https://doi.org/10.26651/allelo.j/2023-59-2-1442 0971-4693/94 Euro 20.00
Allelopathy Journal 59 (2): 197-206 (July, 2023) *International Allelopathy Foundation* 2023
Table: 1, Figs: 1

Recent advances in hydrogel-based drug delivery for wound healing therapy: A Systematic Review

Aishwaray*, Saumya Das*, Avijit Mazumder and Gajender
Noida Institute of Engineering and Technology (Pharmacy Institute),
Department of Pharmacology, Plot no.-19, Knowledge Park-II,
Greater Noida, 201306, Uttar Pradesh, India
E. Mail: mudgalaishu@gmail.com, awasthi.saumya22@gmail.com

(Received in revised form : June 8, 2023)

CONTENTS

ABSTRACT

A network of hydrophilic polymers makes the hydrogels, polymeric substances with a high water absorption and retention capacity. These materials are advantageous in many biomedical uses, including wound healing. The medicinal potential of multiple hydrogel for wound healing is explained in this review. Alginate, chitosan and hyaluronic acid are 3 types of hydrogels, these were combined to prepare the multiple hydrogel formulation. Alginate can collect much wound exudate, whereas, chitosan is antibacterial and encourage cell growth. Whereas, hyaluronic acid aid in tissue repair. Wound healing involves four perfectly synchronized processes (hemostasis, inflammation, proliferation, and remodeling). For successfully healing of wounds, these four steps need to take place in the right order and timeframe. To heal the wound and prevent secondary infections, the appropriate wound dressing is crucial. There are numerous formulations, where hydrogel is most suitable and frequently used presently, due to its anti-inflammatory, microbiological and easily accessible qualities.

*Correspondence author

Keywords: Acute wound, applications, chronic wound, hydrogel formulations, phases of wound, wound healing.

1. INTRODUCTION

A crucial physiological process called cutaneous wound healing involves the association of various cell strains and their products (21). For wound healing to occur as a regular biological process in body, it has 4- stages: hemostasis, inflammation, proliferation, and remodelling. Various factors can prevent one or many phases of formation, which will affect how well or how slowly wounds heal. Features discuss containing infection, oxygenation, sex hormones, age, anxiety hyperglycemia, obesity, medicines, intoxication, smoking, and nutriment (14). Wound healing occurs by involving the progressive activation of numerous types of cells and signaling paths in a sequenced manner (25). It takes a complex interaction between many different cell types, including mediators, cytokines, and the vascular system for a wound to heal. To limit bleeding, platelet aggregation, and the first blood vessel constriction are scheduled in a certain order. Starting with neutrophils various kinds of the influx of inflammatory cell was followed and then release cytokines and mediators to encourage re-epithelialization, angiogenesis, and thrombosis at last fibroblasts serve as scaffolding (31). Granulation tissue, neovascularization, and re-epithelialization are characteristics of the proliferative phase. This phase can last for some weeks (7). Successful wound healing requires coordination between these stages, as well as proper nutrition and immune response Wound achieves tremendous strength as it grows during the maturation and remodelling period (29).

2. WOUND HEALING PHASES AND PHYSIOLOGY

These stages are completed very fast in acute wounds. Chronic wounds are those that persist for 12 weeks after their initial trauma.

2.1 Hemostasis Phase

Vascular damage happens during surgical incisions on the micro or macrovascular level. The body's first reaction is to stop exsanguination and encourage hemostasis. In the layer of the vessel wall, increased intracellular calcium levels cause damaged arterial arteries to immediately constrict by constriction of smooth muscle. If the wound occurs in a transversal plane vessel may entirely shut through a contraction. The decreased flow of blood caused by constriction of arterioles causes tissue hypoxia and acidity just in a short period of time. NO, Vasoactive metabolites, and adenosine are produced more readily resulting in reflex vasodilation and relaxation of arteries. Mast cell production of Histamine causes an increase in vascular permeability and vasodilatation, which makes it easier for inflammatory cells to enter the extracellular region around the lesion. This explains why early wounds have a recognizable warm, red, swollen appearance (12).

