










# Histological properties of biological materials in the wound healing process: an integrative review



## Propriedades histológicas de materiais biológicos no processo de cicatrização de feridas: uma revisão integrativa

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### Abstract

**Introduction:** Cutaneous wounds offer clinical challenges directly impacting the life of patients, as multiple aspects influence the healing process, including anatomical site, skin type, and the surgical techniques employed. In Brazil, chronic treatment of wounds imposes considerable economic impacts, accounting for 1% to 3% of healthcare costs. The development of effective and low-cost therapeutic alternatives have driven research toward the use of biomaterials (of natural or synthetic origin) to promote tissue regeneration. **Objective:** This study conducted an integrative review to evaluate the effects of biomaterials on wound healing, with a focus on histological properties. **Methods:** Twelve studies published in PubMed and MEDLINE databases between 2019 and 2024 meeting the inclusion criteria and addressing interventions with biomaterials were analyzed. **Results:** Biomaterials modulate the inflammatory response, promote angiogenesis, increase collagen production, and enhance re-epithelization. Despite the potential of biomaterials, the selection of the optimal material must consider the characteristics of the lesion and therapeutic goals. Additional studies are needed to validate the mechanisms of action and the durability of

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the observed effects. **Conclusion:** Anatomopathological analysis is essential to assess healing, evaluating the efficacy of interventions and guiding advances biomaterials application for cutaneous wounds, establishing biomaterials as innovative tools in clinical practice.

**Keywords:** Histology; Biological material; Wound healing; Wounds and lesions

## Resumo

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**Introdução:** As feridas cutâneas representam um desafio clínico devido à multiplicidade de fatores que influenciam a cicatrização, incluindo localização anatômica, tipo de pele e técnicas cirúrgicas empregadas, com implicações diretas na qualidade de vida dos pacientes. No Brasil, o tratamento de feridas crônicas apresenta elevado impacto econômico, representando entre 1% e 3% dos custos em saúde. A busca por alternativas terapêuticas eficientes e de baixo custo tem direcionado investigações ao uso de biomateriais, que são materiais de origem natural ou sintéticos capazes de interagir com sistemas biológicos para promover a regeneração tecidual.

**Objetivo:** Este estudo realizou uma revisão integrativa para avaliar os efeitos de biomateriais na cicatrização de feridas, com ênfase nas propriedades histológicas. **Métodos:** Foram analisados 12 artigos, publicados entre 2019 e 2024, nas bases de dados PubMed e MEDILINE, que atenderam aos critérios de inclusão e abordaram intervenções com biomateriais. **Resultados:** Os resultados indicaram que esses materiais modulam a resposta inflamatória, promovem angiogênese, aumentam a produção de colágeno e favorecem a reepitelização. Embora os resultados apontem o potencial dos biomateriais, a escolha do material ideal deve considerar as especificidades da lesão e os objetivos terapêuticos. Estudos adicionais são necessários para validar os mecanismos de ação e a durabilidade dos efeitos observados. **Conclusão:** A análise histológica é fundamental para monitorar o processo de cicatrização, permitindo avaliar a eficácia das intervenções e guiar avanços na utilização de biomateriais em feridas cutâneas, consolidando-os como ferramentas inovadoras na prática clínica.

**Palavras-chave:** Histologia; Material biológico; Cicatrização; Ferimentos e lesões

## INTRODUCTION

Multiple aspects pose clinical challenges in the treatment of cutaneous wounds, including anatomical location, skin type, ethnicity, and the surgical technique employed. These variables directly impact the quality of life of patients<sup>1</sup>. In Brazil, the treatment of cutaneous wounds represents a major economic burden, accounting for approximately 1% to 3% of healthcare expenditures due to the prolonged duration and complexity of managements. A Brazilian study reported that the average cost of outpatient treatment for chronic wounds is substantial, contributing to the financial strain on patients and the Unified Health System<sup>2</sup>.

Tissue repair is a dynamic and multifactorial process involving inflammation, re-epithelialization, angiogenesis, and extracellular matrix deposition. Initially, neutrophils and macrophages

remove debris and release chemiotactic mediators. Angiogenesis restores oxygen and nutrient supply, fibroblasts synthesize collagen and promote tissue remodeling, and keratinocytes facilitate re-epithelialization. The precise regulation of these mechanisms is essential for effective healing, as dysregulation may lead to delayed repair or abnormal scar formation<sup>3</sup>.

