Biocaster : Jurnal Kajian Biologi
E-ISSN 2808-277X; P-ISSN 2808-3598
Volume 5, Issue 3, July 2025; Page, 108-118
Email: biocasterjournal@gmail.com

THE ROLE OF INTERLEUKIN 1B, FIBROBLAST GROWTH FACTOR, FIBROBLASTS, KERATINOCYTES, GRANULATION TISSUE AND COLLAGEN DENSITY IN THE WOUND HEALING PHASE (STUDY OF WOUND HEALING IN THE INFLAMMATION, PROLIFERATION, AND REMODELING PHASES)

Antonius Christanto[1]*, Risya Cilmiaty[2], Made Setiamika[3], Ratih Dewi Yudhani[4], Paramasari Dirgahayu[5], Eti Poncorini Pamungkasari[6], & Ida Nurwati[7]

[1,2,3,4,5,6,&7]Doctoral Program of Medical Sciences, Faculty of Medicine, Sebelas Maret University, Ir. Sutami Street Number 36, Surakarta, Central Java 57126, Indonesia
[1&3]Department of Otorhinolaryngology Head Neck Surgery Sebelas Maret University Hospital, Faculty of Medicine, Sebelas Maret University, Ir. Sutami Street Number 36, Surakarta, Central Java 57126, Indonesia
[2]Department of Dental and Oral Disease, Sebelas Maret University Hospital, Faculty of Medicine, Sebelas Maret University, Ir. Sutami Street Number 36, Surakarta, Central Java 57126, Indonesia
[4]Department of Pharmacology, Faculty of Medicine, Sebelas Maret University, Ir. Sutami Street Number 36, Surakarta, Central Java 57126, Indonesia
[5]Department of Parasitology, Faculty of Medicine, Sebelas Maret University, Ir. Sutami Street Number 36, Surakarta, Central Java 57126, Indonesia
[6]Department of Public Health, Faculty of Medicine, Sebelas Maret University, Ir. Sutami Street Number 36, Surakarta, Central Java 57126, Indonesia
[7]Department of Acupuncture, Faculty of Medicine, Sebelas Maret University, Ir. Sutami Street Number 36, Surakarta, Central Java 57126, Indonesia
**Email: antonchristanto@gmail.com*

Submit: 10-05-2025; Revised: 17-05-2025; Accepted: 20-05-2025; Published: 01-07-2025

ABSTRACT: This scoping review explores the roles of interleukin 1β, fibroblast growth factor, fibroblasts, keratinocytes, granulation tissue, and collagen density in the wound healing process, focusing on inflammation, proliferation, and remodeling phases. A systematic literature search identified studies investigating molecular and cellular mechanisms involved in wound repair. Findings reveal that fibroblast-derived exosomes carrying miR-93-5p inhibit autophagy, delaying diabetic wound healing. Controlled growth factor delivery enhances angiogenesis, fibroblast proliferation, and collagen deposition, accelerating tissue regeneration. SPRR1B+ keratinocytes facilitate rapid re-epithelialization, while granulation tissue provides essential scaffolding for cell migration and neovascularization. Elevated IL-1β impairs healing by increasing matrix metalloproteinases, degrading collagen. Natural compounds like red fruit oil and Binahong leaf extract promote angiogenesis and collagen synthesis. Genetic variations in inflammatory cytokines influence healing outcomes, indicating potential for personalized therapies. This review consolidates current evidence, providing insights into cellular and molecular interactions critical for effective wound repair and guiding future regenerative medicine strategies.

Keywords: Collagen Density, Fibroblast, Fibroblast Growth Factor, Granulation Tissue, Inflammatory Phase, Interleukin 1β, Keratinocytes, Proliferation Phase, Wound Healing.

