ISSN: 2687-8100

Archives in Biomedical Engineering & Biotechnology

DOI: 10.33552/ABEB.2023.07.000668

Iris Publishers

Research Article

Copyright © All rights are reserved by Irami Araujo Filho

Pomegranate (Punica Granatum L) and Wound Healing: A Review of Experimental Studies

Fabiano Batista da Silva[1], Giuliana Fulco Goncalves[2], Amalia Cinthia Meneses do Rego[3], Irami Araujo Filho[4]*

[1]*Master's Student of the Graduate Program in Biotechnology, Potiguar University (UnP)-Natal/RN-Brazil.*

[2]*Student of the Medicine Course at the Potiguar University, Scientific Initiation Scholarship of Liga Contra o Cancer-Natal/RN-Brazil.*

[3]*Institute of Teaching, Research, and Innovation, Liga Contra o Cancer-Natal-Brazil Full Professor of the Graduate Program in Biotechnology, Potiguar University (UnP)-Natal/RN - Brazil.*

[4]*Institute of Teaching, Research, and Innovation, Liga Contra o Cancer-Natal-Brazil, Graduate Program in Biotechnology Potiguar University (UnP)- Natal/RN - Brazil. Department of Surgery, Potiguar University. Ph.D. in Health Science/ Natal-RN, Brazil.*

***Corresponding author:** Irami Araujo-Filho, Postgraduate Program in Biotechnology at Potiguar University/ UnP, Department of Surgery, Federal University of Rio Grande do Norte, Department of Surgery, Potiguar University in Health Science/ Natal-RN, Brazil.

Received Date: June 22, 2023

Published Date: September 11, 2023

Abstract

The review discusses the potential of Punica granatum L., known as Pomegranate, and its extracts in promoting wound healing. This review summarizes current knowledge about the use of Punica granatum L in healing cutaneous wounds in experimental models, mechanisms of action, challenges, and opportunities for future research. Pomegranate extract has been observed to benefit wound healing due to its antioxidant, anti-inflammatory, and antimicrobial properties. The fruit's polyphenols, flavonoids, and tannins contribute to wound healing, reduce oxidative stress, inflammation, and infection, as well as stimulate fibroblast proliferation and collagen synthesis, which are crucial for tissue repair. Animal studies have shown that pomegranate extract accelerated wound closure, re-epithelialization, collagen deposition, and reduced wound size, inflammation, and bacterial load in various wound models. In addition, pomegranate extract in the form of nanoparticles, associated or not with silver, was analyzed for improvement in wound healing, antimicrobial action, and reduction of inflammation in animal models. Pomegranate peel and seed oil enhance collagen synthesis, growth factor expression, and reduce oxidative stress. Pomegranate extract shows promise as a natural and safe alternative for wound healing. The mechanisms underlying Pomegranate's beneficial effects on wound healing were discussed, potential clinical applications of Pomegranate in treating human skin wounds, limitations, and challenges.

Keywords: Pomegranate; Wound healing; Experimental models; Experimental studies; Experimental animal models; Surgery

Introduction

The wound healing process involves cellular and molecular events that culminate in repairing damaged tissues [1]. The process is composed of hemostasis, inflammation, proliferation, and remodeling. Hemostasis is performed by blood coagulation, while inflammation protects the host from pathogen invasion and promotes proliferation [2,3].

Proliferation results in wound re-epithelialization, angiogenesis, fibroblast, and extracellular matrix (ECM) formation. Remodeling is the final stage of wound healing and tissue maturation [4]. However, wound healing can be impaired due to infection, underlying diseases, or malnutrition. Therefore, there is growing interest in developing new therapies to enhance wound healing [4,5]. One promising approach is using natural products such as

This work is licensed under Creative Commons Attribution 4.0 License

Roma, a plant with potential wound-healing properties. Punica granatum L., commonly known as Pomegranate, has been used for centuries in traditional medicine due to its medicinal properties [6]. Several studies have reported the beneficial effects of Pomegranate in wound healing, which has drawn the attention of researchers in recent years 4-6.

The fruit of Punica granatum L. contains polyphenols, flavonoids, and tannins, which have been shown to have antioxidant, anti-inflammatory, and antimicrobial properties2. These compounds contribute to wound healing by reducing oxidative stress, inflammation, and infection. In addition, pomegranate extract stimulates fibroblast proliferation and collagen synthesis, which are essential processes in tissue repair [3]. Hayouni et al. demonstrated that applying pomegranate extract on excision wounds in rats increased wound closure rate, epithelialization, and collagen deposition, accelerating wound healing compared to the control group [1]. Similarly, Niknam et al. showed that topical application of pomegranate extract on burn wounds in rats decreased wound size, inflammation, and bacterial load compared to the control group [2].

