: September 2026

Abstract: This systematic review evaluated the effects of *Aloe vera* on fibroblast activity and the underlying mechanisms involved in wound healing. The review was conducted in accordance with the PRISMA 2020 guidelines. Literature searches were performed in PubMed, Scopus, and ScienceDirect using the keywords "*Aloe vera*," "fibroblast," and "wound healing." Original studies published in English or Indonesian were included if they investigated the effects of *Aloe vera* on fibroblasts or wound-healing processes using in vitro, in vivo, or topical formulation models. Twenty studies met the eligibility criteria. The included studies suggested that *Aloe vera* supports fibroblast proliferation, migration, viability, and collagen synthesis. In vitro studies further demonstrated increased extracellular matrix production, reduced levels of pro-inflammatory mediators, and enhanced antioxidant defenses. In vivo studies reported accelerated wound closure and enhanced angiogenesis, accompanied by increased expression of VEGF, TGF- β , and PDGF-BB, as well as antimicrobial activity. In addition, *Aloe vera*-based biomaterials, including hydrogels, scaffolds, bioactive films, and nanomembranes, provided structural support and sustained-release properties that may facilitate tissue regeneration. Overall, the current literature provides promising preclinical evidence that *Aloe vera* may support multiple mechanisms involved in wound healing. However, high-quality clinical studies are still required to establish its efficacy, safety, optimal formulation, and translational applicability in humans.

Keywords: *Aloe vera*; fibroblast; systematic review; tissue regeneration; wound healing

How to Cite: Windarti, S., & Wahyuni, A. S. (2026). Effects of *Aloe vera* Based Intervention on Fibroblast Activity and Wound Healing Mechanisms: A Systematic Review: English. *Bioscientist: Jurnal Ilmiah Biologi*, 14(3), 1455–1470. <https://doi.org/10.33394/bioscientist.v14i3.22165>



<https://doi.org/10.33394/bioscientist.v14i3.22165>

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INTRODUCTION

Wound healing is a complex and highly coordinated biological process that restores tissue integrity after injury. It involves dynamic interactions among multiple cell types, inflammatory mediators, extracellular matrix (ECM) components, and growth factors, and proceeds through four overlapping phases: hemostasis, inflammation, proliferation, and tissue remodeling (Alimyar et al., 2025). Among the cellular components involved in this process, fibroblasts play a central role, particularly during the proliferative and remodeling phases (Lee et al., 2024). Fibroblasts migrate into the wound bed, proliferate, synthesize collagen (Cardona et al., 2026) and other ECM components, and contribute to granulation tissue formation and tissue remodeling (Abid et al., 2025). These activities are essential for effective wound closure and restoration of tissue architecture. Conversely, impaired fibroblast proliferation, migration, or ECM production may contribute to delayed wound healing (Tertipi et al., 2026), particularly under pathological conditions such as diabetes, in which persistent inflammation, oxidative stress, tissue hypoxia, and impaired angiogenesis can disrupt normal cellular responses (Shedoeva et al., 2019).

Growing interest in complementary and biologically active therapies for wound healing has intensified research on medicinal plants (Raj et al., 2024), particularly those containing compounds with multiple pharmacological activities (Padmakar et al.,

2023). *Aloe vera* is among the most extensively investigated medicinal plants in this context (Agrawal, 2025; Lestari et al., 2025), and its potential role in promoting wound healing has been widely studied (Khan et al., 2025). *Aloe vera* gel contains a diverse range of bioactive constituents, including polysaccharides such as acemannan, flavonoids, phenolic compounds, mannose-6-phosphate, vitamins, and other antioxidant components. These constituents have been associated with anti-inflammatory, antioxidant, antimicrobial, immunomodulatory, and tissue-regenerative activities, suggesting that *Aloe vera* may influence multiple biological processes involved in wound repair (Manhas & Malairaman, 2025). Importantly, the potential effects of *Aloe vera* may extend beyond general wound closure because its bioactive constituents may directly or indirectly modulate fibroblast-mediated processes that are essential for tissue regeneration (Adel Alawadi et al., 2024).

The biological effects of *Aloe vera* on wound healing are likely to involve several interconnected mechanisms (Akgül et al., 2021). Fibroblast proliferation and migration are fundamental to repopulating injured tissue and initiating granulation tissue formation, whereas fibroblast-mediated collagen synthesis and ECM remodeling are required for subsequent tissue maturation (Tracy et al., 2016). These cellular responses are regulated by intracellular signaling pathways and extracellular mediators, including PI3K/Akt and ERK/MAPK signaling (Shen et al., 2025), as well as growth factors involved in fibroblast activation and tissue regeneration (H. Wang et al., 2026). Fibroblast function is also strongly influenced by the inflammatory and oxidative microenvironment within the wound (Chelu et al., 2023). Persistent inflammation and excessive oxidative stress can impair fibroblast viability, proliferation, migration, and ECM synthesis, whereas resolution of inflammation and restoration of redox balance may create a microenvironment that is more favorable for tissue repair. Thus, the wound-healing effects of *Aloe vera* may reflect coordinated modulation of multiple biological processes rather than the activity of a single signaling pathway (Shen et al., 2025).