A study of individuals with chronic wounds demonstrated an association between these lesions, reduced functional capacity and psychological distress. Chronic pain and limitations in daily activities are major contributors to decreased health-related quality of life in such patients<sup>4</sup>.

In this context, research has increasingly focused on developing new high-efficacy and low-cost materials. Conventional treatments (e.g., dressings and antibiotics) may generate considerable costs for patients and healthcare systems. In contrast, polymer membranes offer an accessible alternative, serving as temporary skin substitutes that provide physical and mechanical barrier to support wound management<sup>5,6</sup>.

Moreover, several studies have explored biomaterials as promising therapeutic alternatives for chronic wound treatment, acting through multiple mechanisms in wound healing. Biomaterials dressings create a favorable microenvironment for tissue regeneration by regulating inflammatory responses, promoting angiogenesis, and stimulating cell proliferation<sup>7</sup>.

Therefore, this integrative literature review aimed to analyze the effects of biomaterials as therapeutic interventions in wound healing, focusing on its histological parameters.

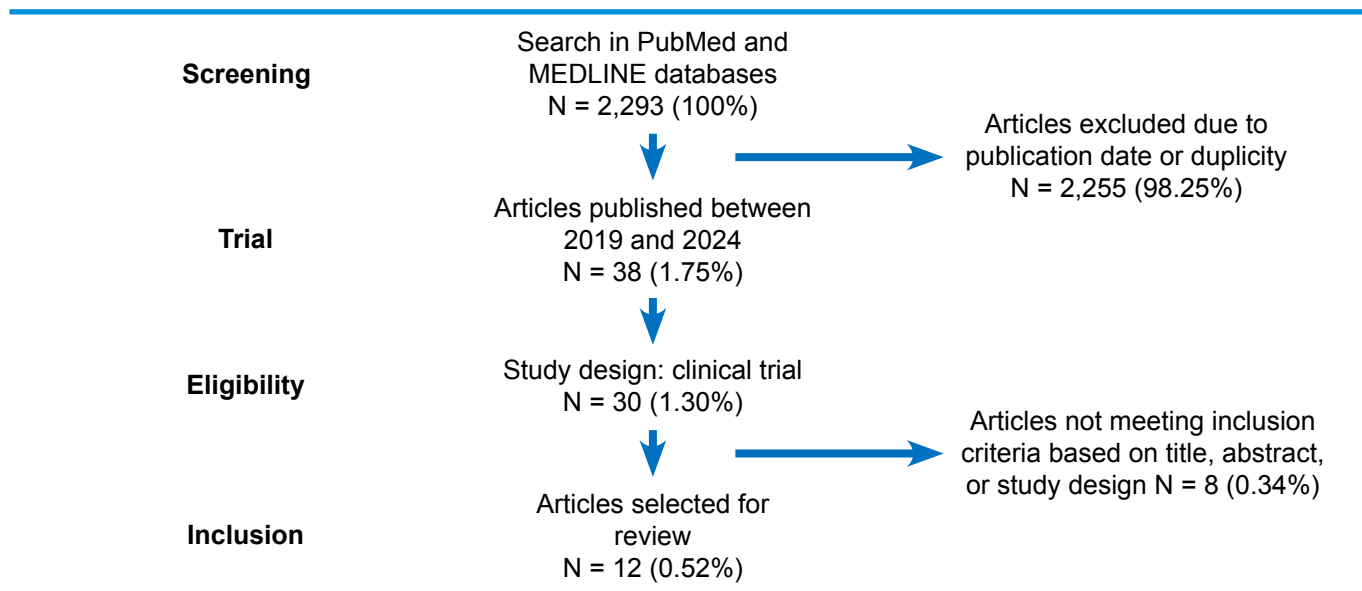
## **MATERIALS AND METHODS**

This integrative literature review was designed to examine and synthesize previous studies employing multiple methodologies to investigate the use of plant extracts and biomaterials in wound healing. The main research questions were “Which materials are effective in wound healing?” and “What are their main histological properties related to this process?”. Data were gathered and critically analyzed using a qualitative approach based on previous evidence. Integrative reviews allow the integration of previous evidence to support evidence-based healthcare practice, providing valuable insights to consolidate current evidence and support professional practice using scientific evidence<sup>8</sup>.