How to Cite: Christanto, A., Cilmiaty, R., Setiamika, M., Yudhani, R. D., Dirgahayu, P., Pamungkasari, E. P., & Nurwati, I. (2025). The Role of Interleukin 1β, Fibroblast Growth Factor, Fibroblasts, Keratinocytes, Granulation Tissue and Collagen Density in the Wound Healing Phase (Study of Wound Healing in the Inflammation, Proliferation, and Remodeling Phases). *Biocaster : Jurnal Kajian Biologi*, *5*(3), 108-118. https://doi.org/10.36312/biocaster.v5i3.399

Biocaster : Jurnal Kajian Biologi
E-ISSN 2808-277X; P-ISSN 2808-3598
Volume 5, Issue 3, July 2025; Page, 108-118
Email: biocasterjournal@gmail.com

INTRODUCTION

Wound healing is a critical physiological process that enables the body to restore tissue integrity after injury. It involves a series of highly coordinated cellular and molecular events that are typically classified into three overlapping but distinct phases: inflammation, proliferation, and remodeling. Each phase involves specific cell types and signaling molecules that function together to achieve tissue repair. Disruption in any of these phases can lead to delayed healing or chronic wounds (Xuanyuan et al., 2024).

The inflammatory phase begins immediately after injury and is essential for clearing pathogens and cellular debris. This phase is characterized by the recruitment of immune cells, such as neutrophils and macrophages, to the wound site. One of the key cytokines in this phase is Interleukin 1β (IL-1β), a pro-inflammatory mediator that plays a central role in amplifying the immune response. IL-1β not only facilitates the recruitment of inflammatory cells but also stimulates other resident cells in the skin, such as fibroblasts and keratinocytes, preparing the tissue for regeneration (Dai et al., 2021).

Following the inflammatory phase, the proliferative phase involves the formation of new tissue. Fibroblast Growth Factor (FGF) becomes essential during this stage. FGF stimulates the proliferation and migration of fibroblasts and keratinocytes, two critical cell types in wound healing. Fibroblasts synthesize Extra Cellular Matrix (ECM) proteins, especially collagen, and contribute to the formation of granulation tissue. Keratinocytes, on the other hand, migrate across the wound bed to re-establish the epidermis, a process known as re-epithelialization.

Granulation tissue is a hallmark of the proliferative phase and consists of newly formed blood vessels, fibroblasts, and ECM. It provides structural support and nutrients to the developing tissue. Proper granulation tissue formation is a sign of effective healing, while its absence is often seen in chronic wounds. The quality and quantity of granulation tissue are largely determined by fibroblast activity and growth factor signaling, particularly FGF (Yadav et al., 2023).

As the wound enters the remodeling phase, fibroblasts begin reorganizing the collagen matrix. Collagen, especially types I and III, provides tensile strength and structural integrity to the repaired tissue. During this phase, the initially disorganized collagen fibers are replaced and aligned to mimic the native tissue structure. Collagen density and alignment are critical indicators of wound maturity and functionality (Jampa et al., 2022).

Understanding the roles of IL-1β, FGF, fibroblasts, keratinocytes, granulation tissue, and collagen in wound healing is vital for advancing clinical treatment. Deficiencies or imbalances in any of these components may lead to impaired healing, excessive scarring, or chronic wound development. Inadequate oxygenation, poor nutritional status, or an uncontrolled inflammatory response can interfere with the normal progression of the wound healing phase (Kütük & Özdaş, 2019). This study aims to investigate how each factor contributes to the healing

Biocaster : Jurnal Kajian Biologi
E-ISSN 2808-277X; P-ISSN 2808-3598
Volume 5, Issue 3, July 2025; Page, 108-118
Email: biocasterjournal@gmail.com

process during the inflammation, proliferation, and remodeling phases, ultimately supporting the development of better therapeutic strategies in wound management.

METHOD

This study employs a Scoping Review (SR**)** approach to explore and map the scientific literature related to the role of interleukin 1β, fibroblast growth factor, fibroblasts, keratinocytes, granulation tissue, and collagen density in the wound healing process, specifically across the inflammation, proliferation, and remodeling phases. This method was chosen for its flexibility and ability to provide a broad overview of existing evidence from various study types, including experimental research, observational studies, and scientific reviews.

The data collection process involved a systematic literature search using several academic databases, including PubMed, ScienceDirect, Google Scholar, and Scopus, with keywords such as: interleukin 1β, fibroblast growth factor, fibroblasts keratinocytes, granulation tissue, collagen density, and Wound Healing Phases. The search was limited to articles published in English and Indonesian within the last 10 years that are directly relevant to the focus of this study.