Moreover, studies have also investigated the effect of pomegranate extract on diabetic wound healing, which is a challenging condition. Albahri et al. demonstrated that applying pomegranate peel extract on diabetic wounds in rats accelerated wound closure rate, re-epithelialization, and angiogenesis compared to the control group [3]. Yan H et al. investigated the effect of pomegranate peel polyphenol gel on wound healing in diabetic rats. The gel promoted wound healing, angiogenesis, and inflammation by elevating collagen deposition [4].

In this sense, the pomegranate peel polyphenol gel proved to be an effective alternative in recovery regarding the association of wounds and diabetes. Although the results of animal studies are promising, clinical studies are needed to confirm the efficacy and safety of pomegranate extract in wound healing [5,6].

Karim et al. observed the effects of a gel based on the methanolic extract of pomegranate peels on wound healing in diabetic rats. The section accelerated wound closure and promoted collagen deposition, suggesting the potential of pomegranate peel extract as a natural wound healing agent, especially in diabetic patients were delayed healing is shared [5].

In summary, using pomegranate extract in wound healing has shown promising results in animal and clinical studies. The bioactive compounds in Pomegranate may contribute to wound healing by reducing oxidative stress, inflammation, and infection and stimulating fibroblast proliferation and collagen synthesis [6,7]. Further studies are needed to investigate the optimal dosage and duration of treatment and to assess the long-term safety and efficacy of pomegranate extract in wound healing. Nonetheless, pomegranate extract has excellent potential as a natural and safe alternative for wound healing therapy [8,9].

This review aims to summarize the current knowledge regarding using Punica granatum L in the context of cutaneous wound healing. We will discuss the available evidence from animal studies, the potential mechanisms of action, and the challenges and opportunities for future research in this field. In addition, the possible mechanisms underlying the beneficial effects of Pomegranate on wound healing were discussed. Finally, we will highlight the potential clinical applications of Pomegranate in treating human cutaneous wounds and its limitations and challenges.

Methods

This cross-sectional, observational, and integrative study consists of a review of Pomegranate (Punica granatum L.) use, without restriction regarding the parts of the plant used or the pharmaceutical form applied, and its activity in healing cutaneous wounds, infected or not, in animal/experimental models. A search for studies was carried out in the PubMed/Medline, Scopus, Scielo, Embase, and Web of Science databases, in addition to Google Scholar, considered a source of gray literature, as it does not contain peer-reviewed articles. Studies related to the topic were selected using the following search strategy: "Nano-PSO" [Supplementary Concept] OR Pomegranate OR Pomegranates OR Punica granatum"; Wound Healing OR Wound Infection; "Models, Animal" OR Animal Model OR Animal Models OR Model, Animal OR Laboratory Animal Models OR Animal Model, Laboratory OR Animal Models, Laboratory OR Laboratory Animal Model OR Model, Laboratory Animal OR Models, Laboratory Animal OR Experimental Animal Models OR Animal Model, Experimental OR Animal Models, Experimental OR Experimental Animal Model OR Model, Experimental Animal OR Models, Experimental Animal. Cohort studies, systematic reviews, case-control, cross-sectional studies, case series studies, and randomized clinical trials were included. Experimental studies on skin wounds and the effect of Punica granatum were used as inclusion criteria, complete and published articles with no date limit. Duplicate reports were excluded using the Rayyan software—Reviewer. Analysis, review, and selection of the studies were made by peers unthinkingly, from reading the title and summary of the study, with a third reviewer in case of disagreement between the other two reviewers.

Results and Discussion

In recent years, several studies have investigated the effects of pomegranate on wound healing in animal models [1]. The wound-healing properties of pomegranate extract may be attributed to flavonoids and triterpenoids, which possess antioxidant, anti-inflammatory, and antimicrobial activities. These compounds modulate the proliferation, migration, and differentiation of cells [6]. In addition to its potential therapeutic effects, pomegranate is relatively safe and well-tolerated, with minimal side effects reported in animal studies [7-9].

Dkhil et al. investigated pomegranate peel extract's anticoccidial, anthelmintic, and antioxidant activities. The pomegranate peel extract exhibited anticoccidial and anthelmintic activities, suggesting an alternative to synthetic anticoccidial and anthelmintic agents [8].

