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Pomegranate Peel Extract-Loaded Hydrogels for Wound Healing: Bioactive Constituents, Mechanisms, Formulation Strategies and Recent Advances

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ABSTRACT
Wound healing is a coordinated biological process involving hemostasis, inflammation, proliferation, angiogenesis, re-epithelialization, extracellular-matrix deposition and tissue remodeling. Delayed healing may be associated with oxidative stress, persistent inflammation, microbial infection, impaired angiogenesis and inadequate tissue regeneration. Pomegranate (*Punica granatum* L.) peel is a rich source of polyphenolic constituents, particularly hydrolyzable tannins and phenolic acids, including punicalagin, punicalin, ellagic acid and gallic acid. These constituents have demonstrated antioxidant, anti-inflammatory and antimicrobial activities in experimental studies. However, direct topical application of plant extracts may be limited by instability, short residence time and uncontrolled release. Hydrogel wound dressings provide hydrated polymeric networks that can maintain a moist wound environment, absorb exudate and support localized delivery of bioactive compounds. Experimental investigations have examined pomegranate peel extract (PPE) in gelatin membranes, hyaluronic-acid/silver-nanoparticle systems, pH-responsive starch-based films, chitosan/PEG/ZnO nanocomposites, carbomer gels and gelatin methacryloyl (GelMA) hydrogels containing pomegranate-peel-derived extracellular vesicles. These studies report encouraging preclinical findings, including improvements in wound closure, epithelialization, granulation tissue formation, collagen deposition and infection-associated outcomes. This review focuses on the phytochemical composition of pomegranate peel, biological mechanisms relevant to wound repair, hydrogel and related polymeric dressing strategies, formulation and characterization considerations, recent technological developments, limitations and future perspectives. The available evidence supports further investigation of PPE-based delivery systems; however, extract standardization, mechanistic validation, long-term safety assessment, manufacturing reproducibility and clinical evaluation remain necessary before clinical translation.

Keywords: *Punica granatum*; pomegranate peel; pomegranate peel extract; hydrogel; wound healing; wound dressing; polyphenols; punicalagin; ellagic acid; controlled release.

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INTRODUCTION

The skin forms an essential protective barrier between the body and the external environment. When skin integrity is disrupted by trauma, burns, infection, surgery or chronic disease, a coordinated wound-healing response is initiated. This response involves overlapping phases of hemostasis, inflammation, proliferation and remodeling, with associated angiogenesis, re-epithelialization and extracellular-matrix formation. [1,2]

Although the body has an intrinsic capacity for tissue repair, healing may be delayed by microbial infection, excessive or persistent inflammation, oxidative stress, impaired angiogenesis and inadequate extracellular-matrix formation. Consequently, wound dressings that protect the wound while supporting tissue regeneration remain an important area of pharmaceutical and biomedical research. [2,3]

Conventional topical formulations, including creams, ointments and simple gels, may require frequent application and may provide limited control over the local release of therapeutic agents. Hydrogels are hydrated, three-dimensional polymeric networks that can maintain a moist environment, absorb wound exudate and provide a matrix for localized delivery. Their performance depends on polymer composition, crosslinking, swelling, mechanical properties, degradation and release characteristics. [3,4]

Pomegranate (*Punica granatum* L.) peel, a by-product of fruit processing, contains hydrolyzable tannins, phenolic acids, flavonoids and other secondary metabolites. Punicalagin, punicalin, ellagic acid and gallic acid are among the constituents frequently associated with its biological activity. Reviews of pomegranate peel have described antioxidant, anti-inflammatory, antimicrobial and other biomedical applications [10]. Experimental studies have also examined pomegranate-derived materials in gels, membranes, nanocomposites and hydrogel systems. [4-9,11,12]

Despite this growing body of work, a focused comparison of PPE-loaded hydrogel and related polymeric wound-dressing systems is needed. The reported formulations differ in extract preparation, phytochemical composition, polymer selection, crosslinking strategy, release characteristics and biological evaluation. These differences complicate comparisons of formulation performance and therapeutic outcomes. Accordingly, this review integrates pomegranate peel phytochemistry with hydrogel formulation science and wound-healing biology, with emphasis on formulation strategies, characterization, preclinical evidence, technological advances and barriers to clinical translation.