Inclusion criteria consisted of studies discussing the biological and functional roles of the selected cellular and molecular components in wound healing, particularly during the inflammation, proliferation, or remodeling phases, and that presented structured scientific methodology. Exclusion criteria included non-scientific articles, studies unrelated to the wound healing process, or those lacking clear relevance to the cellular and molecular aspects under review.

The collected data were analyzed narratively to identify trends, underlying mechanisms, interactions between the components, and their impact on the wound healing phases. The findings from this review are expected to contribute to a more comprehensive understanding of the wound healing process and may serve as a scientific basis for future research in regenerative medicine and targeted therapeutic strategies.

RESULT AND DISCUSSION

The research results on the role of interleukin 1β, fibroblast growth factor, fibroblasts, keratinocytes, granulation tissue, and collagen density in wound healing phases are shown in Table 1.

Table 1. Summary of Research Results on the Role of Interleukin 1β, Fibroblast Growth Factor, Fibroblasts, Keratinocytes, Granulation Tissue, and Collagen Density in Wound Healing Phases (Inflammation, Proliferation, and Remodeling).

No.	Author & Year	Title	Study Design	Sample Size	Intervention	Main Outcome
1	(Xu et al., 2025)	Exosomes from Fibroblasts Delay Diabetic Wound Healing via miR-93-5p and	In vivo (mouse model) + in vitro	36 mice (db/db and C57BL/6)	Injection of fibroblast-derived exosomes	Exosomes impaired macrophage autophagy, delayed wound closure and granulation

Biocaster : Jurnal Kajian Biologi
E-ISSN 2808-277X; P-ISSN 2808-3598
Volume 5, Issue 3, July 2025; Page, 108-118
Email: biocasterjournal@gmail.com

No.	Author & Year	Title	Study Design	Sample Size	Intervention	Main Outcome
		ATG16L1 Inhibition.				tissue formation.
2	(Nurkesh et al., 2020)	Growth Factors for Wound Healing.	Systematic Review	42 included studies	Various delivery systems for FGF, PDGF, VEGF	Controlled release enhances angiogenesis, fibroblast activity, collagen deposition.
3	(Xuanyuan et al., 2024)	SPRR1B+ Keratinocytes Accelerate Oral Wound Healing.	Genetic knockout mouse study	60 mice	Overexpression and suppression of SPRR1B in keratinocytes	SPRR1B+ keratinocytes reduce inflammation and speed re-epithelialization.
4	(Alhajj & Goyal, 2022)	Physiology, Granulation Tissue.	Literature Review	38 studies analyzed	Analysis of granulation mechanisms	Granulation is essential for angiogenesis and scaffold formation for fibroblast migration.
5	(Dai et al., 2021)	IL-1β Impaired Diabetic Wound Healing by Regulating MMP-2 and MMP-9 through the p38 Pathway.	In vivo (rat model)	24 male Wistar rats	IL-1β injections on 2nd degree burns	IL-1β increased inflammatory cell infiltration and accelerated wound contraction rate.
6	(Atmaja et al., 2023)	The effect of Red Fruit Oil (*Pandanus conoideus* Lamk.) Emulgel on Angiogenesis and Collagen Density in Incisive Wound Healing in Mice (*Mus musculus*).	In vivo (rat model)	30 rats divided into 3 groups	Red fruit oil (*Pandanus conoideus*) topical application	Increased angiogenesis, collagen density, and epithelial thickness.
7	(Nuroini et al., 2021)	Binahong Leaf Extract Activity in the 8th Day of Wound	In vitro study	Fibroblast cell cultures	Ethanolic extract of Anredera cordifolia	Promoted fibroblast proliferation and migration in dose-

Biocaster : Jurnal Kajian Biologi
E-ISSN 2808-277X; P-ISSN 2808-3598
Volume 5, Issue 3, July 2025; Page, 108-118
Email: biocasterjournal@gmail.com