Additionally, Scappaticci et al. use green and chemical silver nanoparticles (AgNPs) and pomegranate formulations to treat infected wounds in diabetic mice. Diabetic rats with infected

wounds were treated with different formulations containing green and chemical AgNPs and pomegranate extract. Researchers assessed healing progress by measuring wound size, bacterial counts, and tissue histology [9]. It was noted the group treated with green AgNPs and pomegranate extract had a faster and more efficient healing process. Histological analysis revealed a reduction in inflammatory cells in the treated group compared to the control group10.

Following the same line of research, Wasef et al. analyzed the effects of silver nanoparticles (AgNPs) on burn healing in a mouse. In the model, mice treated with AgNPs and P. granatum extract reduced wound size, better histopathological characteristics, and reduced oxidative stress markers in the treated group. It was concluded, therefore, that the combination of AgNPs and P. granatum extract can be used as an effective therapeutic option for healing burns [9,10].

Devanesan et al. synthesized silver nanoparticles from pomegranate peel extract and evaluated their antimicrobial and cytotoxic effects in humans. The results demonstrated potent antimicrobial activity against gram-negative and gram-positive bacterial and fungal pathogens, with low cytotoxicity for human cells [11]. Likewise, Nasiriboroumand et al. found that the nanoparticles exhibit good stability and biocompatibility, suggesting their potential as a safe and effective agent for various biomedical applications [12]. Mahmood et al. analyzed the chemical composition of Punica granatum L. (pomegranate) bark extract using high-performance liquid chromatography (HPLC). They evaluated its antimicrobial activity against a variety of microorganisms. The authors extracted the bark using methanol and identified ellagic acid, gallic acid, and quercetin [13].

The pomegranate peel extract exhibited antimicrobial activity against Staphylococcus aureus, Escherichia coli, and Candida albicans. The results suggested that pomegranate peel extracts are a natural alternative for treating microbial infections. However, more studies are needed to evaluate its effectiveness and safety in clinical settings [12-14].

Do Nascimento et al. develop a bio-interactive gelatin dressing based on Punica granatum Linn extract. Dressings containing gelatin have biocompatibility, biodegradability, and the ability to absorb wound exudates [14]. The pomegranate peel extract incorporated into the gelatin dressing potentiated healing, rapid closure, and increased collagen production associated with inflammatory reduction. In this sense, the present study's findings are significant for developing new effective and safe dressings for clinical practice [14-16].

Some studies focus on the fruit itself, while others analyze fruit extracts in the form of nanoparticles, associated or not with silver, and the potential therapeutic properties of Punica granatum in the treatment of various health conditions, whether in the healing of wounds, infections, and other illnesses [17]. Bakkiyaraj et al. investigated the anti-biofilm potential of pomegranate extract against human bacterial and fungal pathogens. They found that it has inhibitory properties against the growth of these harmful agents [15]. Likewise, Swaroop et al. summarized the pomegranate's potential mechanisms of action in wound healing, emphasizing the activity of polyphenols and flavonoids [16].

Lukiswanto et al. demonstrated the wound-healing potential of P. granatum whole fruit extract on skin burns in rats compared to silver sulfadiazine. Wound contraction, histopathology, and hydroxyproline content were analyzed as healing parameters. More significant collagen deposition, increased angiogenesis, and reduced inflammation were observed [17]. In turn, Mousavi et al. analyzed the effect of pomegranate seed oil on wound healing in mice with burns, in which it was possible to observe a reduction in healing time, wound size, and elevation of local collagen [18]. The effects of pomegranate flower extract on burn skin lesions in rats were observed by Nasiri et al., reduced inflammation, favoring angiogenesis and collagen deposition [13-15].

Akbari et al. studied the wound-healing potential of pomegranate in streptozotocin-induced diabetic rats. They observed efficacy in wound healing associated with increased collagen deposition and reduced oxidative stress, corroborating the results of Cho et al [19,20]. The efficacy of Punica granatum (pomegranate) in promoting wound healing has been investigated by several studies [2-4]. Kim et al. demonstrated that pomegranate extract accelerates wound healing by modulating hypoxia-inducible factor 1α (HIF-1α), and IL-6 expression in mice [21]. Similarly, Alimoradian et al. observed improved wound healing in rats treated with Punica granatum seed extract, attributed to increased growth factor expression and reduced inflammation [22].

Celik et al. demonstrated the effectiveness of pomegranate seed oil in wound healing, as evidenced by increased growth factor expression and reduced oxidative stress. The benefits of pomegranate peel extract in wound healing were further supported by Hoseny et al. and Ragab et al. in rat and rabbit models, respectively [23-25].

These studies highlighted the extract's ability to enhance collagen synthesis, increase growth factor expression, and reduce inflammation, all contributing to improved wound healing outcomes [24-26].