The literature search was conducted between October and November 2024 in PubMed and MEDLINE databases using the keywords “histology,” “clinical study,” and “wound.” Keywords were combined with the Boolean operator “AND”, and filters were applied to include only clinical trials published within the last five years. During the initial screening phase, titles and abstracts were assessed according to predefined inclusion criteria. Subsequently, independent reviewers performed full-text assessment of all eligible studies. The results of the search strategy are shown in Figure 1.

Inclusion criteria considered full-text, open-access available articles (original studies and

clinical trials) published between 2019 and 2024 in Portuguese or English, specifically addressing the use of biomaterials in wound healing. Studies that did not directly address the research questions were excluded.



**Figure 1.** Flowchart of the results of the search strategy.

## RESULTS

A total of 12 studies met the inclusion criteria and were analyzed. All studies were published between 2019 and 2024 in Brazilian or international journals. Each study was identified and cataloged according to title, authorship, publication year, study population, and research objectives (Box 1).

**Box 1.** Summary of the studies included in the integrative review (n = 12)

Author and Year	Title	Study Population and Intervention	Objective	Conclusions
Casali <i>et al.</i> , 2019.	Topical estradiol increases epidermal thickness and dermal collagen of foreskin prior to hypospadias surgery- Randomized double blinded controlled trial	Children scheduled for hypospadias surgery. Topical application of estradiol before surgery.	To investigate whether topical estradiol increases epidermal thickness and dermal collagen compared with testosterone and placebo in children undergoing hypospadias surgery.	Topical estradiol effectively enhanced epidermal thickness and dermal collagen in the foreskin, suggesting its potential for tissue preparation prior to surgery.

Chen, <i>et al.</i> , 2019.	O efeito da injeção de gordura de quilo em cicatrizes hipertróficas humanas em um modelo animal: Uma nova estratégia para o tratamento de cicatrizes hipertróficas.	Animal model simulating hypertrophic scars. Injection of chyle fat into scars.	To evaluate the effects of chyle fat injection as a treatment for hypertrophic scars.	Chyle fat injection improved scar appearance and structure, indicating this method as a promising therapeutic strategy.
Salvaggio <i>et al.</i> , 2020.	Effect of the topical Klox fluorescence biomodulation system on the healing of canine surgical wounds	Dogs undergoing surgery. Topical application of Klox fluorescence biomodulation system	To assess the effect of Klox fluorescence biomodulation system in wound healing in dogs.	Phobia-based therapy improved re-epithelialization, reduced dermal inflammation, and enhanced matrix deposition in uncomplicated cutaneous wounds by regulating key biological mediators.
Liu Y, <i>et al.</i> , 2020.	Ensaio clínico multicêntrico analisando a eficácia e a segurança do fluido composto tópico Cortex Phellodendri no tratamento de úlceras do pé diabético.	Patients with diabetic foot ulcers. Application of Cortex phellodendri compound fluid.	To evaluate the clinical efficacy of Cortex phellodendri compound fluid in diabetic foot ulcer treatment.	Topical treatment with Cortex phellodendri compound fluid promoted ulcer healing and increased growth factor concentration, while demonstrating good safety safe and well-tolerated.
Lee <i>et al.</i> , 2022.	Self-assembling RADA16 peptide hydrogel supports hemostasis, synechiae reduction, and wound healing in a sheep model of endoscopic nasal surgery	Sheep model of endoscopic nasal surgery. Application of RADA16 self-assembling peptide hydrogel.	To evaluate the effect of RADA16 hydrogel on hemostasis, synechiae reduction, and wound healing.	RADA16 and gelatin–thrombin accelerated hemostasis; however, only RADA16 reduced postoperative synechiae formation and improved mucosal regeneration.
Kodie <i>et al.</i> , 2022.	Nigeria bee honey-enhanced adherence, neovascularisation and epithelisation of full-thickness skin autografts on distal extremities of dogs	Dogs model with full-thickness skin grafts on distal limbs. Application of Nigerian bee honey to improve adhesion, angiogenesis, and skin graft epithelization	To assess the effect of Nigerian bee honey on graft adherence, neovascularization, and epithelialization.	Nigerian bee honey significantly improved graft adherence, neovascularization, and epithelialization, underscoring its therapeutic potential in veterinary surgical applications.
Nolan <i>et al.</i> , 2022.	Histological analysis of fat grafting with platelet-rich plasma for diabetic foot ulcers - A randomised controlled trial	Patients with diabetic foot ulcers. Fat grafting combined with platelet-rich plasma.	To analyze the histological effects of fat grafting with platelet-rich plasma in diabetic foot ulcer treatment in a randomized controlled trial.	Platelet-rich plasma fat grafting led to favorable histological outcomes compared with standard care. Furthermore, increased neovascularization and graft survival in diabetic foot ulcers were also observed.
Rambe <i>et al.</i> , 2022.	The effect of roselle leaf ( <i>Hibiscus sabdariffa</i> L.) extract gel on wound healing	In vivo rat model. Application of roselle ( <i>Hibiscus sabdariffa</i> L.) leaf extract gel.	To evaluate the wound healing effect of roselle leaf extract gel in rats.	No significant difference in wound healing or epithelial thickness were observed between groups.