The clot formation has following 3- main processes, this stops further loss of blood at this stage:

2.1.1 Intrinsic Pathway: Tissue injury causes endothelium damage, which allows blood to enter the sub-endothelial areas**,** which activates factor XII (Hageman factor) through the contact activation route of the intrinsic clotting cascade. As a result, factor X is activated, prothrombin is transformed into thrombin, fibrinogen is transformed into fibrin, and forming a fibrin plug (26).

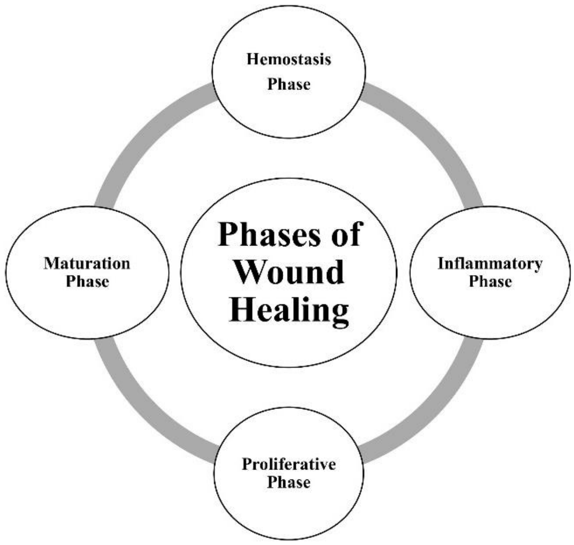

Figure 1. Stages of wound healing

2.1.2 Extrinsic Pathway: Extrinsic coagulation system allows tissue factor, which the bulk of cells contain, to enter the bloodstream, as a result of endothelial injury**.** As a result, factor VII and the remaining extrinsic pathway of the coagulation system are activated, leading to the activation of thrombin (11).

2.1.3 Platelet Activation: After activation by ADP, thrombin or thromboxane Platelets alter the appearance and secrete the material. To create a thrombocyte, plug and momentarily stop bleeding, activated platelets cling to exposed collagen sites. Both filaments of actin and myosin found in platelets, as well as von Willebrand factor and fibrin, all contribute to the strength of this plug (13).

2.2 Inflammatory Phase

Infection prevention is the primary goal of this period. Neutrophils are the main defence against infection at the wound. For eliminating trash and bacteria, they primarily use three processes. It will firstly phagocytose, which is the direct absorption and removal of foreign materials. Secondly, there will be a degranulation of neutrophils and the discharge of several poisonous compounds that kill germs and dead host tissue. Additionally, neutrophils have the ability to produce "traps" of chromatin and proteases that can entrap and destroy bacteria in the extracellular environment. The action of neutrophil granulocytes stimulates the formation of oxygen-free radicals, which have been shown to have an antibacterial effect and, in interaction with chlorine, can disinfect a wound (18).

Macrophages are phagocytic cells that are significantly bigger and reach their maximum number in wounds 48 to 72 h after an injury. The abundance of growth factors in macrophages, such as EGF and TGF-β, is important for regulating the inflammatory responses, promoting angiogenesis, as well as boosting granulation tissue production (17). Lymphocytes become visible inside the wound after 72 hours. If it's necessary, this prevention phase of healing will continue, ensuring that all surplus germs and debris from the site are eliminated (10).

2.3 Proliferative Phase

Once the damaging stimulus is stopped, the proliferative phase of the wound healing cascade begins repairing the defect**.** Hemostasis is accomplished, the inflammatory reaction has been controlled, and the wound is free from debris. This multi-step process includes simultaneous angiogenesis, collagen deposition, the development of granulation tissue, epithelialization, and wound retraction (36).

2.3.1 Angiogenesis: When the hemostatic plug forms, platelets produce TGF-, PDGF, and the fibroblasts growth factor, which initiates angiogenesis. VEGF, which is produced in response to hypoxia and secreted together with other cytokines, stimulates endothelial cells to encourage neovascularization and repair of blood vessel ruptures (33). As the angiogenesis process progresses, healthy vessel outgrowths create a dense vascular network of capillaries that spreads throughout the wound. To further exacerbate tissue edema and the emergence of healing granulation tissue, the capillaries are initially weak and porous (32).

