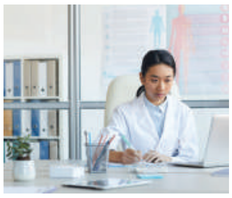


Scarless Wound Healing: Recent Advances and Innovations

Flora Ramona Sigit Prakoeswa,[1,2] Dykall Naf'an Dzikri[3]
[1]Faculty of Medicine, Universitas Muhammadiyah Surakarta,
[2]Department of Dermatology and Venerology, PKU Muhammadiyah Surakarta Hospital,
[3]Faculty of Medicine, Sebelas Maret University, Surakarta, Indonesia

ABSTRACT

Scarless wound healing, a hallmark of mid-gestation fetal skin, is characterized by minimal inflammation, balanced transforming growth factor-β isoforms, and a provisional extracellular matrix rich in type III collagen and hyaluronan. Decades of mechanistic studies have mapped how these features collectively enable rapid, regenerative closure without fibrosis. Contemporary adult-tissue strategies therefore focus on recapitulating the fetal milieu through targeted cytokine modulation, notably down-regulating TGF-β1/β2 while supplementing antifibrotic TGF-β3. Mesenchymal stem cells (MSCs) and their secretome have emerged as potent immunomodulators and angiogenic stimulants that steer wounds toward regeneration rather than scarring. Genetic engineering, biomaterial scaffolds, and extracellular-vesicle delivery platforms further enhance MSC persistence, homing, and paracrine potency. Parallel advances in bio-inspired hydrogels, microneedle arrays, and nanofiber dressings provide spatiotemporal release of growth factors, antimicrobial agents, and oxygen to orchestrate orderly repair. Such combinatorial nanotechnologies not only accelerate re-epithelialization but also limit hypertrophic collagen deposition, leading to flatter, more elastic neodermis.

Keywords: Regenerative medicine, scarless healing, wound healing.

ABSTRAK

Penyembuhan luka tanpa bekas, yang secara alami terjadi pada kulit janin pertengahan gestasi, ditandai oleh respon inflamasi minimal, keseimbangan isoform transforming growth factor-β, serta matriks ekstraseluler sementara yang kaya kolagen tipe III dan hialuronan. Riset dasar selama puluhan tahun telah memetakan bagaimana faktor-faktor tersebut bekerja sinergis menghasilkan penutupan luka cepat dan regeneratif tanpa fibrosis. Upaya terapeutik dewasa terkini berfokus meniru lingkungan janin melalui modulasi sitokin terarah, khususnya menekan TGF-β1/β2 sekaligus menambah TGF-β3 yang bersifat antifibrotik. Sel punca mesenkimal (MSC) dan sekretomanya muncul sebagai imunomodulator kuat serta stimulator angiogenesis yang mengarahkan proses perbaikan menuju regenerasi, bukan skar. Rekayasa genetik, *scaffold* biomaterial, dan platform vesikula ekstraseluler semakin meningkatkan persistensi, homing, dan potensi parakrin MSC. Kemajuan paralel pada hidrogel biomimetik, *microneedling* berinti-selubung, dan balutan nanofiber menghadirkan pelepasan spasio-temporal faktor pertumbuhan, antimikroba, serta oksigen guna mengatur perbaikan jaringan secara terstruktur. Teknologi nano kombinatorial tersebut tidak hanya mempercepat epitelisasi ulang tetapi juga membatasi pengendapan kolagen hipertrofik, yang mengarah pada neodermis yang lebih rata dan elastis.**Flora Ramona Sigit Prakoeswa, Dykall Naf'an Dzikri. Penyembuhan Luka Tanpa Bekas Luka: Kemajuan dan Inovasi Mutakhir**

Kata kunci: Pengobatan regeneratif, penyembuhan tanpa bekas luka, penyembuhan luka.

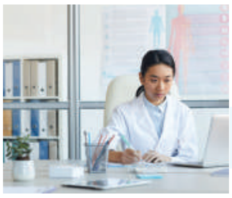
INTRODUCTION

Scarless wound healing has been a long-standing goal in regenerative medicine, with significant implications for improving patient outcomes and quality of life.[1] The ability to heal wounds without scarring, as observed in fetal tissue, has inspired decades of research aimed at understanding and replicating this phenomenon in adult tissues. Recent advances and innovations in this field have brought us closer to achieving scarless healing in clinical practice.