Although an increasing number of experimental studies have investigated *Aloe vera* as a wound-healing intervention, the available evidence remains heterogeneous with respect to wound models, *Aloe vera* preparations and formulations (H. Wang et al., 2026), experimental conditions, and biological outcomes. More importantly, mechanistic evidence specifically related to fibroblast function has not yet been systematically integrated (Raj et al., 2024). Previous studies have generally evaluated individual outcomes, such as wound closure, collagen deposition, inflammation (Tazeze et al., 2021), or fibroblast proliferation, without adequately clarifying how these biological responses are interconnected. In particular, the relationships among *Aloe vera*-associated fibroblast proliferation and migration, PI3K/Akt and ERK/MAPK signaling, growth-factor regulation, ECM remodeling, inflammatory responses, and oxidative stress have not been comprehensively synthesized (Fouché et al., 2020).

This lack of integrated mechanistic evidence limits a clear understanding of how *Aloe vera* may influence fibroblast-mediated wound repair and which biological processes are most closely associated with its potential therapeutic effects (Khan et al., 2025). A focused synthesis is therefore needed to move beyond viewing *Aloe vera* solely as a general wound-healing agent and to clarify its potential role in modulating fibroblast-centered mechanisms of tissue repair (Meza-Valle et al., 2021; Sánchez et al., 2020). Such an approach may also help distinguish direct effects on fibroblast activity from indirect effects mediated through inflammation, oxidative stress, angiogenesis, and ECM remodeling.

Therefore, this systematic review aims to evaluate the effects of *Aloe vera* on fibroblast activity during wound healing and to synthesize evidence regarding the underlying biological mechanisms. Specifically, this review integrates evidence on fibroblast proliferation and migration, PI3K/Akt and ERK/MAPK signaling, growth-factor regulation, ECM synthesis and remodeling, inflammation, and oxidative stress. By integrating these processes within a fibroblast-centered framework, this review seeks to provide a more comprehensive mechanistic understanding of the potential role of *Aloe vera* in wound healing (Cardona et al., 2026).

METHOD

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines to evaluate the effects of *Aloe vera* on fibroblast activity and wound-healing mechanisms. The research question was formulated using the Population, Intervention, Comparison, and Outcome (PICO) framework.

The population comprised fibroblast cells and experimental wound-healing models. The intervention included *Aloe vera* extracts, preparations, or topical formulations, administered either alone or in combination with other bioactive ingredients. Studies evaluating combination preparations were included when *Aloe vera* was a clearly defined component of the intervention and the study assessed outcomes related to fibroblast activity or wound healing. Comparators included untreated controls, vehicle controls, placebo, or standard therapy, where applicable. The outcomes of interest included fibroblast proliferation, cell migration, collagen synthesis, and other biological mechanisms associated with wound healing.

Table 1. PICO framework

Component	Description
Population (P)	Fibroblast cells and experimental wound-healing models
Intervention (I)	<i>Aloe vera</i> extracts, preparations, or topical formulations, used alone or in combination with other bioactive ingredients
Comparison (C)	Untreated control, vehicle control, placebo, or standard therapy, where applicable
Outcomes (O)	Fibroblast proliferation, cell migration, collagen synthesis, and wound-healing mechanisms, including anti-inflammatory, antioxidant, antimicrobial, and angiogenic activities

Original experimental studies published in English or Indonesian were eligible for inclusion. Studies were included if they investigated the effects of *Aloe vera* extracts, preparations, or topical formulations on fibroblast activity or wound-healing outcomes. Eligible study designs included in vitro studies using fibroblast cells, in vivo studies using experimental wound models, and studies evaluating topical formulations containing *Aloe vera*. Both *Aloe vera*-only interventions and combination preparations were considered eligible, provided that *Aloe vera* was a clearly defined component of the formulation and that relevant outcomes were reported. Combination interventions included *Aloe vera* with other plant extracts, snail mucus, chitosan, or other bioactive ingredients. To avoid overattributing the observed effects to *Aloe vera*, studies evaluating combination preparations were interpreted separately from those investigating *Aloe vera* alone, unless the study design provided sufficient evidence to support a specific contribution of *Aloe vera*.

Studies were excluded if they were review articles, editorials, conference abstracts, or studies unrelated to wound healing. Studies lacking relevant experimental data or providing insufficient information on the intervention or wound-healing outcomes were also excluded. Data from the included studies were extracted using a standardized data-extraction form. The extracted variables included author, year of publication, study design, experimental model, type of *Aloe vera* intervention, formulation or preparation, presence of additional bioactive ingredients, concentration or dose, assay methods, comparator groups, main findings, and reported wound-healing mechanisms.