2.3.2 Fibroblast Migration: Growth factors emitted from the hemostatic clot encourage fibroblasts to proliferate and subsequently move to the wound. On day 3, the wound is colonized by fibroblasts, that form collagen and fibronectin by depositing extracellular matrix protein (2). When enough matrix has been deposited, fibroblasts transform into myofibroblasts and produce pseudopodia. This makes it possible for them to attach to nearby fibronectin and collagen proteins and aid in wound contraction. The main factor in giving strength to tissues is collagen produced by fibroblasts (1).

2.3.3 Epithelialization: Following early damage, epithelial cells proliferate along the ends of the incision till a thick layer of cells fully encircles the lesion and connects to the matrix. Epithelial cells acquire motility through an embryological procedure which is named epithelial-mesenchymal transition (EMT), which can move across the wound's surface. This stage could be completed in wounds that have largely healed within a day. To replenish epithelial cell levels and finish wound healing, epithelial cells respond to changes in cytokine concentration by transitioning from a motile to a proliferative state (34).

2.3.4 Wounds Retraction: Seven days after the initial damage, wounds start to close, primarily through the action of myofibroblasts. Actin and myosin interactions draw bodies of the cell close together, reducing the amount of tissue that needs to repair. Shorter scars can result from contraction that happens at a pace of 0.75 mm each day. Numerous factors, including the geometry of the wound, affect how quickly it heals, with circular wounds healing more slowly than linear ones. Deformity and the development of contractures might result from disorders during this healing phase (24).

2.4 Maturation Phase

It is also referred to as remodeling. The last stage of wound healing, Which might require two years, causes the injured tissue to stabilize and normal epithelial development. As collagen and some different proteins formed in the wound become more cohesive, this phase requires a balance between synthesis and breakdown. They will start developing a structure that resembles healthy tissue. Although, tissue strength in wounds is never the same, averaging just 80% over the long term and 50% of the initial tensile strength after three months. Vascularity reduces as the scar ages, and its colour later shifted from red to pinkish to grey (8).

3. HYDROGELS FORMULATIONS IN WOUND HEALING

In 2022, a patch with hydrogel electrode was designed to treat wound healing with fewer side effects and faster healing as electric stimulation increases healing with high efficacy and improves wound management. The patch showed antibacterial properties as the hydrogel was made of two components: methacrylate alginate and silver nanowire. In SD rats, the wound healed within 7 days because the patch stimulated the expression of growth factors by 'NIH 3T3' (35).

Chitosan-based hydrogel was prepared to treat ulcers, by the cross-linking of polyethylene glycol diacid and showed self-healing properties and good antibacterial, anti-inflammatory, and biocompatible effects due to the high efficiency of intermolecular reversible hydrogen bonding. This formulation can be used in treating ulcers by improving the activity of elastin and collagen (6).

Free radical polymerization was used to make hydrogel membranes. In the incidence of the intruder ammonium peroxide sulfate (APS) and sodium hydrogen sulfite, the polymer PEG-4000 was cross-linked with the monomer 2-acrylamide-2-methylpropane sulfonic acid (AMPS) in an aqueous solution (SHS). To create hydrogel membranes, N, N-Methylene-bis-acrylamide (MBA) was utilized as a cross-linker. Developed sheaths exhibited flexibility, were clear, and were spherical. The polymeric system was characterized using FTIR, TGA/DSC, and SEM. Additionally, assessed were the effects of swelling, preparation loading, and delivering patterns at pH levels 5.4 and 7.5, irritant studies, *ex vivo* medication -penetration, and accumulation studies [22].