Mhlongo F, <i>et al.</i> , 2022	Avaliação das propriedades de cicatrização de feridas de plantas medicinais sul-africanas usando peixe-zebra e bioensaios in vitro.	Zebrafish model. Extracts of South African medicinal plants.	To screen ethnomedical South African plants for pro-angiogenic and wound healing activity, employing a zebrafish transgenic larvae model and cell culture assays.	Extracts showed good activity in dose-dependent, anti-inflammatory activity in RAW 264.7 macrophages, and increased collagen production (122% increase compared with control) using MRHF cultured cells. All four selected extracts significantly stimulated MRHF proliferation in vitro. No significant toxicity was shown in vitro by all active extracts measured by MTT assay.
Thamm <i>et al.</i> , 2023.	Sublesional fat grafting leads to a temporary improvement of wound healing in chronic leg ulcers: A prospective, randomised clinical trial	Patients with chronic leg ulcers. Sublesional fat grafting.	To assess the impact of sublesional fat grafting on the healing of chronic leg ulcers.	Sublesional fat grafting temporarily improved wound healing in chronic leg ulcers.
Bienz <i>et al.</i> , 2024.	Clinical and histological wound healing patterns of collagen-based substitutes: An experimental randomized controlled trial in standardized palatal defects in humans	Indivíduos humanos com defeitos palatinos padronizados. Substitutos à base de colágeno	To evaluate clinical and histological healing patterns in palatal defects treated with collagen substitutes in a randomized controlled trial.	Collagen-based substitutes showed promising clinical and histological healing patterns, providing effective defect coverage, although no significant effect was shown in wound closure or pain.
Soheilifar M, <i>et al.</i> , 2024.	Avaliação in vitro e in vivo das propriedades de cicatrização de feridas diabéticas de pétalas de açafreão ( <i>Crocus sativus</i> L.)	Human umbilical vein endothelial cells (HUVECs), human dermal fibroblasts, and mice. Application of <i>C. sativus</i> petal extract .	To assess the in vitro and in vivo effects of <i>C. sativus</i> petal extract on fibroblast migration and endothelial angiogenesis, and the efficacy in wound healing in a model of excisional cutaneous wound in rats.	The extract of <i>C. sativus</i> enhanced the viability, migration of human dermal fibroblasts and HUVECs. Tube forming in Matrigel-cultivated HUVECs was increased, indicating its angiogenic potential.

## DISCUSSION

This study underscores the therapeutic potential of biological materials in wound healing, particularly regarding their histological effects on treated tissues. Despite methodological variability across studies, beneficial outcomes were consistently reported, especially in promoting collagen synthesis, re-epithelialization, and epidermal thickness.

Collagen-stimulating materials showed promising regenerative effects. The topical application of estradiol before hypospadias surgery significantly increased epidermal thickness and dermal collagen in the foreskin. In contrast, testosterone failed to promote comparable results, reinforcing the specific effect of estradiol and suggesting that hormonal modulation may optimize tissue preparation and improve surgical outcomes<sup>8</sup>.