The included studies were classified according to predefined criteria to facilitate comparison across study designs, interventions, and reported outcomes. These criteria included the experimental model, classified as *in vitro* or *in vivo*; the type of intervention, categorized as *Aloe vera* alone or in combination with other ingredients; the preparation type, including extracts, isolated preparations, or topical formulations; and the primary outcomes, such as fibroblast proliferation, cell migration, collagen synthesis, and other wound-healing-related mechanisms. For combination preparations, additional ingredients and their potential contributions to the observed effects were also recorded. All extracted data were checked for completeness and consistency before qualitative synthesis.

The extracted data were analyzed using a qualitative narrative synthesis. Findings were organized according to the experimental model, type of intervention, and reported biological outcomes. Studies were first grouped into *in vitro* and *in vivo* investigations and were then further classified according to whether *Aloe vera* was used as a single intervention or as part of a combination preparation. The effects of *Aloe vera* alone were synthesized separately from those of multi-component formulations to minimize the risk of attributing combined effects exclusively to *Aloe vera*. Reported outcomes were categorized as fibroblast proliferation, cell migration, collagen synthesis, anti-inflammatory activity, antioxidant activity, antimicrobial activity, angiogenesis, and other wound-healing mechanisms. For combination preparations, the synthesis also considered the potential contribution of additional ingredients and the extent to which the study design supported an association between *Aloe vera* and the observed outcomes.

Differences in experimental models, intervention characteristics, concentrations or doses, treatment durations, assay methods, and outcome measurements were considered when interpreting the findings. Because of the substantial heterogeneity among the included studies, particularly in study models, intervention formulations, dosing regimens, treatment durations, assay methods, and outcome measures, a meta-analysis was not performed.

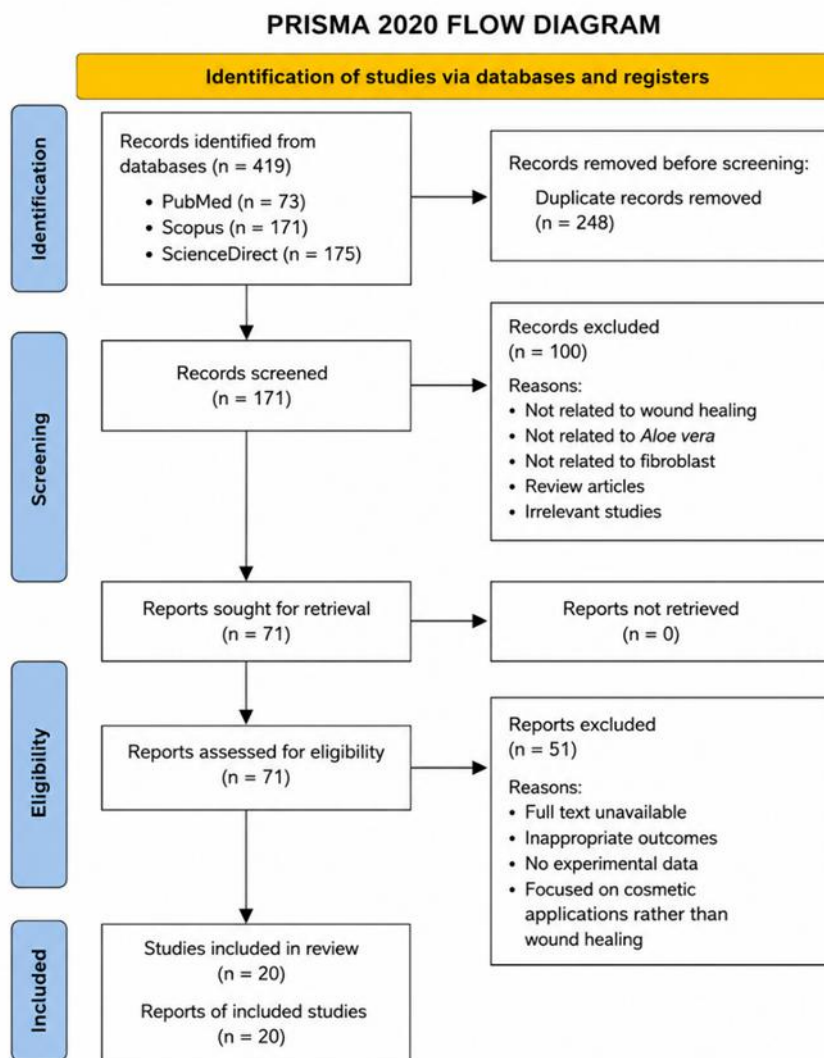


Figure 1. PRISMA 2020 flow diagram

RESULTS AND DISCUSSION

Study Selection and Characteristics

Following the PRISMA 2020 guidelines, 20 studies met the eligibility criteria and were included in this systematic review. Table 2 summarizes the characteristics of all included studies, including the author, year of publication, study model, type of *Aloe vera* intervention, concentration or dose, comparator, outcomes assessed, and main findings. This comprehensive presentation enables readers to trace the evidence supporting the conclusions of this review and addresses a limitation of previous reviews that presented only selected or “representative” studies (Meşe et al., 2026).