Burns are the most prevalent and deadly type of wound. They frequently come with irregular swelling, insufficient production of extracellular matrix, decreased angiogenesis, and an absence of development factor inspiration, all these aspects can cause complications and knowingly slow down the healing process. Chinese traditional medicine has employed pearl powder to indulge in wound healing. In the current investigation, we discovered that pearl peptides with a size range of ">10kd" that was supercritical CO2 extracted have a great deal of possibility to accelerate wound healing at the cellular stage. Utilizing block-functionalized PEG/PPG polymers containing selenium, antioxidant

Table 1. Formulations of Curcumin for wound dressing

Sl. No	Different Topical Formulation	Composition	Preparation Route	Observation
1	Bandage (Polymeric)	Oleic Acid, Chitosan Curcumin, Alginate,	Crosslinking and Ionic interaction	For an extended span of 10 days, there was a let go of further than 40% of curcumin. Control, empty bandage, and curcumin bandage-treated injuries respectively reduce by 70%, 80%, and 94% after application on the 10th day.[19]
2	Collagen film	Curcumin, Bovine collagen	Crosslinking	More than 60% of the curcumin was released, according to the *in vitro* release kinetics, after 12 days of research. The administration of collagen films accommodates curcumin resulting in an exorbition assertion of collagen and the creation of granulation tissue.[28]
3	Hydrogel nanocomposite	MPEG-PCL copolymer, oxidized alginate, chitosan, curcumin	Method of thin-film evaporation.	The hydrogel nanocomposite controls and tolerates the release outline of curcumin. On day 14, an *in vivo* inspection presented that the wound had fully cured, enhanced collagen deposition, reepithelization, and granulation tissue growth.[3]
4	Gel-core hyaluronate (nanovesicle)	Hyaluronic acid, curcumin, Lipoid1 S100, and Tween1 80	Curcumin, Lipoid1 S100, Tween1 80, hyaluronic acid	Following a two-hour *in vitro* investigation, there is a 50% release of curcumin. On day 10, the wound was cured with no scars when connected to other sets, with better granulation tissue development, collagen fibre deposition, re-epithelization, and tissue rejuvenation.[27]
5	Polymeric bio-adhesive emulsion	Neem and turmeric extract, shellac, casein, polyvinyl alcohol, and the maleic anhydride	Emulsion method	It has bacterial functions and is biodegradable and harmless.[5]
6	Hydrogel system containing micellar curcumin	PEG-PCL micellar curcumin, PEG-PCL-PEG copolymer hydrogel	Curcumin micelle by solid dispersion method and hydrogel by crosslinked methods	Enlarged collagen content, better granulation, and better wound development were all seen in the wound dressing study. Curcumin sustained 60% release over a lengthy 14-day period.[4]
7	Nanovesicles	Oramix1, Lipoid1 S75, PEG400, and curcumin	Sonication procedure	It is minute, sphere-shaped, multi-or oligolamellar, and biocompatible. After application to the skin inactivated by tissue plasminogen activator (TPA), less oxidative inflammation was observed. Histology data exposed thick epidermis in numerous layers along with considerable re-epithelization.[23]

hydrogels were created. Polymeric polymers containing pearl peptide components were created to create brand-new, promising wound dressings. It was demonstrated that pearl peptide hydrogels improved cellular resilience to oxidative stress, accelerated tissue remodeling, and encouraged increased stimulation of wound healing and angiogenesis [15].

Keratin, a bio-sourced polymer with a high sulfur content that is found in feathers, hair, hooves, horns, and wool, is the major component of these materials. Keratin-based formulations (KFs), which have high biocompatibility and inherent bioactivity, have generated a lot of academic interest. Abundant uses, like tissue manufacturing, drug delivery, and wound healing, have made extensive use of KFs. Along with pure KFs, mixed systems of keratin and other (bio) polymers have garnered significant attention as innovative keratinous formulations recently [30]. Ginseng and Sodium alginate Nano hydrogel formulation was formulated, and rats were treated with surgically excised wounds, which increased dermal integrity, decreased reduced oxidative stress and inflammation, and increased the amount quantity of collagen deposition. This formulation increased the wound-healing properties of ginseng [20]. A hydrophobic block polymer and the constituent of pearl polypeptide interacted to create a multifunctional thermal gel system with efficient wound healing regulation. The temperature-sensitive hydrogel can control the slow-release effect of pearl peptides, increase the pearl peptides' solubility and wound-healing activity, and significantly improve wound healing activity. Thermal gels and pearl peptides both have antioxidant activity, which inhibits the scavenging of unusually produced free radical molecules [16].