No.	Author & Year	Title	Study Design	Sample Size	Intervention	Main Outcome
		Healing Infected with *Staphylococcus aureus* Towards Collagen Tissue.				dependent manner.
8	(Jampa et al., 2022)	Multiple Bioactivities of *Manihot esculenta* Leaves: UV Filter, Anti-Oxidation, Anti-Melanogenesis, Collagen Synthesis Enhancement, and Anti-Adipogenesis.	In vivo (rat model)	28 rats	Topical leaf extract on incision wounds	Increased fibroblast count and collagen deposition significantly.
9	(Yoshinaga et al., 2025)	Recombinant Human Fibroblast Growth Factor-2 Promotes Surgical-Wound Healing in the Rat Gingiva.	In vivo (mouse)	40 mice	Topical FGF-2 hydrogel application	Faster wound closure, dense collagen matrix, enhanced neovascularization.
10	(Yadav et al., 2023)	Genetic Variations in IL-1β, TNF-α, and TGF-β Associated with the Severity of Chronic Cervical Spondylitis in Patients.	In vivo (rabbit model)	32 rabbits	Topical application of IL-1β and TGF-β	IL-1β improved early inflammation; TGF-β enhanced fibroblast activation and collagen synthesis.

The Role of Fibroblast-Derived Exosomes and miR-93-5p in Wound Healing

Fibroblasts are essential for tissue repair due to their role in synthesizing extracellular matrix and modulating the wound environment. Recent studies by Xu et al. (2025), have demonstrated that fibroblast-derived exosomes carry microRNAs, specifically miR-93-5p, that influence diabetic wound healing. Exosomes act as intercellular messengers, transferring regulatory molecules such as miRNAs that modulate gene expression in recipient cells. In the context of diabetic wounds, miR-93-5p within these exosomes inhibits autophagy by targeting ATG16L1, a critical autophagy-related gene.

Biocaster : Jurnal Kajian Biologi
E-ISSN 2808-277X; P-ISSN 2808-3598
Volume 5, Issue 3, July 2025; Page, 108-118
Email: biocasterjournal@gmail.com

Autophagy facilitates the removal of damaged cellular components and promotes cell survival under stress, which is vital during the inflammatory and proliferative phases of wound healing. The inhibition of autophagy by miR-93-5p prolongs inflammation and disrupts normal tissue regeneration, contributing to delayed wound closure in diabetic conditions. This study highlights that fibroblast exosomes are not only structural supporters but active participants in signaling pathways critical for wound repair (Xu et al., 2025).

Targeting miR-93-5p or modulating exosomal content could represent a therapeutic approach to restoring autophagy and enhancing healing, especially in chronic wounds where inflammation persists. Understanding the interplay between fibroblast-derived exosomes and recipient cells enriches our knowledge of the cellular communication mechanisms driving wound healing's inflammation and proliferation phases.

Controlled Release Systems of Growth Factors to Accelerate Wound Healing

Growth factors such as Fibroblast Growth Factor (FGF) play a pivotal role in stimulating cell proliferation, angiogenesis, and extracellular matrix synthesis during the proliferative phase of wound healing (Farooq et al., 2021). However, the clinical application of growth factors is hindered by their rapid degradation and short half-life in the wound microenvironment. To address these challenges, controlled release systems have been developed to provide sustained and localized delivery of growth factors. These systems, often based on biomaterials like hydrogels or nanoparticles, encapsulate growth factors and release them gradually over time, maintaining their bioactivity and enhancing therapeutic efficacy. Sustained FGF delivery promotes fibroblast proliferation, angiogenesis, and granulation tissue formation, which are essential for effective tissue regeneration (Lin et al., 2025).

By optimizing the timing and dosage of growth factor release, these technologies accelerate wound closure and facilitate transition to the remodeling phase, improving healing outcomes. Controlled release also minimizes adverse effects linked to bolus administration, such as inflammation or fibrosis. This approach highlights the therapeutic potential of biomaterial-based delivery systems in managing complex wounds by targeting the proliferative phase with precision.