Table 2. Complete characteristics of all 20 included studies (2017–2026)

Author	Year	Model	Intervention	Concentration/Dose	Comparator	Outcomes	Main Findings
Atiba et al.	2022	In vivo (rat burn)	Topical gel + oral	200 mg/kg oral; 2x/day topical	Silver sulfadiazine	Wound closure, TGF-β1, VEGF, bFGF, Prdx6	Accelerated healing, ↑ angiogenesis

Author	Year	Model	Intervention	Concentration/Dose	Comparator	Outcomes	Main Findings
Esfahani et al.	2018	In vivo (rat)	Combination gel	10% w/w	Simple ointment	TGF- β , VEGF, collagen	Enhanced tissue regeneration
Genesi et al.	2023	In vivo (rat)	Chitosan film + AV	5% extract	Chitosan alone	VEGF, CD31, cell proliferation	Improved angiogenesis
Gharaboghaz et al.	2020	In vivo (diabetic mice)	Extract + herbal combo	100 mg/kg	Insulin	IGF-1, VEGF, collagen	Diabetic wound healing
Huang et al.	2026	In vivo + in vitro	Polysaccharide	50–200 μ g/mL	PBS	NLRP3, M2 markers	Immunomodulation
Iosageanu et al.	2024	In vitro (fibroblasts)	Phenolic + polysaccharide	0.1–3.0 mg/mL	Untreated	Cytokines, ROS, proliferation	Multifraction activity
Jiang et al.	2025	In vivo + scRNA-seq	Polysaccharide–collagen scaffold	2% w/v	Collagen alone	Immune cells, VEGF	Scaffold biomaterial
Khumfu et al.	2026	In vitro (diabetic fibroblasts)	Thermoresponsive gel	1–10% w/v	Gel base	IL-6, TNF- α , migration	Diabetic model
Kim et al.	2021	In vitro (fibroblasts)	Peel-derived EVs	100 μ g/mL	Untreated	Nrf2, ROS, proliferation	Antioxidant healing
Kim & Park	2022	In vitro (macrophages)	A. saponaria EVs	50 μ g/mL	Control EVs	STAT3, M1/M2 markers	Chronic wound healing
Kumar et al.	2020	In vitro (fibroblasts)	AgNP + PBM + AV	25 μ g/mL	Individual treatments	Migration rate	Combination therapy
Heupt et al.	2022	In vitro (fibroblasts)	AV + RPR	1:1 ratio	RPR alone	Migration, growth factors	Oral wound healing
Mekarat et al.	2026	In vitro + material	cWPU + AV coating	3% w/w	cWPU alone	Fibroblast signaling	Biomaterial coating
Miya et al.	2025	In vivo (diabetic rat)	Plant-mixture EVs	200 μ g/kg	Free EVs	Oxidative stress, MMPs	Multitarget therapy
Negahdari et al.	2017	In vitro (fibroblasts)	Herbal extracts + AV	5–2000 μ g/mL	Individual extracts	TGF- β , VEGF	Fibroblast regulation
Manhas et al.	2025	In vitro + in vivo	Hydroalcoholic extract	100–500 μ g/mL	Metformin	Glucose, cytokines	Diabetic wound healing
Wang et al.	2024	In vitro + in vivo	AV-based hydrogel	2% w/v	Commercial hydrogel	TNF- α , TGF- β	Hydrogel therapy
Wu et al.	2024	In vivo + molecular	AV + AA + QUE	50 mg/kg each	Individual compounds	NF- κ B, PI3K/AKT	Burn wound healing
Sianipar et al.	2025	In vivo (rat burn)	AV + snail mucus	1:1 ratio	Silver sulfadiazine	PDGF-BB, collagen	Burn wound healing
Razia et al.	2022	In vitro (fibroblasts)	Flower extract + gel	10–500 μ g/mL	Untreated	MFAP4, ERK, AKT	ECM remodeling

Abbreviations: AV = *Aloe vera*; EVs = extracellular vesicles; scRNA-seq = single-cell RNA sequencing; cWPU = waterborne polyurethane; RPR = platelet-rich plasma; AA = ascorbic acid; QUE = quercetin; AgNP = silver nanoparticles; PBM = photobiomodulation.