The discovery of scarless fetal wound healing in the 1970s marked a turning point in wound healing research.[2] Subsequent studies in various animal models, including sheep, rats, mice, pigs, monkeys, and humans, confirmed this remarkable ability during early gestation.[3,4] These findings sparked intense interest in characterizing the mechanisms underlying fetal wound healing, with the hope of identifying key factors that could be applied to adult wound healing.[5]

One of the primary focuses of research has been on understanding the differences between fetal and adult skin, including variations in growth factors, cytokines, extracellular matrix composition, and cellular responses to injury.[6] For instance, the

Alamat Korespondensi *email: frsp291@ums.ac.id*



transforming growth factor-β (TGF-β) family of proteins has been identified as a critical regulator of the wound healing response, with different isoforms playing distinct roles in fetal and adult wound healing.[7]

Recent advances in stem cell research have opened new avenues for promoting scarless healing. Mesenchymal stem cells (MSCs), in particular, have shown promise due to their ability to modulate the wound healing environment and promote regenerative pathways.[8] The paracrine effects of MSCs, including the secretion of growth factors and cytokines, have been recognized as a primary mechanism for reducing inflammation, promoting angiogenesis, and stimulating wound repair.[9]

Innovations in stem cell therapy for wound healing include gene modification, nanotechnology, and secretome engineering. Gene modification techniques allow for enhanced expression of beneficial growth factors by stem cells, amplifying their therapeutic potential.[10] Nanotechnology has been utilized to improve the delivery and function of stem cells in wound healing applications.[11] Furthermore, the use of extracellular vesicles (EVs) derived from stem cells has emerged as a promising cell-free approach to wound healing, addressing some of the challenges associated with cell-based therapies.[12]

The integration of biomaterials with stem cell therapy has shown significant potential in enhancing wound healing outcomes. Advanced scaffold-based delivery systems incorporating growth factors and stem cells have demonstrated improved vascularization and wound repair, particularly in chronic wounds.[13] These approaches aim to recreate the complex microenvironment of healthy skin, facilitating regeneration rather than repair.[14]

Recent research has also focused on modulating the immune response in wound healing. Studies have shown that MSCs can attenuate inflammatory responses by decreasing the secretion of pro-inflammatory cytokines while increasing the production of anti-inflammatory factors, creating a more favorable environment for wound healing.[15]

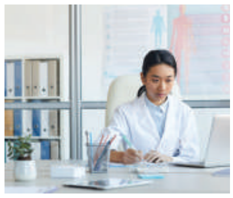
Recent advances in scarless wound healing techniques may have important implications for the treatment of sexually transmitted infections (STIs) that cause genital ulcers or lesions. The development of biomimetic materials and novel drug delivery systems could potentially be applied to improve healing of genital ulcers caused by STIs like herpes, syphilis, and chancroid, reducing scarring and complications. Additionally, innovations in antimicrobial peptides and controlled drug release may help combat antibiotic-resistant STI pathogens.[1,16–18] However, it's important to note that while these wound healing advances are promising, prevention through safe sex practices, hygiene, and regular STI screening remains crucial. Proper genital hygiene, including gentle cleansing and keeping the area dry, can help prevent secondary infections and promote healing of any existing lesions. Ultimately, an integrated approach combining innovative wound healing technologies with education on sexual health and hygiene is likely to yield the best outcomes in managing STI-related genital wounds and ulcers.[14,19]

Despite these advancements, challenges remain in translating scarless wound healing therapies to clinical practice. Issues such as optimal cell sourcing, delivery methods, and long-term safety need to be addressed. However, the continued innovation in this field, particularly in combining stem cell therapy with advanced biomaterials and gene modification techniques, offers promising avenues for improving wound healing outcomes.[20]

As research progresses, the goal of achieving scarless wound healing in adult tissues comes closer to reality. The integration of multiple approaches, including stem cell therapy, biomimetic materials, and immunomodulation, may ultimately lead to more effective strategies for promoting regenerative healing and minimizing scar formation. These advancements hold great potential for improving patient outcomes in a wide range of wound healing scenarios, from surgical incisions to chronic wounds and burns.[20]

Table 1. Recent studies focused on modulating TGF-β signaling.[21-25]

Title	Highlight Result
Exploring the impact of TGF-β family gene mutations and variations in cutaneous wound healing.[21]	This study identifies critical mutations in the TGF-β family genes that affect wound healing processes and suggests these genes as potential biomarker targets for therapeutic intervention in impaired healing, especially concerning non-melanoma skin cancer.
Effect of TGF-β3 on wound healing of bone cell monolayer in static conditions.[22]	The study demonstrated that TGF-β3 treatment significantly improves wound healing outcomes after 24 hours under static conditions, while being even more effective when combined with dynamic conditions, achieving full wound closure within 18 hours.
Scarless wound healing: Transitioning from fetal research to regenerative healing.[23]	The study discusses the differences between fetal and adult skin that facilitate scarless healing in adults, emphasizing that various growth factors and cytokines, alongside extracellular matrix substitutes, play crucial roles in the healing process, particularly noting the significance of TGF-β signaling.
TGF-β signaling in health, disease and therapeutics.[24]	TGF-β signaling is critical for various biological processes including embryonic development, wound healing, tissue homeostasis, and immune regulation. It also plays a significant role in diseases, making targeted therapies important for treatment options.
TGF-β signaling: critical nexus of fibrogenesis and cancer.[25]	The study explores the dual roles of TGF-β signaling in both fibrogenesis and tumorigenesis, emphasizing its complexity and relevance in therapeutic strategies for regenerative healing and cancer treatment.