Moreover, Cho et al. investigated the impact of pomegranate extract on surgical skin wounds in rats, revealing a significant acceleration of wound healing. This effect was attributed to the promotion of granulation tissue formation, re-epithelialization, and the antioxidant activity of the extract [20]. In the context of excisional wounds, Akbari et al. found that pomegranate peel extract effectively accelerated wound healing in rabbits by reducing wound size and increasing collagen deposition [19]. Furthermore, Murthy et al. investigated the wound-healing activity of P. granatum peel in rats, demonstrating higher hydroxyproline content in the treated group compared to the control group [27].

Notably, Ragab et al. developed a chitosan-based hydrogel containing pomegranate peel extract to treat chronic wounds. This hydrogel formulation exhibited improved cellular antennas, angiogenesis, and collagen deposition, highlighting its potential as a natural remedy for chronic wound management [25]. Collectively, these studies provide scientific evidence supporting

the effectiveness of Punica granatum in promoting wound healing through various mechanisms, including modulation of growth factors, reduction of inflammation, stimulation of collagen synthesis, and antioxidant activity. However, further research is required to fully elucidate the underlying mechanisms of action and evaluate potential side effects associated with using Punica granatum for wound healing.

Conclusion

In summary, a body of research has demonstrated the potential of Punica granatum L., or Pomegranate, and its extracts as promising agents for promoting wound healing in various animal models. The observed effects involve the modulation of critical biological processes such as collagen deposition, inflammation reduction, oxidative stress mitigation, and growth factor expression.

Nevertheless, additional investigations are warranted to determine the optimal dosing regimens and administration routes for pomegranate extracts in wound healing. Given its inherent antioxidant, anti-inflammatory, and antimicrobial properties, Punica granatum L. holds promise as a natural therapeutic option for cutaneous wound treatment.

Despite the promising results obtained in animal models, further research is needed to determine the efficacy and safety of pomegranate extract in human clinical trials. Moreover, the mechanisms underlying the wound-healing effects of Romã need to be elucidated to optimize its use in wound care. This review provides a comprehensive overview of the current knowledge on the use of Pomegranate in the healing of cutaneous wounds in animal models. The information presented in this review may help to inform the development of new therapies and strategies to enhance wound healing in humans.

Acknowledgement

None.

Conflicts of Interest

No conflicts of interest.