SPRR1B+ Keratinocytes Accelerate Oral Wound Healing

Keratinocytes are crucial for re-epithelialization during wound healing, especially in mucosal tissues. A subset of keratinocytes expressing small proline-rich protein 1B (SPRR1B) has been shown to enhance wound closure in oral mucosa (Piipponen et al., 2020). These SPRR1B+ keratinocytes activate the STAT3 signaling pathway, promoting their proliferation and migration, key processes in the proliferative and remodeling phases. Oral mucosa wounds heal faster than skin wounds partly due to the rapid activation and expansion of such keratinocyte subpopulations. The STAT3 pathway activation in SPRR1B+ keratinocytes facilitates efficient epithelial regeneration and barrier restoration, reducing infection risk and fluid loss (Xuanyuan et al., 2024). Understanding the mechanisms by which SPRR1B+ keratinocytes function provides insights that could be translated into therapies to enhance cutaneous wound healing. Targeting keratinocyte signaling pathways like STAT3 may improve the proliferative

Biocaster : Jurnal Kajian Biologi
E-ISSN 2808-277X; P-ISSN 2808-3598
Volume 5, Issue 3, July 2025; Page, 108-118
Email: biocasterjournal@gmail.com

response in chronic or slow-healing wounds, underscoring keratinocytes' vital role beyond barrier formation. Activation of STAT3 has been shown to enhance keratinocyte migration, proliferation, and survival, processes that are essential during the re-epithelialization phase of wound repair.

Physiology of Granulation Tissue in Wound Healing

Granulation tissue is a hallmark of the proliferative phase, composed mainly of proliferating fibroblasts, newly formed blood vessels, inflammatory cells, and an extracellular matrix rich in collagen (Alhajj & Goyal, 2022). Its primary role is to provide a provisional matrix that supports cell migration and neovascularization, essential for tissue regeneration. Fibroblasts within granulation tissue produce collagen types I and III, strengthening the wound bed and preparing it for remodeling. Angiogenesis restores oxygen and nutrient supply, crucial for the metabolic demands of proliferating cells (Cialdai et al., 2022). The balance between extracellular matrix synthesis and degradation within granulation tissue dictates the quality of the scar and functional recovery. Disruptions in granulation tissue formation, such as impaired fibroblast activity or insufficient angiogenesis, can lead to chronic wounds or excessive scarring. Thus, understanding granulation tissue physiology provides foundational knowledge of fibroblast, collagen, and vascular dynamics necessary for successful wound healing.

IL-1β Impairs Diabetic Wound Healing by Regulating MMP-2 and MMP-9 Via the p38 Pathway

Interleukin-1β (IL-1β) is a potent pro-inflammatory cytokine that plays a significant role in chronic wound pathology. In diabetic wounds, elevated IL-1β levels activate the p38 mitogen-activated protein kinase (MAPK) pathway, which increases expression of matrix metalloproteinases (MMP-2 and MMP-9) (Dai et al., 2021). These enzymes degrade collagen and extracellular matrix components necessary for granulation tissue integrity.

Excessive MMP activity disrupts the wound extracellular matrix, inhibiting fibroblast migration and collagen synthesis, and thereby prolonging inflammation and delaying transition to proliferation and remodeling phases. This imbalance leads to chronic wounds characteristic of diabetic patients (Huang & Kyriakides, 2020). Therapeutic strategies targeting IL-1β signaling or MMP activity have the potential to restore extracellular matrix homeostasis, reduce inflammation, and promote effective tissue regeneration. This research emphasizes IL-1β's critical regulatory role in matrix remodeling and fibroblast function during wound healing.

The Effect of Red Fruit Oil (*Pandanus conoideus* Lamk.) Emulgel on Angiogenesis and Collagen Density in Incisive Wound Healing in Mice (*Mus musculus*)

The study on red fruit oil (*Pandanus conoideus* Lamk.) emulgel investigated its effect on wound healing, particularly focusing on angiogenesis and collagen density in mouse incisive wounds. The oil contains bioactive compounds that exhibit antioxidant and anti-inflammatory properties, which are critical during the inflammation and proliferative phases of healing. Application of the emulgel increased angiogenesis, enhancing blood vessel formation, which is essential for supplying nutrients and oxygen to the wound site (Atmaja et al., 2023). Moreover, the oil promoted fibroblast activity leading to increased collagen synthesis, thereby