TRANSITIONING FROM FETAL RESEARCH TO REGENERATIVE HEALING: GROWTH FACTORS, CYTOKINES, AND BIOMIMETIC PRODUCTS IN SCARLESS WOUND HEALING

The field of scarless wound healing has made significant strides in recent years, transitioning from fetal research to innovative regenerative approaches. This progress has been particularly evident in the areas of growth factors, cytokines, and biomimetic products **(Table 1)**.[21-25]

Growth factors and cytokines play crucial roles in orchestrating the complex process of wound healing. Research has shown that the unique cytokine and growth factor profile in fetal wounds contributes significantly to scarless healing.[6] This insight has led to the development of various strategies aimed at mimicking the fetal wound environment in adult tissues.

One of the key growth factor families involved in this process is the transforming growth factor-beta (TGF-β) family. The relative proportions of TGF-β isoforms have been found to be critical in determining wound repair outcomes.[7] Recent studies have focused on modulating TGF-β signaling to promote regenerative healing. For instance, Sen *et al*, (2009) demonstrated improved diabetic wound healing by reactivating a fetal repair protein, NPGPx, using tissue nanotransfection technology.[15]

Cytokines such as interleukin-10 (IL-10) have also been identified as important mediators of scarless healing. IL-10 helps in resolving inflammation and promoting tissue repair.[6] Recent research has explored various delivery methods for these growth factors and cytokines, including nanoparticle-based systems and hydrogels, to enhance their efficacy and longevity in the wound environment.[26]

The transition from fetal research to regenerative healing has also seen significant advancements in biomimetic products. These products aim to recreate the complex microenvironment of healthy skin, facilitating regeneration rather than repair. A notable example is the development of biomimetic hydrogels derived from decellularized dermal matrix. Yu, *et al*, (2023) demonstrated the efficacy of a light-sensitive decellularized dermal ECM-derived hydrogel in promoting skin wound healing. This hydrogel exhibited excellent cell biocompatibility, induced cellular infiltration, and enhanced angiogenesis. Importantly, it promoted an accelerated M1-to-M2 macrophage phenotype transition, orchestrating a pro-regenerative microenvironment conducive to scarless healing.[11]

Another innovative approach in biomimetic products involves the bioengineering of biomimetic corneal stroma for scarless corneal wound healing. Huang, *et al*, (2024) developed a biomimetic corneal stroma with immunomodulatory properties using stromal keratocytes derived from human amniotic epithelial stem cells (hAESC-SKs) and a photocurable gelatin-based hydrogel. This engineered tissue effectively restored corneal structure and reshaped the tissue microenvironment, reducing scar formation by approximately 75% while promoting wound healing in a rabbit corneal defect mode [28] **(Table 2)**.

The integration of nanotherapeutics with biomimetic approaches has also shown promise. For instance, biomimetic dual nanozymes have been developed to address the challenges of diabetic wound healing. These systems mimic glucose oxidase (GOx) and peroxidase (POD) activities, depleting glucose and acidifying the wound environment to inhibit bacterial growth while providing adequate hydrogen peroxide in an alkaline environment.[11]

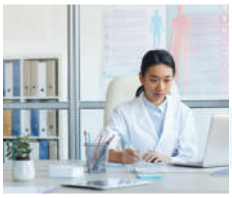
The transition from fetal research to regenerative healing in the context of scarless wound healing has led to significant advancements in growth factor and cytokine therapies, as well as the development of innovative biomimetic products. These approaches aim to recreate the fetal wound environment in adult tissues, promoting regenerative healing and minimizing scar formation. As research continues, the integration of multiple approaches, such as combining growth factor therapies with advanced biomaterials, may lead to even more effective strategies for achieving scarless wound healing in clinical practice.[31]

STEM CELL THERAPY FOR WOUND HEALING

Stem cell therapy has emerged as a promising approach for enhancing wound healing and reducing scarring over the past decade. The potential of stem cells, particularly mesenchymal stem cells (MSCs), to modulate the wound healing environment and promote regenerative pathways has been extensively explored and refined. MSCs have demonstrated

Table 2. Recent studies focused on biomimetic.[11,27-30]

Title	Highlight Result
Sprayable biomimetic double mask with rapid autophasing for scarless wound healing.[27]	The study demonstrates the efficacy of a sprayable biomimetic double wound mask (BDM) designed to promote scarless wound healing through a programmed stepwise healing cascade.
Biomimetic hydrogel derived from decellularized dermal matrix.[11]	The bioactive hydrogel derived from decellularized dermal matrix significantly enhances skin wound healing by promoting M1-to-M2 macrophage transition and improving the overall healing microenvironment.
Biomimetic Corneal Stroma for Scarless Corneal Wound Healing via Structural Restoration and Microenvironment Modulation.[28]	A biomimetic corneal stroma with immunomodulatory properties is bioengineered to promote scarless corneal wound healing.
Scarless wound healing programmed by core-shell microneedles.[29]	PF-MNs (programmed function microneedles) promote scarless wound repair in mouse models of both acute and chronic wounds, inhibiting scar formation.
Biomimetic Materials for Skin Tissue Regeneration and Electronic Skin.[30]	The study highlights various biomimetic materials, including collagen and gelatin, that support tissue regeneration and promote wound healing.