POMEGRANATE PEEL AS A SOURCE OF BIOACTIVE COMPOUNDS

Pomegranate peel contains hydrolyzable tannins, phenolic acids, flavonoids and other secondary metabolites. The relative abundance of these constituents varies with cultivar, geographical origin, fruit maturity, drying and storage conditions, extraction solvent and processing method. Therefore, phytochemical characterization and standardization using appropriate marker compounds are important for reproducible formulation development. [10]

Punicalagin

Punicalagin is a major hydrolyzable ellagitannin associated with pomegranate peel and is an important contributor to its antioxidant capacity. It has also been investigated for anti-inflammatory and antimicrobial activities. Its concentration may vary considerably among extracts, making quantitative analysis important when comparing PPE-based formulations. [10]

Punicalin

Punicalin is another hydrolyzable tannin reported in pomegranate peel. It contributes to the polyphenolic profile of the extract and may participate in antioxidant and other biological activities. Its presence and concentration should be confirmed analytically in the specific extract used for formulation.

Ellagic Acid

Ellagic acid is a phenolic compound associated with pomegranate and its hydrolyzable tannins. It exhibits antioxidant and anti-inflammatory properties and has been used as a marker in some PPE-containing delivery systems. For example, pH-responsive hydrogel films have been evaluated for pH-dependent ellagic-acid release. [6]

Gallic Acid

Gallic acid is a phenolic acid found in pomegranate peel. It contributes to the antioxidant activity of the extract and has been investigated for antimicrobial and anti-inflammatory effects. Its concentration should be measured when it is selected as a marker for extract standardization.

Other Phenolic Compounds

Flavonoids, including catechin, epicatechin, quercetin and rutin, as well as other tannins and phenolic constituents, may contribute to the overall activity of PPE. Not all compounds are present at comparable concentrations in every extract. Therefore, the chemical profile of the extract should be established using suitable analytical methods rather than assuming a uniform composition across studies. [10]

Table 1: Major phytochemical constituents reported in pomegranate peel and their potential relevance to wound healing.

Sr. No.	Phytochemical constituent	Chemical class	Biological activities	Relevance to wound healing
1	Punicalagin	Ellagitannin	Antioxidant, anti-inflammatory, antimicrobial	May reduce oxidative stress and inflammation
2	Punicalin	Hydrolyzable tannin	Antioxidant	May provide antioxidant protection
3	Ellagic acid	Phenolic compound	Antioxidant, anti-inflammatory	May protect cells from oxidative damage
4	Gallic acid	Phenolic acid	Antioxidant, antimicrobial	May protect against oxidative stress and microbes
5	Catechin	Flavan-3-ol	Antioxidant, anti-inflammatory	May support cellular protection
6	Epicatechin	Flavan-3-ol	Antioxidant, anti-inflammatory	May support cellular protection
7	Quercetin	Flavonol	Antioxidant, anti-inflammatory	May reduce oxidative stress and inflammation
8	Rutin	Flavonol glycoside	Antioxidant, anti-inflammatory	May support vascular and tissue protection
9	Anthocyanins	Flavonoid pigments	Antioxidant	May scavenge free radicals
10	Other tannins	Polyphenols	Antioxidant, astringent	May protect the wound surface

Wound Healing - Process

Wound healing is commonly described in four overlapping phases: hemostasis, inflammation, proliferation and remodeling. The phases are not strictly sequential; cellular and molecular events may overlap throughout the repair process. [1,2]