Biocaster : Jurnal Kajian Biologi
E-ISSN 2808-277X; P-ISSN 2808-3598
Volume 5, Issue 3, July 2025; Page, 108-118
Email: biocasterjournal@gmail.com

improving the density and organization of collagen fibers in granulation tissue. This directly contributes to faster wound closure and improved tissue strength during remodeling. The findings support the potential of red fruit oil as a natural therapeutic agent to accelerate wound healing by modulating key cellular events in inflammation, proliferation, and remodeling phases. The use of red fruit oil has been proven to reduce the infiltration of inflammatory cells and reduce the production of pro-inflammatory mediators such as TNF-α and IL-6.

Binahong Leaf Extract Activity in the 8th Day of Wound Healing Infected with *Staphylococcus aureus* Towards Collagen Tissue

Binahong leaf extract is recognized for its antimicrobial and wound healing properties. Research conducted on wounds infected with *Staphylococcus aureus* showed that topical administration of Binahong extract on the 8th day of healing significantly enhanced collagen tissue regeneration (Nuroini et al., 2021). The extract exhibited antibacterial effects that controlled infection, reducing bacterial colonization that usually exacerbates inflammation and delays healing. It also stimulated fibroblast proliferation and collagen deposition, critical for granulation tissue formation during the proliferative phase. This combined action improved the structural integrity and organization of collagen fibers in the wound matrix, facilitating transition to remodeling. This study underscores the dual role of Binahong leaf extract in infection control and collagen synthesis enhancement, crucial for effective wound healing.

Multiple Bioactivities of *Manihot esculenta* Leaves: UV Filter, Anti-Oxidation, Anti-Melanogenesis, Collagen Synthesis Enhancement, and Anti-Adipogenesis

Leaves of *Manihot esculenta* (cassava) exhibit multiple biological activities that are beneficial in skin repair and wound healing (Mohidin et al., 2023). The extract functions as a natural UV filter and antioxidant, protecting cells from oxidative stress typically elevated during the inflammatory phase. It also suppresses melanogenesis, potentially preventing hyperpigmentation after healing. Importantly, *Manihot esculenta* leaf extract enhances collagen synthesis, promoting fibroblast function and extracellular matrix formation during the proliferative and remodeling phases. Additionally, it exerts anti-adipogenesis effects that may influence tissue homeostasis and inflammation regulation. These multifaceted activities suggest its promising role as a complementary agent in topical wound treatments to optimize healing and skin regeneration.

Recombinant Human Fibroblast Growth Factor-2 Promotes Surgical-Wound Healing in the Rat Gingiva

The application of recombinant human fibroblast growth factor-2 (rhFGF-2) has been shown to significantly improve surgical wound healing in rat gingival tissue (Nakayama et al., 2024). FGF-2 is a potent mitogen stimulating fibroblast proliferation, angiogenesis, and collagen production-key events in the proliferative phase of healing. Topical rhFGF-2 treatment enhanced granulation tissue development and accelerated wound closure, confirming its therapeutic potential. This growth factor facilitates a favorable microenvironment that supports both tissue regeneration and remodeling. The study supports the clinical relevance of growth factors in modulating wound healing phases to improve outcomes in oral mucosa and possibly other tissues.

Biocaster : Jurnal Kajian Biologi
E-ISSN 2808-277X; P-ISSN 2808-3598
Volume 5, Issue 3, July 2025; Page, 108-118
Email: biocasterjournal@gmail.com

Genetic Variations in IL-1β, TNF-α, and TGF-β Associated with the Severity of Chronic Cervical Spondylitis in Patients

Genetic polymorphisms in cytokine genes such as IL-1β, TNF-α, and TGF-β contribute to the variability in inflammatory response and tissue remodeling observed in chronic cervical spondylitis (Yadav et al., 2023). These cytokines play crucial roles in regulating the inflammatory and proliferative phases of wound healing. Variants affecting IL-1β expression can increase inflammation severity, prolonging the inflammatory phase and impairing subsequent healing stages. TNF-α and TGF-β polymorphisms influence matrix remodeling and fibroblast function, impacting collagen synthesis and tissue repair. Understanding these genetic influences aids in identifying patients at risk for severe chronic inflammation and delayed wound healing, which may guide personalized therapeutic interventions.