Synthesis of Evidence by Level of Evidence

To provide a clearer overview of the evidence hierarchy, the findings were categorized into four levels: (1) direct effects on fibroblasts in vitro, (2) indirect effects mediated through inflammatory and antioxidant mechanisms, (3) in vivo evidence from animal models, and (4) biomaterial and combination-formulation studies. Figure 2 illustrates the distribution of studies across these categories. Because several studies assessed more than one biological outcome, individual studies could contribute to multiple categories.

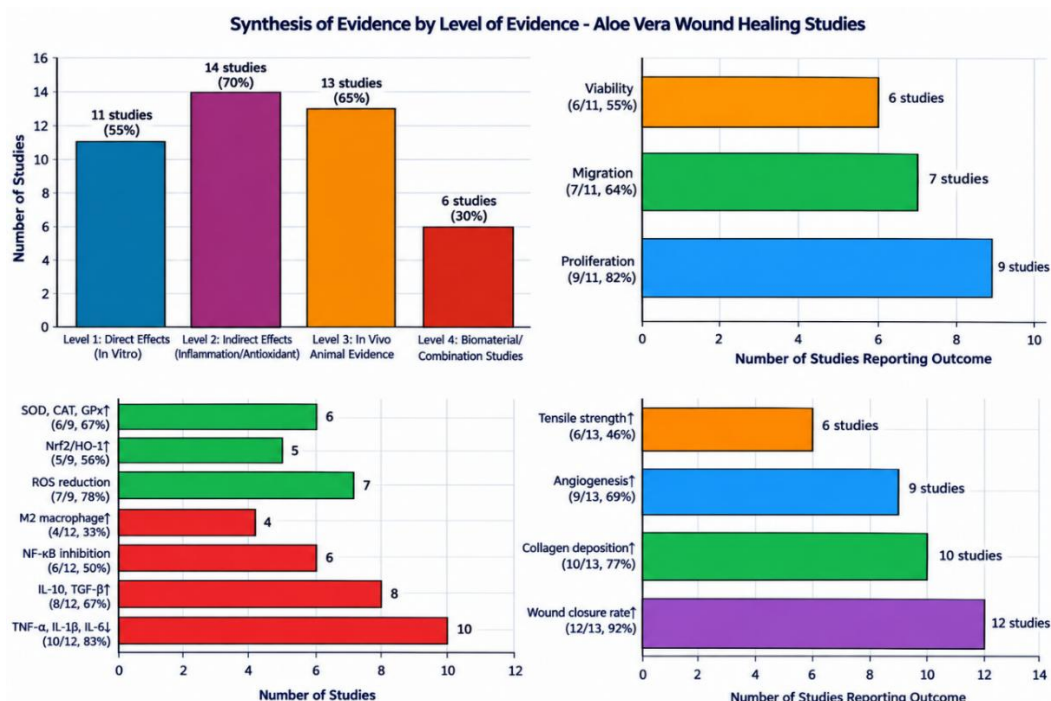


Figure 2. Synthesis of evidence by level of evidence-*Aloe vera* wound healing studies

Direct Effects on Fibroblast Activity

Eleven of the 20 included studies (55%) directly examined the effects of *Aloe vera*-based interventions on fibroblast proliferation, migration, and/or viability using in vitro models (Iosageanu et al., 2024; Khumfu et al., 2026; M. K. Kim et al., 2021; M. Kim & Park, 2022; Kumar et al., 2020; Manhas & Malairaman, 2025; Mekarat et al., 2026; Müller-Heupt et al., 2022; Negahdari et al., 2017; Razia et al., 2022; X. Wang et al., 2024). Overall, these studies suggested that *Aloe vera* may support fibroblast-associated processes involved in wound repair (Ashkani-Esfahani et al., 2019). Most studies reported increased fibroblast proliferation or migration following exposure to *Aloe vera* extracts, polysaccharide-rich fractions, extracellular vesicles, or *Aloe vera*-containing formulations (Iosageanu et al., 2024). However, these findings should be interpreted cautiously because the included studies varied substantially in cell type, intervention composition, concentration, exposure duration, and outcome-assessment methods.

Among the 11 in vitro studies, nine studies (81.8%) reported increased fibroblast proliferation (Ashkani-Esfahani et al., 2019; Atiba et al., 2022; Genesi et al., 2023), as assessed using metabolic-activity or proliferation assays, including MTT, CCK-8, and BrdU-based methods (Calabrese et al., 2026; Phimnuan et al., 2023). Seven studies (63.6%) reported enhanced fibroblast migration, primarily assessed using scratch-wound or wound-healing assays (Khumfu et al., 2026; Negahdari et al., 2017). In addition, six studies (54.5%) reported improved fibroblast viability, particularly under conditions relevant to impaired wound healing, such as oxidative stress, inflammatory stimulation, or high-glucose exposure (Huang et al., 2026; Iosageanu et al., 2024; Jiang et al., 2025; Khumfu et al., 2026). Collectively, these findings suggest that *Aloe vera*-based interventions may support several complementary cellular processes required during the proliferative phase of wound healing.