To stop bleeding from wounds, a hydrogel was created utilizing in situ wound dressing. This decreases inflammation and pain, which helps the wound heal more quickly. In addition to the two poloxamers (407 and 188), the matrix also contained a variety of other substances that had varying effects on the treatment. These substances included chitosan, which promotes wound healing by increasing its activity, aminocaproic acid, which stops wound bleeding, and povidone-iodine, which fights infections. This study demonstrated the effectiveness of hydrogel in accelerating wound healing, reducing hemostasis, and exhibiting significant bacteriostatic activity [9].

4. CONCLUSIONS

The wound-healing process depends upon the type of dressing or dressing which can provide a sustainable environment for healing the wound. Hydrogels have been demonstrated to make certain enticing benefits in the area of wound care due to their improved biochemical and mechanical capabilities. Wounds are of different types and different physiology and need different treatments because of their mechanism. The subject of wound care is constantly expanding due to technological developments. While carefully using the patient’s own tissues for rebuilding is still the best option available by providing protection against healing barriers, enhancing variables that promote wound healing, helping to bridge the gap between temporary and permanent restoration, and improving the outcomes of wound reconstruction, carefully planned reconstructive methods and novel products can aid in the ultimate healing process. Hydrogel shows one disadvantage its mechanical strength is poor the stability is very poor in swollen part of the wound. So, more research is needed to make hydrogel the ideal wound dressing. Hydrogel-based natural product outweighs when compared to synthetic ones. Current wound healing products and techniques increase a wound practitioner's toolkit for treating all aspects of wound care.

ACKNOWLEDGMENTS

I would like to thank on behalf of all co-authors firstly the almighty god without home nothing is possible. I am heartly thankful to the Chairman of NIET (Pharmacy Institute) Dr. O. P Agarwal Sir and AMD mam Dr. Neema Agarwal for providing all kinds of research facilities and encouragement to successfully complete this review paper.

DECLARATION

We declare that all authors of this manuscript made a significant contribution, and we have not excluded any author that substantially contributed. We have followed the ethical norms established by our respective institutions.

CONFLICT OF INTEREST

None

FINANCIAL SUPPORT

None

ETHICS STATEMENT

None

5. REFERENCES

1. Addis, R., Cruciani, S., Santaniello, S., Bellu, E., Sarais, G., Ventura, C., Maioli, M. and Pintore, G. (2020). Fibroblast proliferation and migration in wound healing by phytochemicals: Evidence for a novel synergic outcome. *International Journal of Medical Sciences* **17(8):** 1030-1042.
2. Al Sadoun, H. (2022). Macrophage phenotypes in normal and diabetic wound healing and therapeutic interventions. *Cells* **11(15):**2430.
3. Barrett-Catton, E., Ross, M.L. and Asuri, P. (2021). Multifunctional hydrogel nanocomposites for biomedical applications. *Polymers* **13(6):**856.
4. Castangia, I., Nácher, A., Caddeo, C., Valenti, D., Fadda, A.M., Díez-Sales, O., Ruiz-Saurí, A. and Manconi, M. (2014). Fabrication of quercetin and curcumin bionanovesicles for the prevention and rapid regeneration of full-thickness skin defects on mice. *Acta Biomaterialia* **10(3):**1292-1300.
5. Chen, L., Din, Z.U., Yang, D., Hu, C., Cai, J. and Xiong, H. (2021). Functional nanoparticle reinforced starch-based adhesive emulsion: Toward robust stability and high bonding performance. *Carbohydrate Polymers* **269:**118270.
6. Chijcheapaza-Flores, H., Tabary, N., Chai, F., Maton, M., Staelens, J.N., Cazaux, F., Neut, C., Martel, B., Blanchemain, N. and Garcia-Fernandez, M.J. (2023). Injectable chitosan-based hydrogels for trans-cinnamaldehyde delivery in the treatment of diabetic foot ulcer infections. *Gels* **9(3):**262.
7. Coger, V., Million, N., Rehbock, C., Sures, B., Nachev, M., Barcikowski, S., Wistuba, N., Strauß, S. and Vogt, P.M. (2019). Tissue concentrations of zinc, iron, copper, and magnesium during the phases of full thickness wound healing in a rodent model. *Biological Trace Elements Research* **191(1):**167-176.