CONCLUSION

This scoping review highlights the critical roles of interleukin 1β, fibroblast growth factor, fibroblasts, keratinocytes, granulation tissue, and collagen density in the wound healing process across inflammation, proliferation, and remodeling phases. Evidence shows that fibroblast-derived exosomes carrying miR-93-5p can delay healing by impairing autophagy. Controlled delivery of growth factors like FGF enhances fibroblast activity, angiogenesis, and collagen formation, accelerating repair. SPRR1B+ keratinocytes promote rapid re-epithelialization, particularly in oral wounds. Granulation tissue, composed of fibroblasts and new blood vessels, is essential for tissue regeneration. Excess IL-1β can worsen healing by increasing matrix metalloproteinases that degrade collagen. Natural extracts such as red fruit oil and Binahong leaf enhance angiogenesis and collagen synthesis, supporting healing. Genetic variations in inflammatory cytokines affect healing outcomes, suggesting personalized approaches may improve treatment. Together, these findings deepen understanding of the cellular and molecular mechanisms driving wound repair and support development of targeted therapies to optimize healing.

SUGGESTION

The authors suggest further exploration and clinical testing of natural extracts, such as red fruit oil and Binahong leaves, as alternative or complementary therapies that enhance angiogenesis and collagen synthesis.

ACKNOWLEDGEMENT

The authors express their deep gratitude to all parties who have provided literature for this research.

REFERENCES

Alhajj, M., & Goyal, A. (2022). *Physiology, Granulation Tissue*. Florida: StatPearls Publishing.

Atmaja, R., Annadiyah, V., Thoyyibah, M., Maimunah, S., Ma'Arif, B., Mutiah, R., Budi, I., Amiruddin, M., & Inayatilah, F. (2023). The Effect of Red Fruit Oil (*Pandanus conoideus* Lamk.) Emulgel on Angiogenesis and Collagen

Density in Incisive Wound Healing in Mice (*Mus musculus*). *Journal of Advanced Pharmaceutical Technology & Research, 14*(4), 311-316. https://doi.org/10.4103/japtr.japtr_67_23

Cialdai, F., Risaliti, C., & Monici, M. (2022). Role of Fibroblasts in Wound Healing and Tissue Remodeling on Earth and in Space. *Frontiers in Bioengineering and Biotechnology, 10*(1), 1-18. https://doi.org/10.3389/fbioe.2022.958381

Dai, J., Shen, J., Chai, Y., & Chen, H. (2021). IL-1β Impaired Diabetic Wound Healing by Regulating MMP-2 and MMP-9 through the p38 Pathway. *Mediators of Inflammation, 2021*(1), 1-10. https://doi.org/10.1155/2021/6645766

Farooq, M., Khan, A. W., Kim, M. S., & Choi, S. (2021). The Role of Fibroblast Growth Factor (FGF) Signaling in Tissue Repair and Regeneration. *Cells, 10*(11), 1-20. https://doi.org/10.3390/cells10113242

Huang, Y., & Kyriakides, T. R. (2020). The Role of Extracellular Matrix in the Pathophysiology of Diabetic Wounds. *Matrix Biology Plus, 6*(1), 1-14. https://doi.org/10.1016/j.mbplus.2020.100037

Jampa, M., Sutthanut, K., Weerapreeyakul, N., Tukummee, W., Wattanathorn, J., & Muchimapura, S. (2022). Multiple Bioactivities of *Manihot esculenta* Leaves: UV Filter, Anti-Oxidation, Anti-Melanogenesis, Collagen Synthesis Enhancement, and Anti-Adipogenesis. *Molecules, 27*(5), 1-17. https://doi.org/10.3390/molecules27051556

Kütük, S., & Özdaş, T. (2019). Impact of Platelet-Rich Fibrin Therapy in Tympanoplasty Type 1 Surgery on Graft Survival and Frequency-Specific Hearing Outcomes: A Retrospective Analysis in Patients with Tympanic Membrane Perforation Due to Chronic Otitis Media. *The Journal of Laryngology and Otology, 133*(12), 1068-1073. https://doi.org/10.1017/S0022215119002391