The concentrations associated with beneficial effects varied considerably among studies. Extract-based interventions generally showed biological activity at

concentrations of approximately 50–500 µg/mL (M. Kim & Park, 2022; Manhas & Malairaman, 2025), whereas extracellular-vesicle preparations were commonly evaluated at approximately 50–200 µg/mL (Huang et al., 2026; Khumfu et al., 2026). Nevertheless, concentrations across the overall evidence base ranged from 0.1 mg/mL to 2,000 µg/mL (Calabrese et al., 2026). Such variability may reflect differences in the source material, plant part, extraction procedure, bioactive-compound composition, formulation type, and experimental cell model. Some studies further suggest that responses to *Aloe vera* extracts may be nonlinear or hormetic, whereby low-to-moderate concentrations produce beneficial effects, whereas higher concentrations may result in diminished responses or reduced cell viability.

Considerable heterogeneity was also evident in the fibroblast models employed. The included in vitro studies used human dermal fibroblasts ($n = 5$), rat-derived fibroblasts ($n = 3$), mouse-derived fibroblasts ($n = 2$), and fibroblasts derived from diabetic or hyperglycemic models ($n = 1$). These models may differ in basal proliferation rates, inflammatory responses, susceptibility to oxidative stress, and capacity for ECM synthesis. Therefore, direct comparison of effect sizes across studies is not appropriate. Exposure durations also ranged from 24 hours to 7 days, which may influence whether the measured outcome primarily reflects early cytoprotection, acute migration, or sustained proliferative activity.

As shown in Figure 2, fibroblast proliferation was the most frequently reported biological outcome and was identified in 11 studies. However, the mechanistic categories were not mutually exclusive because individual studies could be assigned to more than one category when multiple outcomes were assessed. For example, Kim et al. (2021) evaluated fibroblast proliferation, cell migration, angiogenesis-related activity, and antioxidant responses and therefore contributed to several categories in the frequency analysis. Accordingly, the frequencies presented in Figure 2 represent the number of studies reporting a particular mechanism and should not be interpreted as independent evidence counts, pooled effect estimates, or indicators of the relative magnitude of individual biological effects.

Indirect Effects Through Inflammation and Oxidative Stress

Fourteen studies (70%) evaluated the anti-inflammatory and/or antioxidant mechanisms associated with *Aloe vera*, either independently or alongside direct effects on fibroblasts. Collectively, these findings suggest that *Aloe vera* may modulate the wound microenvironment in ways that favor fibroblast-mediated tissue repair. Among the 12 studies examining anti-inflammatory mechanisms, 10 (83%) reported downregulation of pro-inflammatory cytokines such as TNF- α , IL-1 β , and IL-6, whereas eight (67%) demonstrated increased levels of the anti-inflammatory mediators IL-10 and TGF- β . In addition, six studies (50%) documented inhibition of NF- κ B nuclear translocation, while four studies (33%) reported a shift toward pro-reparative M2 macrophage polarization.

With regard to antioxidant activity, seven of nine studies (78%) reported reduced intracellular reactive oxygen species (ROS), five studies (56%) described activation of the Nrf2/HO-1 pathway, and six studies (67%) reported increased activity of antioxidant enzymes, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). Importantly, these anti-inflammatory and antioxidant effects appeared to depend on concentration and treatment timing. Iosageanu et al. (2024) reported that phenolic fractions showed maximal anti-inflammatory activity at 1.0 mg/mL, whereas polysaccharide fractions were most effective at 2.5 mg/mL.

Furthermore, Huang et al. (2026) demonstrated that *Aloe vera* polysaccharides promoted M2 macrophage polarization through inhibition of NLRP3 inflammasome

activation. However, this effect was observed primarily during the early inflammatory phase (days 1–3) and not during subsequent proliferative phases. These findings highlight the importance of treatment timing and wound-healing stage when interpreting the potential therapeutic effects of *Aloe vera* (Calabrese et al., 2026).

In Vivo Animal Evidence

Thirteen studies (65%) provided in vivo evidence across different animal wound models, thereby extending the in vitro findings by incorporating systemic factors, immune responses, and tissue-level interactions that cannot be fully reproduced in cell-based models. The included studies investigated normal excisional or incisional wounds (n = 5), burn wounds (n = 4), diabetic wounds (n = 3), and infected or chronic wounds (n = 1). Across these models, *Aloe vera*-based treatment accelerated wound closure in 12 of 13 studies (92%), with reported reductions in healing time ranging from 20% to 60% relative to control groups.

Histological analyses further demonstrated increased collagen deposition in 10 of 13 studies (77%), as assessed using Masson's trichrome or picrosirius red staining, while enhanced angiogenesis was reported in nine studies (69%), as indicated by increased microvessel density or CD31-positive cells. Improved tensile strength was reported in six of 13 studies (46%), suggesting functional improvement in repaired tissue (Gharaboghaz et al., 2020; Miya et al., 2025; Sianipar et al., 2025; Wu et al., 2024).