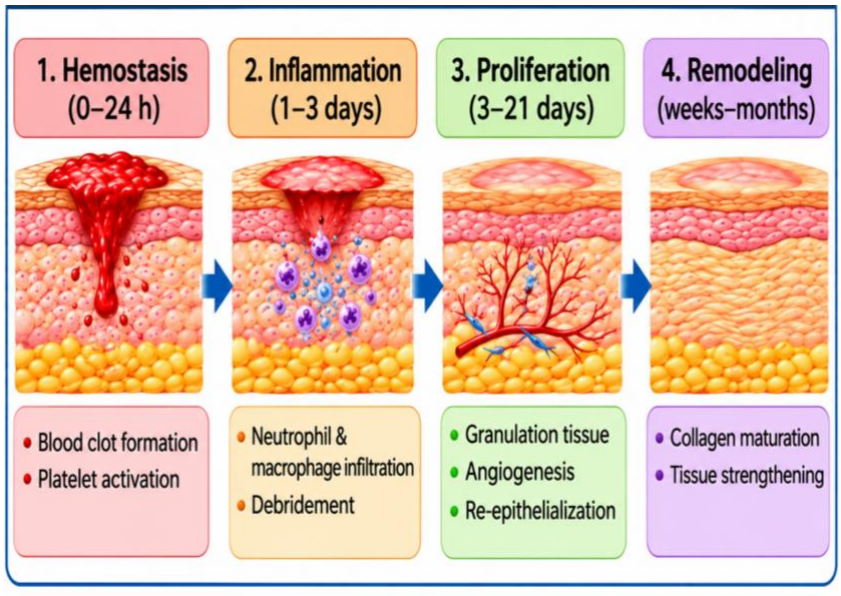


Figure 1: Different phases of wound healing.

Hemostasis

Immediately after injury, vasoconstriction, platelet activation and coagulation contribute to clot formation. The clot limits blood loss and provides a provisional matrix for the migration of inflammatory and reparative cells.

Inflammatory Phase

Neutrophils and macrophages migrate to the wound site and contribute to the removal of microorganisms, foreign material and damaged tissue. A controlled inflammatory response is necessary for repair, whereas persistent or excessive inflammation can delay tissue regeneration.

Proliferative Phase

The proliferative phase involves fibroblast migration and proliferation, extracellular-matrix synthesis, angiogenesis, granulation-tissue formation and re-epithelialization. Collagen deposition and the formation of new blood vessels support the development of new tissue.

Remodeling Phase

During remodeling, newly deposited collagen undergoes maturation, reorganization and crosslinking. These processes gradually increase the strength and structural integrity of the repaired tissue. The final scar may not completely reproduce the structure and function of uninjured skin.

Biological Mechanisms of Pomegranate-Mediated Wound Healing

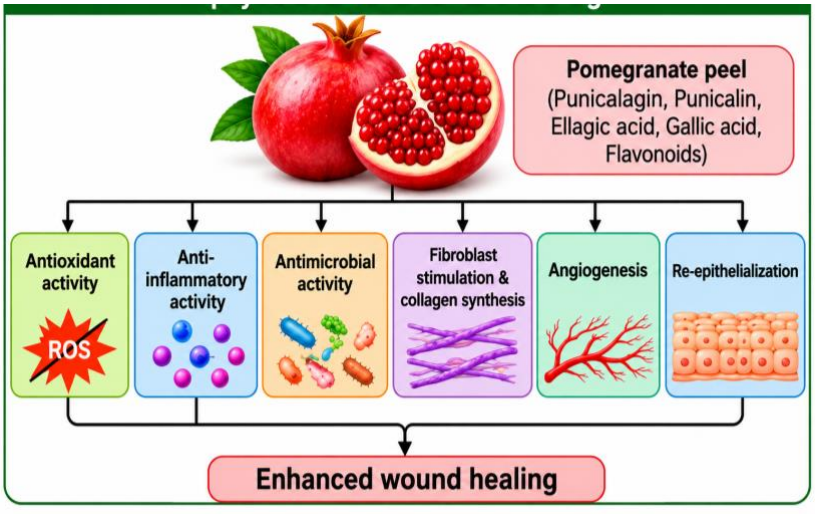


Figure 2: Proposed biological mechanisms through which pomegranate phytochemicals may contribute to wound healing.

Pomegranate peel contains polyphenolic constituents that have been investigated for antioxidant, anti-inflammatory and antimicrobial activities. These activities may influence biological events involved in wound repair. The evidence is derived predominantly from in vitro and animal

studies; therefore, the mechanisms discussed below should be interpreted as potential or experimentally supported mechanisms rather than established clinical effects.

Antioxidant Activity

Excessive production of reactive oxygen species (ROS) can damage cellular membranes, proteins and nucleic acids and may interfere with normal wound repair. Polyphenolic constituents of PPE can scavenge free radicals in chemical antioxidant assays and may help protect cells against oxidative damage. Antioxidant activity has been reported for standardized pomegranate extracts and PPE-containing formulations. [4,9,10] However, the extent to which chemical antioxidant activity translates into beneficial redox modulation in living wound tissue requires further investigation.