8. Čoma, M., Fröhlichová, L., Urban, L., Zajíček, R., Urban, T., Szabo, P., Novák, Š.,Fetissov, V., Dvořánková, B., Smetana, K. and Gál, P. (2021). Molecular changes underlying hypertrophic scarring following burns involve specific deregulations at all wound healing stages (inflammation, proliferation and maturation). *International Journal of Molecular Sciences* **22(2):**897.
9. Du, L., Tong, L., Jin, Y., Jia, J., Liu, Y., Su, C., Yu, S. and Li, X. (2012). A multifunctional in situ–forming hydrogel for wound healing. *Wound Repair and Regeneration* **20(6):**904-910.
10. El Ayadi, A., Jay, J.W. and Prasai, A. (2020). Current approaches targeting the wound healing phases to attenuate fibrosis and scarring. *International Journal of Molecular Sciences* **21(3):** 1105.
11. Guo, B., Dong, R., Liang, Y. and Li, M. (2021). Haemostatic materials for wound healing applications. *Nature Reviews Chemistry* **5(11):**773-791.
12. Gushiken, L.F.S., Beserra, F.P., Bastos, J.K., Jackson, C.J. and Pellizzon, C.H. (2021). Cutaneous wound healing: An update from physiopathology to current therapies. *Life* **11(7):**665.
13. Hoemann, C.D. and Rivard, G.E. (2021). Chitosan–platelet interactions. *In Chitosan for biomaterials* **III:** (pp. 319-342).
14. Kurek-Górecka, A., Komosinska-Vassev, K., Rzepecka-Stojko, A. and Olczyk, P. (2020). Bee venom in wound healing. *Molecules* **26(1):** 148.
15. Liu, M., Chen, Y., Zhu, Q., Tao, J., Tang, C., Ruan, H., Wu, Y. and Loh, X.J. (2022). Antioxidant thermogelling formulation for burn wound healing. *Chemistry, an Asian Journal* **17(16):** e202200396.
16. Liang, Y., He, J. and Guo, B. (2021). Functional hydrogels as wound dressing to enhance wound healing. *ACS Nano* **15(8):** 12687-12722.
17. Lux, C.N. (2022). Wound healing in animals: A review of physiology and clinical evaluation. *Veterinary Dermatology* **33(1):** 91-e27.
18. Mathew-Steiner, S.S., Roy, S. and Sen, C.K. (2021). Collagen in wound healing. *Bioengineering* **8(5):** 63.
19. Matoori, S., Veves, A. and Mooney, D.J. (2021). Advanced bandages for diabetic wound healing. *Science Translational Medicine* **13(585):** eabe4839.
20. Md, S., Abdullah, S., Alhakamy, N.A., Shaik, R.A., Ansari, A.R., Riadi, Y., Ahmad, J., Ali, R., Gorain, B. and Karim, S. (2022). Sustained-release ginseng/sodium alginate Nano hydrogel formulation, characterization, and in vivo assessment to facilitate wound healing. *Journal of Drug Delivery Science and Technology* **74:** 103565.
21. Mills, S.J., Hofma, B.R. and Cowin, A.J. (2020). Pathophysiology of wound healing. Mechanisms of Vascular Disease: A Reference Book for Vascular Specialists 541-561.
22. Minhas, M.U., Ahmad, S., Khan, K.U., Sohail, M., Abdullah, O., Khalid, I. and Malik, N.S. (2022). Synthesis and evaluation of polyethylene glycol-4000-co-poly (AMPS) based hydrogel membranes for controlled release of Mupirocin for efficient wound healing. *Current Drug Delivery* **19(10):** 1102-1115.
23. Nayak, A.K., Hasnain, M.S., Aminabhavi, T.M. and Torchilin, V.P. (Eds.). (2022). *Systems of nanovesicular drug delivery*. Academic Press.
24. Nurden, A.T. (2022). Molecular basis of clot retraction and its role in wound healing. *Thrombosis Research*.
25. Oliveira, A., Simões, S., Ascenso, A. and Reis, C.P. (2022). Therapeutic advances in wound healing. *Journal of Dermatological Treatment* **33(1):** 2-22.
26. Overmiller, A.M., Sawaya, A.P., Hope, E.D. and Morasso, M.I. (2022). Intrinsic networks regulating tissue repair: Comparative studies of oral and skin wound healing. *Cold Spring Harbor Perspectives in Biology* **14(11):** a041244.
27. Paşcalău, V., Tertis, M., Pall, E., Suciu, M., Marinca, T., Pustan, M., Merie, V., Rus, I., Moldovan, C., Topala, T., Pavel, C. and Popa, C. (2020). Bovine serum albumin gel/polyelectrolyte complex of hyaluronic acid and chitosan based microcarriers for sorafenib targeted delivery. *Journal of Applied Polymer Science* **137(34):** 49002.
28. Rathod, L., Bhowmick, S., Patel, P. and Sawant, K. (2022). Calendula flower extract loaded collagen film exhibits superior wound healing potential: Preparation, evaluation, in-vitro and *in*-vivo wound healing study. *Journal of Drug Delivery Science and Technology* **72:** 103363.
29. Raziyeva, K., Kim, Y., Zharkinbekov, Z., Kassymbek, K., Jimi, S. and Saparov, A. (2021). Immunology of acute and chronic wound healing. *Biomolecules* **11(5):** 700.
30. Sharma, S., Rostamabadi, H., Gupta, S., Kumar Nadda, A.K., Kharazmi, M.S. and Jafari, S.M. (2022). Nano/micro-formulations of keratin in biocomposites, wound healing and drug delivery systems; recent advances in biomedical applications. *European Polymer Journal* **180:** 111614.
31. Sorg, H. and Sorg, C.G.G. (2022). Skin wound healing: Of players, patterns and processes. *European Surgical Research. Europaische Chirurgische Forschung. Recherches Chirurgicales Europeennes*.