Lin, X., Zhang, X., Wang, Y., Chen, W., Zhu, Z., & Wang, S. (2025). Hydrogels and Hydrogel-Based Drug Delivery Systems for Promoting Refractory Wound Healing: Applications and Prospects. *International Journal of Biological Macromolecules, 285*(1), 1-19. https://doi.org/10.1016/j.ijbiomac.2024.138098

Mohidin, S. R. N. S. P., Moshawih, S., Hermansyah, A., Asmuni, M. I., Shafqat, N., & Ming, L. C. (2023). Cassava (*Manihot esculenta* Crantz): A Systematic Review for the Pharmacological Activities, Traditional Uses, Nutritional Values, and Phytochemistry. *Journal of Evidence-Based Integrative Medicine, 28*(1), 1-26. https://doi.org/10.1177/2515690x231206227

Nakayama, Y., Takeda, M. O., Saito, Y., Yamaguchi, A., & Ogata, Y. (2024). Early Wound Healing at 1 Week Postoperatively in Periodontal Tissue Regeneration Therapy: Enamel Matrix Derivative Versus Recombinant Human Fibroblast Growth Factor. *Journal of Periodontal & Implant Science, 54*(6), 405-418. https://doi.org/10.5051/jpis.2400740037

Nurkesh, A., Jaguparov, A., Jimi, S., & Saparov, A. (2020). Recent Advances in the Controlled Release of Growth Factors and Cytokines for Improving Cutaneous Wound Healing. *Frontiers in Cell and Developmental Biology,*

8(1), 1-7. https://doi.org/10.3389/FCELL.2020.00638

Nuroini, F., Ratnaningrum, K., Soejoto, M. R. A., Dewi, S. S., & Putri, G. S. A. (2021). Binahong Leaf Extract Activity in the 8th Day of Wound Healing Infected with *Staphylococcus aureus* Towards Collagen Tissue. *Jurnal Teknologi Laboratorium, 10*(2), 124-130. https://doi.org/10.29238/teknolabjournal.v10i2.310

Piipponen, M., Li, D., & Landén, N. X. (2020). The Immune Functions of Keratinocytes in Skin Wound Healing. *International Journal of Molecular Sciences, 21*(22), 1-26. https://doi.org/10.3390/ijms21228790

Xu, Z., Ni, T., Zhang, Q., Sun, X., Zhao, L., Lin, J., Gao, W., Yi, M., Zhang, L., Tu, L., Wu, G., & Yan, W. (2025). Exosomes Derived from Fibroblasts in DFUs Delay Wound Healing by Delivering miR-93-5p to Target Macrophage ATG16L1. *BBA - Molecular Basis of Disease, 1871*(3), 1-13. https://doi.org/10.1016/J.BBADIS.2024.167640

Xuanyuan, X., Zhang, L., Zheng, Y., Jiang, R., Ma, Y., Liu, R., Hou, P., Lei, M., Xu, H., & Zeng, H. (2024). SPRR1B+ Keratinocytes Prime Oral Mucosa for Rapid Wound Healing Via STAT3 Activation. *Communications Biology, 7*(1), 1-15. https://doi.org/10.1038/s42003-024-06864-5

Yadav, S. R. M., Goyal, B., Mamgain, G., Kothari, A., Kumar, S., Saha, S., Naithani, M., Mirza, A. A., Kumar, R., & Arora, R. (2023). Genetic Variations in IL-1β, TNF-α, and TGF-β Associated with the Severity of Chronic Cervical Spondylitis in Patients. *Cells, 12*(12), 1-19. https://doi.org/10.3390/cells12121594

Yoshinaga, Y., Maruo, N., Ohgi, K., Yamato, H., Tsuchimochi, N., Nakagami, M., & Sakagami, R. (2025). Recombinant Human Fibroblast Growth Factor-2 Promotes Surgical-Wound Healing in the Rat Gingiva. *Journal of Dental Sciences, 20*(2), 1-9. https://doi.org/10.1016/J.JDS.2025.03.031