Anti-Inflammatory Activity

Inflammation is necessary during the early stages of wound healing, but prolonged inflammatory activity may delay tissue regeneration. Pomegranate-derived polyphenols have been associated with modulation of inflammatory mediators. In a preclinical study, a formulation containing PPE, hyaluronic acid and silver nanoparticles was evaluated in Candida albicans-infected wounds and was reported to improve infection-associated and inflammatory outcomes. [5] Specific cytokine changes should be attributed to the original study only where they are reported in the full publication.

Antimicrobial Activity

Microbial contamination and infection can prolong inflammation and interfere with wound repair. Pomegranate peel extracts have shown antimicrobial activity in experimental assays. PPE-containing nanocomposite systems have been evaluated against selected bacteria and fungi. [5,8,9] A 2026 study of pomegranate-peel-derived extracellular vesicles incorporated into GelMA hydrogel reported antibacterial activity against *Staphylococcus aureus*, [11] The antimicrobial spectrum and magnitude of activity depend on extract composition, formulation components, microorganism and experimental method.

Fibroblast Activity and Collagen Deposition

Fibroblasts contribute to extracellular-matrix synthesis, collagen deposition and granulation-tissue formation. In vitro and animal studies of pomegranate-containing preparations have reported fibroblast-related and tissue-repair outcomes. A carbomer gel containing 2.5% w/w dry crude PPE was reported to support fibroblast proliferation and wound healing in rats. [9] Other pomegranate-containing dressings have reported improvements in granulation tissue and

collagen deposition. [4-6] These findings do not establish that a single constituent is responsible for the observed effects.

Angiogenesis

Angiogenesis is the formation of new blood vessels that supply oxygen and nutrients to regenerating tissue. Some preclinical investigations of PPE-containing wound-dressing systems have reported changes in angiogenesis-associated markers or histological features. [5,6] Such findings suggest a possible contribution to vascular responses, but direct causal pathways and the roles of individual phytochemicals remain to be established.

Re-epithelialization

Re-epithelialization involves migration and proliferation of keratinocytes across the wound surface to restore the skin barrier. Improved epithelial development and wound closure have been reported in experimental investigations of pomegranate-containing membranes, gels and hydrogel films. [4,6,9] Differences in wound models and outcome measurements should be considered when comparing these studies.

Overall, pomegranate peel constituents may influence several biological events involved in wound repair. Further work is needed to connect standardized concentrations of individual phytochemicals with defined molecular targets and clinically relevant outcomes.

ROLE OF HYDROGELS IN WOUND DRESSING

Hydrogels are three-dimensional polymeric networks capable of retaining substantial quantities of water. Their hydrated structure can provide a moist environment that supports wound management and can serve as a carrier for therapeutic compounds. Depending on their composition and structure, hydrogel dressings may absorb exudate, conform to irregular wound surfaces and permit localized delivery of active substances. [3,4]

Important properties of hydrogel wound dressings include water-holding capacity, swelling behaviour, moisture regulation, suitable water-vapour transmission, mechanical integrity, tissue compatibility, adhesion or conformability, ease of application and removal, and appropriate degradation or stability. The relative importance of these properties depends on the wound type and intended use.

When PPE is incorporated into a hydrogel, the formulation may combine the biological activity of pomegranate-derived constituents with local retention and release from the polymeric matrix. However, the presence of PPE can alter the pH, viscosity, swelling, crosslinking and mechanical properties of the final formulation. These effects should be evaluated during formulation development.

Pomegranate-Based Hydrogel and Related Wound-Dressing Systems

Experimental studies have investigated pomegranate peel or pomegranate-derived materials in several polymeric delivery systems. These include gelatin-based membranes, hyaluronic-acid/silver-nanoparticle systems, pH-responsive starch-based hydrogel films, chitosan/PEG/ZnO nanocomposites, carbomer topical gels and GelMA hydrogels containing pomegranate-peel-derived extracellular vesicles. [4-9,11] The systems are not identical dosage forms: a topical gel, a hydrogel film, a membrane and a three-dimensional hydrogel network should be distinguished when comparing their properties.

Table 2: Comparative overview of selected pomegranate-based hydrogel and related polymeric wound-dressing systems.