the ability to enhance several key mechanisms of wound healing, including angiogenesis, cell proliferation, and collagen synthesis. A study by Wu, *et al*, (2007) showed that MSCs significantly improved wound healing in diabetic mice by promoting angiogenesis and enhancing the expression of growth factors such as VEGF. This highlights the multifaceted role of stem cells in addressing complex wound healing challenges.[8]

The paracrine effects of stem cells have gained increasing attention as a primary mechanism for their beneficial impact on wound healing. Barrientos, *et al*, (2014) emphasized that MSC paracrine signaling is likely the primary mechanism for reducing inflammation, promoting angiogenesis, and stimulating wound repair. This understanding has led to the development of cell-free therapies based on stem cell secretomes.[9]

Recent innovations include gene modification, nanotechnology, and secretome engineering. Gene modification allows for the enhanced expression of beneficial growth factors by stem cells, thereby amplifying their therapeutic potential. Foppiani *et al.* (2019) reviewed various genetic engineering tools employed for MSC modification, highlighting the potential to improve their survival, migration, and therapeutic efficacy through the expression of specific proteins and soluble factors **(Table 3)**.[10]

Nanotechnology has been utilized to improve the delivery and function of stem cells in wound healing applications. Yu, *et al*, (2023) demonstrated the efficacy of a biomimetic hydrogel derived from decellularized dermal matrix, which significantly enhanced skin wound healing by promoting M1-to-M2 macrophage transition and improving the overall healing microenvironment.[11]

Secretome engineering, particularly the use of extracellular vesicles (EVs), has opened new avenues for cell-free translational therapies. Li, *et al*, (2018) showed that EVs derived from MSCs can promote wound healing by delivering regenerative molecules directly to the wound site. This approach addresses some of the challenges associated with cell-based therapies, such as poor cell survival and potential tumorigenicity.[12]

The integration of stem cell therapy with biomaterials has also shown promise. Kamolz, *et al*, (2022) utilized Matrigel with Matriderm for the delivery of MSCs to wound sites, incorporating growth factors within scaffolds to improve vascularization and wound repair. This combination of stem cells, scaffold-based delivery systems, and growth factors demonstrated enhanced wound healing effects, particularly in chronic wounds.[13]

Advanced delivery methods have been developed to optimize the efficacy of stem cell therapies. Nurkesh, *et al*, (2020) reviewed recent advances in the controlled release of growth factors and cytokines for improving cutaneous wound healing, highlighting the potential of nanoparticle-based systems and hydrogels to enhance the longevity and efficacy of stem cell-derived factors in the wound environment.[26]

The potential of stem cells to modulate the immune response in wound healing has been a focus of recent research. Sen, *et al*, (2022) demonstrated that MSCs can attenuate inflammatory responses by decreasing the secretion of pro-inflammatory cytokines while increasing the production of anti-inflammatory factors, thus creating a more favorable environment for wound healing.[15]

Despite these advancements, challenges remain in translating stem cell therapies to clinical practice. Issues such as optimal cell sourcing, delivery methods, and long-term safety need to be addressed. However, the continued innovation in this field, particularly in combining stem cell therapy with advanced biomaterials and gene modification techniques, offers promising avenues for improving wound healing outcomes.[36]

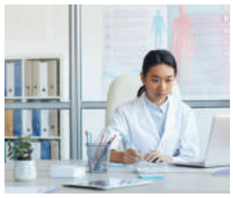
The field of stem cell therapy for wound healing has seen significant advancements over the past decade. From enhancing our understanding of stem cell mechanisms to developing novel delivery systems and cell-free therapies, these innovations hold great potential for improving wound healing outcomes, particularly for chronic and difficult-to-heal wounds.[36]

NANOTECHNOLOGY IN WOUND HEALING

The application of nanotechnology in wound healing has emerged as a promising field, offering innovative solutions to enhance therapeutic efficacy and promote tissue regeneration. Over the past decade, significant advancements have been made in developing

Table 3. Recent studies focused on stem cells.[20, 32-35]