32. Spałek, M. (2016). Chronic radiation-induced dermatitis: Challenges and solutions. *Clinical, Cosmetic and Investigational Dermatology* **9:** 473-482.
33. Sylakowski, K.J. *Therapeutic strategies of matricellular proteins in cutaneous wound healing: Countervailing chronic wounds and excessive scarring* ([Doctoral Dissertation]. University of Pittsburgh).
34. Tang, F., Li, J., Xie, W., Mo, Y., Ouyang, L., Zhao, F., Fu, X. and Chen, X. (2021). Bioactive glass promotes the barrier functional behaviors of keratinocytes and improves the Re-epithelialization in wound healing in diabetic rats. *Bioactive Materials* **6(10):** 3496-3506.
35. Wang, C., Jiang, X., Kim, H.J., Zhang, S., Zhou, X., Chen, Y., Ling, H., Xue, Y., Chen, Z., Qu, M., Ren, L., Zhu, J., Libanori, A., Zhu, Y., Kang, H., Ahadian, S., Dokmeci, M.R., Servati, P., He, X. and Khademhosseini, A. (2022). Flexible patch with printable and antibacterial conductive hydrogel electrodes for accelerated wound healing. *Biomaterials* **285:** 121479.
36. Xu, Y., Gao, F., Zhang, J., Cai, P. and Xu, D. (2022). Fibroblast growth factor receptor 2 promotes the proliferation, migration, and invasion of ectopic stromal cells via activation of a extracellular-signal-regulated kinase signaling pathway in endometriosis. *Bioengineered* **13(4):** 8360–8371.

PUBLISHER NOTE

Allelopathy Journal remains neutral with regard to jurisdictional claims in published Maps and Institutional Affiliations.