Sr.no	Study	Formulation composition	Evaluation	Major findings
1	do Nascimento et al. (2020) [4]	Gelatin membrane + P. granatum extract	Physicochemical, antioxidant and wound-healing studies	Improved wound closure, granulation and collagen deposition
2	El-Hamid et al. (2024) [5]	PPE + hyaluronic acid + silver nanoparticles	Antifungal and infected-wound studies	Reduced fungal burden and improved wound outcomes
3	Savekar et al. (2024) [6]	PPE-loaded β-cyclodextrin/starch film	Swelling, fluid absorption, release and diabetic wound studies	pH-dependent ellagic acid release and improved healing
4	Mirhaj et al. (2024) [7]	PPE-loaded cellulose/pectin/soy-protein fibres	Material characterization and wound-healing studies	Evaluated as a polymeric fibre dressing
5	Assauqi et al. (2025) [8]	PPE + chitosan + PEG + ZnO nanoparticles	Physicochemical, antibacterial and in vivo studies	Wound-healing and formulation-dependent antibacterial activity
6	Melo et al. (2025) [9]	2.5% PPE carbomer gel	Antioxidant, cytotoxicity and rat wound studies	Antioxidant activity and improved wound healing
7	Li et al. (2026) [11]	PPE-derived extracellular vesicles + GelMA hydrogel	Sustained release, antibacterial and wound-healing studies	Sustained release, anti-S. aureus activity and accelerated healing
8	Ahmed et al. (2026) [12]	PPE-derived silver nanoparticles + hydrogel; 660-nm red light	In vivo wound-healing study	Detailed formulation and outcomes require full-text verification

Abbreviations: PPE, pomegranate peel extract; HA, hyaluronic acid; AgNPs, silver nanoparticles; PEG, polyethylene glycol; ZnO, zinc oxide; GelMA, gelatin methacryloyl; EV, extracellular vesicle.

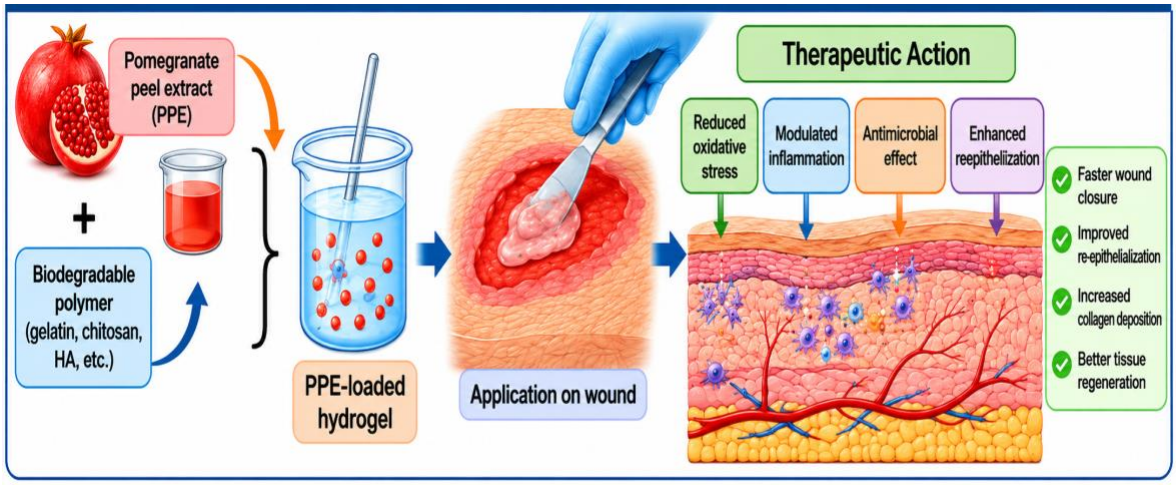


Figure 3: Schematic representation of a PPE-loaded hydrogel wound dressing and its proposed therapeutic functions.

Gelatin-Based Pomegranate Dressing

do Nascimento et al. developed and characterized a biointeractive gelatin wound dressing containing P. granatum extract [4]. The study evaluated the material properties and wound-healing performance of the dressing. The authors reported favorable outcomes in wound closure and tissue-repair parameters. The exact extract composition and quantitative findings should be reproduced only as stated in the original article.