Although the in vivo findings were broadly consistent with those obtained in vitro, several important distinctions were evident. First, the reported magnitude of improvement was generally more modest in vivo, with approximately 20–40% acceleration of healing compared with the 50–200% increases in cellular proliferation reported in vitro. This difference may reflect the greater physiological complexity of whole-organism models (Mu & Zhang, 2026). Second, the magnitude of the observed benefit appeared to vary according to the wound model. Diabetic wound models showed comparatively greater improvements following *Aloe vera* treatment than normal wound models, potentially because *Aloe vera*-based interventions may influence pathological processes associated with impaired healing, including hyperglycemia, oxidative stress, and chronic inflammation. Third, the route of administration appeared to influence treatment outcomes; combined topical and oral administration, as reported by Atiba et al. (2022), produced greater effects than topical treatment alone, suggesting that systemic immunomodulatory actions may complement local wound-healing effects.

Biomaterial and Combination Formulation Studies

Six studies (30%) investigated *Aloe vera* incorporated into advanced biomaterial systems, including hydrogels, scaffolds, films, nanomembranes, or combination formulations containing other bioactive agents. These studies are particularly relevant to translational wound-care applications because they address practical challenges such as sustained therapeutic delivery, dressing stability, and the development of multifunctional wound-healing platforms (Abid et al., 2025). The investigated systems included hydrogels (n = 3), such as chitosan-based, polyurethane-based, and polysaccharide–collagen formulations; scaffolds and films (n = 2), including collagen scaffolds and chitosan films; and plant-derived extracellular vesicles (n = 2), which served as natural nanocarriers for *Aloe vera*-derived bioactive compounds.

Compared with conventional gel formulations, biomaterial-based systems offered several potential advantages. First, these systems enabled more sustained and controlled release of bioactive compounds over approximately 3–7 days, compared

with the rapid release (<24 hours) generally associated with conventional gels (Abid et al., 2025). Second, encapsulation within biomaterial matrices enhanced the stability of labile compounds by protecting them from degradation, thereby potentially extending shelf life while preserving biological activity (H. Wang et al., 2026). Third, these platforms supported multifunctional therapeutic approaches by enabling the co-incorporation of growth factors, antimicrobial agents, and other plant-derived compounds that may act synergistically during wound repair (Tertipi et al., 2026).

A critical synthesis of the available evidence suggests that biomaterial-based formulations may provide advantages over conventional gels across several wound-healing outcomes. Reported wound-closure rates were higher, with improvements of approximately 35–50% compared with 20–30% for conventional gels, while collagen deposition appeared more organized, with greater fiber alignment and reduced scar formation. These formulations may also offer practical benefits through improved moisture retention and reduced frequency of dressing replacement. Nevertheless, substantial heterogeneity in biomaterial composition and *Aloe vera* loading limits direct comparison among studies. For example, Jiang et al. (2025) employed a polysaccharide–collagen scaffold containing 2% *Aloe vera*, whereas X. Wang et al. (2024) evaluated an injectable hydrogel containing 5% *Aloe vera* extract. Standardization of biomaterial composition, *Aloe vera* loading, and release-profile reporting will therefore be necessary to facilitate meaningful comparisons across studies and to guide the development of next-generation *Aloe vera*-based wound-healing systems.