Title	Highlight Result
The Efficacy of Stem Cells in Wound Healing: A Systematic Review.[32]	Adipose tissue-derived mesenchymal stem cells (AD-MSCs) emerged as an optimal choice due to their abundant supply, easy isolation, ex vivo proliferative capacities, and pro-angiogenic factor secretion.
Antler stem cell-derived exosomes promote regenerative wound healing.[33]	Antler stem cell-derived exosomes (AnSC-exos) significantly accelerated wound healing and improved healing quality, including regeneration of cutaneous appendages and inhibition of fibroblast-to-myofibroblast transition.
Innovative Treatment Strategies to Accelerate Wound Healing: Trajectory and Recent Advancements.[34]	Stem cell-based therapies using mesenchymal stem cells and induced pluripotent stem cells (IPSCs) have shown promise in preclinical and clinical trials. Scaffold-based delivery systems with growth factors improved stem cell survival and wound healing.
Emerging biomedical technologies for scarless wound healing.[20]	Review of various biomedical technology-based therapies, including cell therapy, for scarless wound healing, detailing mechanisms of action and practical applications.
Mesenchymal Stem Cells-Derived Extracellular Vesicles as Nanotherapeutics.[35]	MSC-derived extracellular vesicles (EVs) can inhibit inflammatory response, promote angiogenesis and epithelial cell proliferation, and regulate collagen synthesis to inhibit scar proliferation.



nanomaterials and nanoengineered systems that address the complex challenges of wound healing **(Table 4)**.[37-41]

Nanomaterials, including nanoparticles, nanofibers, and nanosheets, have been extensively studied for their potential to improve wound healing outcomes. These materials offer unique properties such as high surface area to volume ratio, tunable physical and chemical characteristics, and the ability to interact with biological systems at the molecular level. Nanoparticles, in particular, have shown great promise in drug delivery applications for wound healing.[39]

One of the key advantages of nanoparticle-based drug delivery systems is their ability to protect therapeutic agents from degradation and ensure sustained release at the wound site. This approach can significantly enhance the efficacy of treatment by maintaining therapeutic concentrations over extended periods.[42]

Targeted therapy is another area where nanotechnology has made significant strides in wound healing applications. By engineering nanomaterials to target specific cells or tissues involved in the wound healing process, researchers have been able to enhance therapeutic efficacy while minimizing systemic side effects. Shen, *et al*, (2015) reviewed various nanomaterial-based approaches for targeting specific cells involved in wound healing, such as fibroblasts and endothelial cells. These targeted approaches have shown promise in promoting angiogenesis, collagen deposition, and overall wound closure.[43]

The use of nanofibers in wound dressings has also gained considerable attention. Nanofibers offer high surface area, mechanical strength, and adjustable porosity, creating an optimal environment for healing and mimicking the extracellular matrix (ECM).[44] These properties make nanofiber-based dressings ideal for promoting cell attachment, proliferation, and migration. Additionally, nanofibers can be functionalized with various bioactive molecules to further enhance their wound healing capabilities.

Antimicrobial properties of certain nanomaterials have been harnessed to develop advanced wound dressings that can prevent and treat infections. Silver nanoparticles, in particular, have been extensively studied for their broad-spectrum antimicrobial activity. Silver nanoparticle-loaded dressings could effectively inhibit bacterial growth and promote wound healing in a mouse model of infected wounds.[39,45,46]

The integration of nanotechnology with other advanced technologies has led to the development of multifunctional wound healing systems. For example, the combination of nanotechnology with 3D bioprinting has enabled the fabrication of complex, biomimetic scaffolds that can more closely replicate the native tissue environment. Murphy and Atala (2014) reviewed the potential of 3D bioprinting in tissue engineering and regenerative medicine, highlighting its applications in wound healing.[47]

Despite the promising results in preclinical studies, the translation of nanotechnology-based wound healing therapies to clinical practice faces several challenges. Safety concerns, including potential toxicity and long-term effects of nanomaterials, need to be thoroughly addressed. Additionally, scalability and cost-effectiveness of nanomaterial production remain important considerations for widespread clinical adoption. [48]

Looking ahead, the field of nanotechnology in wound healing is poised for further innovation. Emerging areas of research include the development of smart nanomaterials that can respond to changes in the wound environment, such as pH or temperature, to provide on-demand release of therapeutic agents. The integration of nanotechnology with gene therapy and stem cell-based approaches also holds promise for enhancing wound healing outcomes.[48]

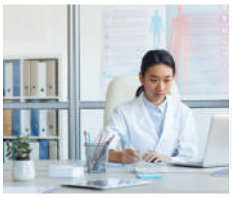
Nanotechnology has significantly advanced the field of wound healing over the past decade. From improved drug delivery systems to targeted therapies and multifunctional wound dressings, nanomaterials offer unique solutions to the complex challenges of wound healing. As research continues to progress, the integration of nanotechnology with other cutting-edge technologies is likely to lead to even more innovative and effective wound healing strategies.