PPE–Hyaluronic Acid–Silver Nanoparticle System

El-Hamid et al. investigated a formulation containing pomegranate peel extract, hyaluronic acid and silver nanoparticles in the context of Candida albicans-infected cutaneous wounds [5]. This system combines a plant-derived extract with a polymeric component and silver nanoparticles. The study reported antifungal and wound-healing-related effects in its experimental model. The contribution of each component should be distinguished where suitable control groups were included.

pH-Responsive PPE Hydrogel Film

Savekar et al. developed a citric-acid-crosslinked, pH-responsive β-cyclodextrin/carboxymethyl tapioca-starch film containing PPE for diabetic wound-healing applications. [6] The formulation was evaluated for swelling, wound-fluid absorption, water-vapour transmission, mechanical properties and pH-dependent ellagic-acid release. The study reported improvements in wound-healing parameters in an experimental diabetic wound model. As a film-based system, it should be described precisely rather than treated as interchangeable with all bulk hydrogels.

Chitosan/PEG/ZnO/PPE Nanocomposite Hydrogel

Assauqi et al. developed a chitosan/PEG/ZnO nanoparticle hydrogel containing PPE and evaluated its physicochemical properties, swelling, antibacterial activity and wound-healing performance. [8] The authors reported wound-healing activity in the experimental model. They also discussed a possible reduction in antibacterial activity following PPE addition, illustrating that combinations of active ingredients do not necessarily produce additive or synergistic effects. The proposed explanation and organism-specific results should be stated in accordance with the original publication.

Carbomer Gel Containing PPE

Melo et al. evaluated dry crude pomegranate peel extract as a bio-input for medicinal gels. [9] The extract was characterized using chromatographic and mass-spectrometric approaches, and the study included antioxidant, hemolysis, cytotoxicity and fibroblast-related assays. A carbomer gel containing 2.5% w/w PPE was evaluated in rats and was reported to promote wound healing, with performance described as comparable to silver sulfadiazine ointment. This formulation is a topical gel rather than a hydrogel dressing and should be classified accordingly.

Extracellular-Vesicle/GelMA Hydrogel

Li et al. incorporated pomegranate-peel-derived extracellular vesicles into GelMA hydrogel. [11] The authors reported that the vesicles affected S. aureus physiology and virulence-associated gene expression. Incorporation into GelMA enabled sustained release, and the resulting system demonstrated antibacterial activity and accelerated wound healing in the experimental model. This study represents a distinct delivery strategy based on pomegranate-derived extracellular vesicles rather than a conventional crude PPE extract.

Pomegranate-Derived Silver Nanoparticle Hydrogel with Red-Light Exposure

Ahmed et al. reported an in vivo investigation of a pomegranate-peel-derived silver nanoparticle hydrogel pre-exposed to 660-nm red light. [12] The title and bibliographic record establish the general approach. However, the accessible bibliographic record does not provide an abstract; therefore, detailed claims about formulation composition, treatment groups, mechanisms or quantitative outcomes should not be included until the full article has been examined.

FORMULATION CONSIDERATIONS

Development of a PPE-loaded hydrogel or related wound dressing requires optimization of both the plant extract and the polymeric system. Extract composition may influence biological activity, while polymer composition and crosslinking determine structural, mechanical and release characteristics. [6,8-10]

Selection and Standardization of Pomegranate Peel Extract

Important variables include cultivar, geographical origin, peel maturity, drying conditions, extraction solvent, extraction time, extraction temperature and storage. A reproducible formulation should include a defined extraction procedure and a phytochemical fingerprint. Suitable marker compounds, such as punicalagin, ellagic acid or gallic acid, may be quantified using validated chromatographic methods. The selected marker should reflect the extract and intended formulation rather than being assumed to represent all biological activity.

Polymer Selection

Potential polymers include gelatin, chitosan, hyaluronic acid, carbomer, cellulose derivatives, starch derivatives, polyethylene glycol and GelMA. Polymer selection should consider biocompatibility, mechanical properties, swelling, degradation, crosslinking chemistry, extract compatibility and release behaviour. The intended dosage form—bulk hydrogel, film, membrane, fibre dressing or topical gel—should be clearly defined.

Crosslinking Strategy

Crosslinking influences mechanical strength, swelling, porosity, degradation and release rate. Physical, ionic and chemical crosslinking approaches may be used depending on polymer chemistry and intended application. Citric-acid crosslinking has been investigated in pH-responsive PPE-containing starch-based films. [6] Residual crosslinking agents and potential effects on cell compatibility should be assessed.