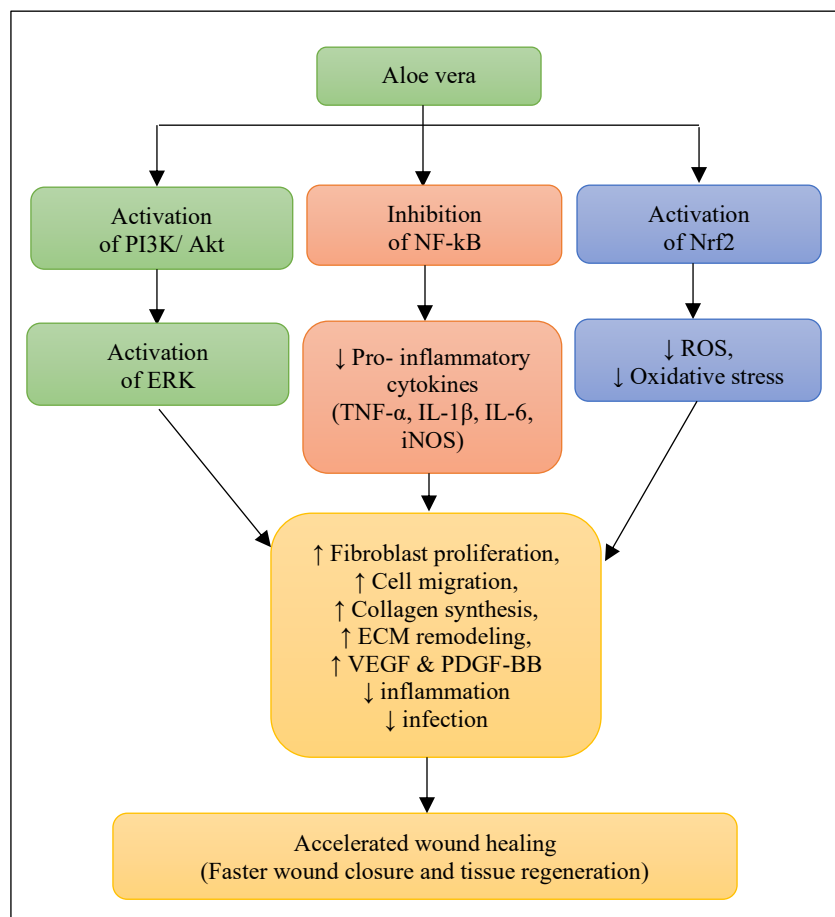


Figure 3. Proposed mechanisms of *Aloe vera* in fibroblast-mediated wound healing

Figure 3 integrates the biological mechanisms through which *Aloe vera*-containing interventions may contribute to wound healing. The available experimental evidence suggests that these effects involve modulation of PI3K/Akt, ERK, Nrf2, and NF- κ B signaling, together with changes in fibroblast activity, extracellular matrix remodeling, angiogenesis, inflammation, and oxidative stress. These pathways appear to interact as part of a broader wound-healing response rather than acting independently. However, because the included studies differed in experimental models, intervention characteristics, and outcome measurements, the proposed relationships should be interpreted as a conceptual, hypothesis-generating framework rather than as a definitively established causal pathway.

The mechanism summarized in Figure 3 should therefore be interpreted as a conceptual, evidence-informed framework rather than a definitively established causal pathway. The model integrates findings from heterogeneous experimental studies that differed in wound model, *Aloe vera* formulation, dose, treatment duration, and outcome measures. Although the available studies collectively suggest involvement of PI3K/Akt, ERK, Nrf2, and NF- κ B-related signaling, together with modulation of fibroblast activity, ECM remodeling, angiogenesis, inflammation, and oxidative stress, the temporal sequence and relative contribution of these pathways remain uncertain. Future studies using standardized experimental conditions and targeted mechanistic approaches are required to validate and refine this proposed framework.

CONCLUSION

This systematic review indicates that *Aloe vera*-based interventions may support fibroblast-mediated wound healing through multiple biological mechanisms, including enhanced fibroblast proliferation and migration, collagen synthesis and extracellular matrix (ECM) remodeling, angiogenesis, anti-inflammatory and immunomodulatory effects, antioxidant activity, and antimicrobial actions. These effects appear to involve modulation of key signaling pathways, including PI3K/AKT, ERK/MAPK, Nrf2/HO-1, and TGF- β /Smad, together with suppression of NF- κ B-mediated inflammatory signaling. In addition, emerging biomaterial-based formulations, such as hydrogels, scaffolds, films, and extracellular vesicles, show potential for sustained delivery and improved therapeutic performance. Nevertheless, the current evidence is predominantly preclinical, and high-quality clinical studies are required to confirm efficacy, safety, optimal formulation, dosing strategies, and translational applicability in humans.

RECOMMENDATION

Future studies should adopt more standardized methodologies to improve the comparability, reproducibility, and interpretability of findings related to the effects of *Aloe vera* on wound healing. Standardization should include the form and preparation of *Aloe vera*, extraction procedures, concentrations or doses, treatment duration, wound models, and fibroblast-related outcomes, including proliferation, migration, viability, and collagen or ECM deposition. Comparative studies evaluating *Aloe vera* as a single intervention versus *Aloe vera* in combination with other bioactive compounds or therapeutic agents are also needed to determine whether combination formulations provide additional or synergistic benefits.

Further well-designed in vivo studies and clinical trials are warranted to validate the biological effects, safety, efficacy, and underlying mechanisms of *Aloe vera* in wound management. Future research should also employ clearly defined and standardized outcome measures to facilitate meaningful comparisons across studies

and enable quantitative synthesis when sufficient methodological homogeneity is achieved.

ACKNOWLEDGMENT

The authors sincerely thank Dr. Arifah Sri Wahyuni, S.Si., M.Sc., Apt. for providing financial support for the publication of this article and for facilitating the conduct of this study. The authors also acknowledge the Faculty of Pharmacy, Universitas Muhammadiyah Surakarta, for its academic support.

The authors used AI-assisted technologies solely to improve the readability and language quality of the manuscript. The authors reviewed and edited the final content and take full responsibility for the manuscript.

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