CONCLUSION

The field of scarless wound healing has made significant strides in recent years, transitioning from fetal research to innovative regenerative approaches. Advancements in understanding growth factors, cytokines, and biomimetic products have led to promising strategies for

Table 4. Recent studies focused on nanotechnology.[37-41]

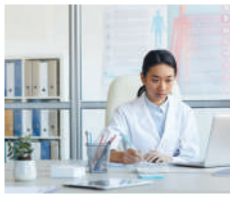
Title	Highlight Result
Porous Se@SiO2 Nanoparticles Enhance Wound Healing by ROS.[37]	Se@SiO2 nanoparticles accelerated dermal wound healing and suppressed hypertrophic scar formation, accompanied by oxidative stress inhibition and activation of the PI3K/Akt pathway.
Hyaluronic acid-modified and verteporfin-loaded polylactic acid nanogels promote scarless wound healing.[38]	The constructed nanogels promoted scarless wound healing by enhancing wound re-epithelialization and controlling scar formation.
Nanotechnology-Driven Therapeutic Interventions in Wound Healing.[39]	Various engineered nanotechnologies demonstrated unique properties and multiple functions addressing specific problems associated with wound repair mechanisms.
Nanotechnology-driven wound healing potential of asiaticoside.[40]	Nanotechnology improved the therapeutic efficacy of asiaticoside in wound healing applications by addressing its physical limitations.
Innovative approaches to wound healing: insights into interactive dressings.[41]	The review discusses advancements in interactive wound dressings, including nanomaterial-based approaches.

mimicking the fetal wound environment in adult tissues. Stem cell therapy, particularly using mesenchymal stem cells, has shown great potential in modulating the wound healing environment and promoting regenerative pathways. The integration of nanotechnology has further enhanced drug delivery systems, targeted therapies, and the development of multifunctional wound dressings. While challenges remain in translating these therapies to clinical practice, the continued innovation in combining stem cell therapy with advanced biomaterials, gene modification techniques, and nanotechnology offers promising avenues for improving wound healing outcomes. As research progresses, the goal of achieving scarless wound healing in adult tissues comes closer to reality, holding great potential for improving patient outcomes in a wide range of wound healing scenarios.

REFERENCES

1. Prakoeswa FRS, Satria YAA, Dewi LM. Bedah Buku Sebagai Upaya Peningkatan Pengetahuan Tata Laksana Terkini Ulkus Plantar Kronis Pada Penderita Kusta: Book Review as an Effort to Improve The Knowledge of The Latest Management on Chronic Plantar Ulcus in Leprosy. J Pengabdi Masy Med. 2023;3(1 SE-Articles):1–5. doi: 10.23917/jpmmedika.v3i1.474.
2. Burrington JD. Wound healing in the fetal lamb. J Pediatr Surg. 1971;6(5):523–8. doi: 10.1016/0022-3468(71)90373-3.
3. Rowlatt U. Intrauterine wound healing in a 20 week human fetus. Virchows Arch A Pathol Anat Histol. 1979;381(3):353–61. doi: 10.1007/BF00432477.
4. Gurtner GC, Werner S, Barrandon Y, Longaker MT. Wound repair and regeneration. Nature 2008;453(7193):314–21. doi: 10.1038/nature07039.
5. Buchanan EP, Longaker MT, Lorenz HP. Fetal skin wound healing. Adv Clin Chem. 2009;48:137–61. doi: 10.1016/s0065-2423(09)48006-5.
6. Larson BJ, Longaker MT, Lorenz HP. Scarless fetal wound healing: a basic science review. Plast Reconstr Surg. 2010;126(4):1172–80. doi: 10.1097/PRS.0b013e3181eae781.
7. Ferguson MWJ, O'Kane S. Scar-free healing: from embryonic mechanisms to adult therapeutic intervention. Philos Trans R Soc Lond B Biol Sci. 2004;359(1445):839–50. doi: 10.1098/rstb.2004.1475.