Similarly, the Klox fluorescence biomodulation system enhanced collagen production in canine surgical wounds, leading to complete re-epithelialization, reduced dermal inflammation, and increased matrix deposition. These effects were attributed to the modulation of biological mediators such as factor VIII, collagen type III, and Ki67<sup>9</sup>. In this context, hydrogel containing synthetic RADA16 peptide promoted mucosal regeneration, accelerated hemostasis, and reduced postoperative synechiae formation in a sheep model of endoscopic sinus surgery<sup>10</sup>.

Another promising biomaterial was Nigerian bee honey, which improved adherence, neo-vascularization, and epithelialization of full-thickness skin grafts in dogs. These findings indicate that honey creates a regenerative microenvironment that stimulates fibroblast proliferation and collagen deposition<sup>11</sup>.

Likewise, fat grafting combined with platelet-rich plasma enhanced tissue regeneration, especially in diabetic foot ulcers<sup>12</sup>, while sublesional fat grafting in chronic leg ulcers improved healing rates (accelerating wound closure compared with control group), although without significant pain reduction<sup>13</sup>.

Collagen-based substitutes used for palatal defect repair improved clinical outcomes and histological healing patterns, particularly in periodontal tissue repair. However, pain was not significantly improved<sup>14</sup>. In the management of hypertrophic scars, chyle fat injection reduced scar thickness and stiffness while enhancing elasticity and overall tissue quality, suggesting a viable strategy for improving fibrotic tissue pliability<sup>15</sup>.

Recent evidence also supports the therapeutic potential role of medicinal plants in wound healing. *Phellodendri*-based phytotherapeutics accelerated wound closure and collagen deposition<sup>16</sup>, while *Crocus sativus L.* (saffron) petal extracts enhanced fibroblast viability and migration, and angiogenesis, promoting accelerated wound closure in diabetic mice<sup>17</sup>.

A study employing South African medicinal plants (*Lobostemon fruticosus* and *Scabiosa columbaria*) demonstrated pro-angiogenic and collagen-stimulating activity in fibroblasts and zebrafish models, validating their ethnomedicinal use in wound care<sup>18</sup>. Similarly, treatment with roselle (*Hibiscus sabdariffa L.*) extract gel increased collagen thickness in rats wound models<sup>18</sup>.

Therefore, despite differences across methodological design and biomaterial composition, evidence support the use of biological materials (collagen, estradiol, honey, platelet-rich plasma, and fat) to enhance wound healing via mechanisms involving re-epithelialization, neo-vascularization, and collagen deposition. However, the selection of the appropriate biomaterial should consider lesion characteristics and therapeutical goals. Further research is warranted to elucidate molecular mechanisms, assess long-term outcomes, and establish clinical protocols for their effective application in regenerative wound management.

## CONCLUSION

The central importance of anatomopathological analysis in wound healing stems from the impact of cutaneous lesions exert in health and quality of life of patients. Histological evaluation of healing tissues enables effective monitoring of lesion progression, early detection of complications, and assessment of therapeutic efficacy. Biomaterials play a relevant role in tissue repair by regulating inflammation within wound microenvironment, promoting angiogenesis, stimulating collagen synthesis, and enhancing re-epithelialization.

## CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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## AUTHOR CONTRIBUTIONS

**BGSP:** Conceptualization, Data curation, Data analysis, Research, Methodology, Project administration, Supervision, Data and Experiments validation, data presentation design, Writing – original draft, Writing – Reviewing and editing. **CSMLT:** Conceptualization, Data curation, Data analysis, Development, Methodology, Research, Validation, Writing – original draft, Writing – reviewing, and editing. **FVFM:** Conceptualization, Data curation, Data analysis, Development, Methodology, Research, Validation, Writing – original draft, Writing – reviewing and editing. **RJMF:** Conceptualization, Data curation, Data analysis, Development, Methodology, Research, Validation, Writing – original draft, riting – Reviewing and editing. **CSJLT:** Conceptualization, Research. **CRO:** Conceptualization, Research. **OTKB:** Conceptualization, Data analysis, Data curation, Data presentation, Methodology, Research, Project administration, Supervision, Validation, Writing – original draft, Writing – Reviewing and editing. All authors approved the final version of the manuscript.

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