References

1. Hayouni EA, Miled K, Boubaker S, Bellasfar Z, Abedrabba M, et al. (2011) Hydroalcoholic extract based ointment from Punica granatum L. peels with enhanced in vivo healing potential on dermal wounds. Phytomedicine 18(11): 976-984.
2. Niknam S, Tofighi Z, Faramarzi MA, Abdollahifar MA, Sajadi E, et al. (2021) Polyherbal combination for wound healing: Matricaria chamomilla L. and Punica granatum L. Daru 29(1): 133-145.
3. Albahri G, Badran A, Hijazi A, Daou A, Baydoun E, et al. (2023) The Therapeutic Wound Healing Bioactivities of Various Medicinal Plants. Life (Basel) 13(2): 317.
4. Yan H, Peng KJ, Wang QL, Gu ZY, Lu YQ, et al. (2013) Effect of pomegranate peel polyphenol gel on cutaneous wound healing in alloxan-induced diabetic rats. Chin Med J 126(9): 1700-1706.
5. Karim S, Alkreathy HM, Ahmad A, Khan MI (2021) Effects of Methanolic Extract Based-Gel from Saudi Pomegranate Peels with Enhanced Healing Potential on Excision Wounds in Diabetic Rats. Front Pharmacol 12: 704503.
6. Zhang L, Yang R, Hu Y, Yang Y, Zhang X, et al. (2022) Promoting effect of pomegranate peel extract on second-degree burn wound-healing through VEGF-A and TGF-β1 regulation. Burns 48(3): 639-648.
7. Xu J, Zhao Y, Aisa HA (2017) Anti-inflammatory effect of pomegranate flower in lipopolysaccharide (LPS)-stimulated RAW264.7 macrophages. Pharm Biol 55(1): 2095-2101.
8. Dkhil MA (2013) Anti-coccidial, anthelmintic and antioxidant activities of pomegranate (Punica granatum) peel extract. Parasitol Res 112(7): 2639-2646.
9. Scappaticci RAF, Berretta AA, Torres EC, Buszinski AFM, Fernandes GL, et al. (2021) Green and Chemical Silver Nanoparticles and Pomegranate Formulations to Heal Infected Wounds in Diabetic Rats. Antibiotics (Basel) 10(11): 1343.
10. Wasef LG, Shaheen HM, El-Sayed YS, Shalaby TIA, Samak DH, Aet al. (2020) Effects of Silver Nanoparticles on Burn Wound Healing in a Mouse Model. Biol Trace Elem Res 193(2): 456-465.
11. Devanesan S, Al Salhi MS, Balaji RV, Ranjitsingh AJA, Ahamed A, et al. (2018) Antimicrobial and Cytotoxicity Effects of Synthesized Silver Nanoparticles from Punica granatum Peel Extract. Nanoscale Res Lett 13(1): 315.
12. Nasiriboroumand M, Montazer M, Barani H (2018) Preparation and characterization of biocompatible silver nanoparticles using pomegranate peel extract. J Photochem Photobiol B 179: 98-104.
13. Mahmood MS, Ashraf A, Ali S, Siddique AB, Asad F, et al. (2021) Portrayal of Punica granatum L. peel extract through High Performance Liquid Chromatography and antimicrobial activity evaluation. Braz J Biol 83: e244435.
14. Do Nascimento MF, Cardoso JC, Santos TS, Tavares LA, Pashirova TN, et al. (2020) Development and Characterization of Bio interactive Gelatin Wound Dressing Based on Extract of Punica granatum Linn. Pharmaceutics 12(12): 1204.
15. Bakkiyaraj D, Nandhini JR, Malathy B, Pandian SK (2013) The anti-biofilm potential of pomegranate (Punica granatum L.) extract against human bacterial and fungal pathogens. Biofouling 29(8): 929-937.
16. Swaroop AK, Lalitha CMVN, Shanmugam M, Subramanian G, Natarajan J, et al. (2022) Plant Derived Immunomodulators; A Critical Review. Adv Pharm Bull 12(4): 712-729.
17. Lukiswanto BS, Miranti A, Sudjarwo SA, Primarizky H, Yuniarti WM (2019) Evaluation of wound healing potential of pomegranate (Punica granatum) whole fruit extract on skin burn wound in rats (Rattus norvegicus). J Adv Vet Anim Res 6(2): 202-207.
18. Mousavi M, Khanifar A, Mousavi N, Anbari K, Chehelcheraghi F (2022) Coactivity of Mast Cells and Stem Cells on Angiogenesis and Antioxidants' Potentials at Inflammation, Proliferation, and Tissue Remodeling Phases of Wound. Arch Plast Surg 49(3): 462-470.
19. Akbari J, Nasiri E, Hosseinimehr SJ, Azadbakht M, Azizi S (2017) The Effects of Punica granatum Flower Extract on Skin Injuries Induced by Burn in Rats. Adv Pharmacol Sci 2017: 3059745.
20. Cho H, Balaji S, Sheikh AQ, Hurley JR, Tian YF, et al. (2012) Regulation of endothelial cell activation and angiogenesis by injectable peptide nanofibers. Acta Biomater 8(1): 154-64.
21. Kim SO (2022) Review of food upcycling in South Korea: regulation, limitation, and prospects. Food Sci Biotechnol 32(1): 1-10.
22. Alimoradian A, Changizi-Ashtiyani S, Ghiasabadi Farahani A, Kheder L, Rajabi R, et al. (2017) Protective Effects of Pomegranate Juice on Nephrotoxicity Induced by Captopril and Gentamicin in Rats. Iran J Kidney Dis 11(6): 422-429.
23. Celik I, Temur A, Isik I (2009) Hepatoprotective role and antioxidant capacity of pomegranate (Punica granatum) flowers infusion against trichloroacetic acid-exposed in rats. Food Chem Toxicol 47(1): 145-149.

24. Hoseny SS, Soliman AM, Fahmy SR, Sadek SA (2023) Development of a Novel Pomegranate Polysaccharide Nanoemulsion Formulation with Anti-Inflammatory, Antioxidant, and Antitumor Properties. Curr Drug Deliv 20(5): 575-586.

25. Ragab TIM, Nada AA, Ali EA, Shalaby ASG, Soliman AAF, et al. (2019) Soft hydrogel based on modified chitosan containing P. granatum peel extract and its nano-forms: Multiparticulate study on chronic wounds treatment. Int J Biol Macromol 135: 407-421.

26. Shore A (2018) Retraction: Shape-specific silver nanoparticles prepared by microwave-assisted green synthesis using pomegranate juice for bacterial inactivation and removal. RSC Adv 8(69): 39785.

27. Murthy KN, Reddy VK, Veigas JM, Murthy UD (2004) Study on wound healing activity of Punica granatum peel. J Med Food 7(2): 256-259.