8. Wu Y, Chen L, Scott PG, Tredget EE. Mesenchymal stem cells enhance wound healing through differentiation and angiogenesis. Stem Cells. 2007;25(10):2648–59. doi: 10.1634/stemcells.2007-0226.
9. Barrientos S, Brem H, Stojadinovic O, Tomic-Canic M. Clinical application of growth factors and cytokines in wound healing. Wound Repair Regen. 2014;22(5):569–78. doi: 10.1111/wrr.12205.
10. Foppiani EM, Candini O, Mastrolia I, Murgia A, Grisendi G, Samarelli AV, et al. Impact of HOXB7 overexpression on human adipose-derived mesenchymal progenitors. Stem Cell Res Ther. 2019;10(1):101. doi: 10.1186/s13287-019-1200-6.
11. Yu Y, Xiao H, Tang G, Wang H, Shen J, Sun Y, et al. Biomimetic hydrogel derived from decellularized dermal matrix facilitates skin wounds healing. Mater Today Bio. 2023;21:100725. doi: 10.1016/j.mtbio.2023.100725.
12. Li X, Xie X, Lian W, Shi R, Han S, Zhang H, et al. Exosomes from adipose-derived stem cells overexpressing Nrf2 accelerate cutaneous wound healing by promoting vascularization in a diabetic foot ulcer rat model. Exp Mol Med. 2018;50(4):1–14. doi: 10.1038/s12276-018-0058-5.
13. Kamolz LP, Keck M, Kasper C. Wharton's jelly mesenchymal stem cells promote wound healing and tissue regeneration. Stem Cell Res Ther. Mei 2014;5(3):62. PMID: 25157597.
14. Luthfia R, Pramuningtyas R, Dasuki MS, Prakoeswa FRS. Status Gizi dan Personal Hygiene Berpengaruh Terhadap Kusta Wanita di Kabupaten Gresik. In Proceeding Book National Symposium and Workshop Continuing Medical Education XIV; 2021.
15. Sen CK, Gordillo GM, Roy S, Kirsner R, Lambert L, Hunt TK, et al. Human skin wounds: a major and snowballing threat to public health and the economy. Vol. 17, Wound repair and regeneration : official publication of the Wound Healing Society [and] the European Tissue Repair Society. United States; 2009. pp. 763–71.
16. Dimawan RSA, Prakoeswa FRS, Pramuningtyas R. Pediatric viral and bacterial skin infection profile. Berk Ilmu Kesehat Kulit dan Kelamin. 2022;34(3):184–8. doi: https://doi.org/10.20473/bikk.V34.3.2022.184-188.
17. Munawaroh R, Prakoeswa FRS, Kurniawati PM, Hazimah JN, Husna A, Kharisma AN, et al. Peran farmasis sebagai konselor terapi HIV. J Pengabdi Masy Med. 2022;2(1 SE-Articles):29–33. doi: https://doi.org/10.23917/jpmmedika.v2i1.461.
18. Wihardiyanto O, Prakoeswa FRS, Prakoeswa CRS. The effect of media exposure, family closeness, and knowledge about sexually transmitted disease on sexually transmitted disease risk behaviors in senior high school students. Berk Ilmu Kesehat Kulit dan Kelamin. 2019;31(1):55–9. doi: https://doi.org/10.20473/bikk.V31.1.2019.55-59.
19. Ratnaasri UD, Pramuningtyas R, Dasuki MS, Prakoeswa FRS. Personal hygiene dan status gizi sebagai faktor risiko kusta anak. In: Personal hygiene and nutritional status as risk factors for leprosy of children. Surakarta: Proceeding Book National Symposium and Workshop Continuing Medical Education XIV; 2021. pp. 554–64.
20. Cao X, Wu X, Zhang Y, Qian X, Sun W, Zhao Y. Emerging biomedical technologies for scarless wound healing. Bioact Mater. 2024;42:449–77. doi: 10.1016/j.bioactmat.2024.09.001.
21. Cui K, Gong S, Bai J, Xue L, Li X, Wang X. Exploring the impact of TGF-β family gene mutations and expression on skin wound healing and tissue repair. Int Wound J. 2024;21(4):e14596. doi: 10.1111/iwj.14596.
22. Al-Attar H, Damiati LA, Keshel SH, Tuinea-Bobe C, Damiati S, Saeinasab M, et al. Effect of TGF-β3 on wound healing of bone cell monolayer in static

and hydrodynamic shear stress conditions. Front Med. 2024;11:1328466. doi: 10.3389/fmed.2024.1328466.

23. Moore AL, Marshall CD, Barnes LA, Murphy MP, Ransom RC, Longaker MT. Scarless wound healing: Transitioning from fetal research to regenerative healing. Wiley Interdiscip Rev Dev Biol. 2018;7(2): 10.1002/wdev.309. doi: 10.1002/wdev.309.
24. Deng Z, Fan T, Xiao C, Tian H, Zheng Y, Li C, et al. TGF-β signaling in health, disease, and therapeutics. Signal Transduct Target Ther. 2024;9(1):61. doi: 10.1038/s41392-024-01764-w.
25. Giarratana AO, Prendergast CM, Salvatore MM, Capaccione KM. TGF-β signaling: critical nexus of fibrogenesis and cancer. J Transl Med. 2024;22(1):594. doi: 10.1186/s12967-024-05411-4.
26. Nurkesh A, Jaguparov A, Jimi S, Saparov A. Recent advances in the controlled release of growth factors and cytokines for improving cutaneous wound healing. Front cell Dev Biol. 2020;8:638. PMID: 32760728.
27. Yang Y, Suo D, Xu T, Zhao S, Xu X, Bei HP, et al. Sprayable biomimetic double mask with rapid autophasing and hierarchical programming for scarless wound healing. Sci Adv. 2024;10(33):eado9479. doi: 10.1126/sciadv.ado9479.
28. Huang J, Jiang T, Li J, Qie J, Cheng X, Wang Y, et al. Biomimetic corneal stroma for scarless corneal wound healing via structural restoration and microenvironment modulation. Adv Healthc Mater. 2024;13(5):e2302889. doi: 10.1002/adhm.202302889.
29. Zhang Y, Wang S, Yang Y, Zhao S, You J, Wang J, et al. Scarless wound healing programmed by core-shell microneedles. Nat Commun. 2023;14(1):3431. doi: 10.1038/s41467-023-39129-6.
30. Youn S, Ki MR, Abdelhamid MAA, Pack SP. Biomimetic materials for skin tissue regeneration and electronic skin. Biomimetics (Basel) 2024;9(5):278. doi: 10.3390/biomimetics9050278.
31. Karcioglu O, Topacoglu H, Dikme O, Dikme O. A systematic review of the pain scales in adults: which to use? Am J Emerg Med. 2018;36(4):707–14. doi: 10.1016/j.ajem.2018.01.008.
32. Farabi B, Roster K, Hirani R, Tepper K, Atak MF, Safai B. The efficacy of stem cells in wound healing: a systematic review. Int J Mol Sci. 2024;25(5):3006. doi: 10.3390/ijms25053006.
33. Zhang G, Wang D, Ren J, Li J, Guo Q, Shi L, et al. Antler stem cell-derived exosomes promote regenerative wound healing via fibroblast-to-myofibroblast transition inhibition. J Biol Eng. 2023;17(1):67. doi: 10.1186/s13036-023-00386-0.
34. Kolimi P, Narala S, Nyavanandi D, Youssef AAA, Dudhipala N. Innovative treatment strategies to accelerate wound healing: trajectory and recent advancements. Cells 2022;11(15):2439. doi: 10.3390/cells11152439.
35. Baek G, Choi H, Kim Y, Lee HC, Choi C. Mesenchymal stem cell-derived extracellular vesicles as therapeutics and as a drug delivery platform. Stem Cells Transl Med. 2019;8(9):880–6. doi: 10.1002/sctm.18-0226.
36. Gao M, Guo H, Dong X, Wang Z, Yang Z, Shang Q, et al. Regulation of inflammation during wound healing: the function of mesenchymal stem cells and strategies for therapeutic enhancement. Front Pharmacol. 2024;15:1345779. doi: 10.3389/fphar.2024.1345779.
37. Yang BY, Zhou ZY, Liu SY, Shi MJ, Liu XJ, Cheng TM, et al. Porous Se@SiO(2) nanoparticles enhance wound healing by ROS-PI3K/Akt pathway in dermal fibroblasts and reduce scar formation. Front Bioeng Biotechnol. 2022;10:852482. doi: 10.3389/fbioe.2022.852482.
38. Chen K, Liu Y, Liu X, Guo Y, Liu J, Ding J, et al. Hyaluronic acid-modified and verteporfin-loaded polylactic acid nanogels promote scarless wound healing by accelerating wound re-epithelialization and controlling scar formation. J Nanobiotechnology. 2023;21(1):241. doi: 10.1186/s12951-023-02014-x.
39. Hamdan S, Pastar I, Drakulich S, Dikici E, Tomic-Canic M, Deo S, et al. Nanotechnology-Driven Therapeutic Interventions in Wound Healing: Potential Uses and Applications. ACS Cent Sci. 2017;3(3):163–75. doi: 10.1021/acscentsci.6b00371.
40. Kumar M, Kumar D, Mahmood S, Singh V, Chopra S, Hilles AR, et al. Nanotechnology-driven wound healing potential of asiaticoside: a comprehensive review. RSC Pharm. 2024;1(1):9–36. doi: http://dx.doi.org/10.1039/d3pm00024a.
41. Yadav R, Kumar R, Kathpalia M, Ahmed B, Dua K, Gulati M, et al. Innovative approaches to wound healing: insights into interactive dressings and future directions. J Mater Chem B. 2024;12(33):7977–8006. doi: 10.1039/D3TB02912C.
42. Wilar G, Suhandi C, Wathoni N, Fukunaga K, Kawahata I. Nanoparticle-based drug delivery systems enhance treatment of cognitive defects. Int J Nanomedicine. 2024;19:11357–78. doi: 10.2147/IJN.S484838.
43. Shen YI, Song HHG, Papa A, Burke J, Volk SW, Gerecht S. Acellular hydrogels for regenerative burn wound healing: translation from a porcine model. J Invest Dermatol. 2015;135(10):2519–29. doi: 10.1038/jid.2015.182.
44. Xue J, Wu T, Dai Y, Xia Y. Electrospinning and electrospun nanofibers: methods, materials, and applications. Chem Rev. 2019;119(8):5298–415. doi: 10.1021/acs.chemrev.8b00593.
45. Haidari H, Garg S, Vasilev K, Kopecki Z, Cowin AJ. Silver-based wound dressings: current issues and future developments for treating bacterial infections. Wound Pract Res. 2020;28(4):173–80. doi: 10.33235/wpr.28.4.173-180.
46. Alven S, Aderibigbe BA. Chitosan-based scaffolds incorporated with silver nanoparticles for the treatment of infected wounds. Pharmaceutics. 2024. pp. 1–28.
47. Murphy S V, Atala A. 3D bioprinting of tissues and organs. Nat Biotechnol. Agustus 2014;32(8):773–85. doi: 10.1038/nbt.2958.
48. Sangnim T, Puri V, Dheer D, Venkatesh DN, Huanbutta K, Sharma A. Nanomaterials in the wound healing process: new insights and advancements. Pharmaceutics 2024;16(3):300. doi: 10.3390/pharmaceutics16030300.