Extract Loading and Compatibility

The amount of PPE incorporated should be optimized with respect to extract solubility, uniformity, polymer compatibility, biological activity and potential cytotoxicity. Polyphenols may interact with polymers, metal ions or nanoparticles, potentially altering colour, viscosity, crosslinking, release and antimicrobial performance. Compatibility studies and appropriate controls are therefore important.

Release and Storage

Release behaviour depends on polymer composition, network structure, swelling, degradation, extract solubility and interactions between the extract and matrix. Stability studies should monitor physical appearance, pH, mechanical properties, marker-compound content and release characteristics under defined storage conditions. Packaging should protect oxidation-sensitive constituents from light, oxygen and moisture where appropriate.

CHARACTERIZATION OF PPE-LOADED HYDROGELS

A comprehensive characterization programme should evaluate the physical, chemical, mechanical, release and biological properties of the formulation. The tests selected should be

appropriate to the dosage form and intended wound application. No single set of tests is sufficient for every hydrogel, film or topical gel.

Table 3: Important characterization parameters for PPE-loaded hydrogel and related wound-dressing formulations.

Sr. No.	Parameter	Purpose / significance	Evaluation method
1	Appearance and homogeneity	Checks colour, texture and uniformity	Visual inspection, microscopy
2	pH	Ensures wound compatibility	Digital pH meter
3	Viscosity and rheology	Determines flow and spreadability	Brookfield viscometer
4	Swelling behaviour	Measures water absorption	Gravimetric method
5	Gel fraction and porosity	Evaluates network structure	Solvent extraction, porosity analysis
6	Water-vapour transmission	Assesses moisture transfer	WVTR method
7	Moisture content and retention	Evaluates moisture retention	Gravimetric method
8	Mechanical properties	Measures strength and flexibility	Texture analyser
9	PPE content	Determines phytochemical loading	HPLC / spectroscopy
10	In vitro drug release	Evaluates phytochemical release	Franz diffusion cell
11	Antioxidant activity	Measures antioxidant potential	DPPH, ABTS, FRAP assays
12	Antimicrobial activity	Evaluates microbial inhibition	Agar diffusion, broth dilution
13	Cytotoxicity	Assesses cell compatibility	MTT, Alamar Blue assay
14	Wound-closure assay	Evaluates cell migration	Scratch assay
15	Stability	Monitors formulation quality during storage	Stability studies
16	Biodegradability	Evaluates polymer degradation	Mass-loss, degradation studies
17	In vivo wound healing	Assesses wound closure and tissue repair	Animal models, histopathology

Abbreviations: PPE, pomegranate peel extract; WVTR, water-vapour transmission rate; HPLC, high-performance liquid chromatography; DPPH, 2,2-diphenyl-1-picrylhydrazyl; ABTS, 2,2′-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid); FRAP, ferric-reducing antioxidant power.

The selection of analytical methods should be justified and validated. In particular, total extract content should not be treated as equivalent to the content of individual marker compounds. Biological testing should include appropriate positive, negative and vehicle controls.

INTEGRATED PROPOSED MECHANISM OF ACTION

PPE-loaded hydrogels are intended to combine the biological properties of pomegranate-derived constituents with the delivery advantages of a hydrated polymeric matrix. Following application to the wound surface, the dressing may absorb exudate, maintain a moist environment and provide localized release of selected bioactive compounds. The released constituents may contribute to modulation of oxidative stress, inflammatory responses and microbial growth.

These effects, together with possible support of fibroblast activity, collagen deposition, angiogenesis and re-epithelialization, may contribute to the overall wound-repair process.

The proposed sequence therefore comprises (i) hydration and local retention of the dressing, (ii) release of PPE-derived constituents, (iii) modulation of oxidative, inflammatory and microbial conditions, and (iv) support of tissue regeneration and wound closure. This integrated model is a conceptual synthesis of predominantly preclinical evidence; it should not be interpreted as a fully established molecular mechanism or as proof of clinical efficacy.

RECENT TECHNOLOGICAL ADVANCES IN POMEGRANATE-BASED WOUND DRESSINGS

Recent technological developments have moved beyond conventional plant-extract gels towards responsive films, nanocomposite systems and biologically derived delivery platforms. The principal technological objective is to improve local retention, release control, antimicrobial performance, material functionality or the biological delivery of pomegranate-derived constituents.

Stimuli-Responsive Hydrogel Films

The pH-responsive β-cyclodextrin/carboxymethyl tapioca-starch film developed by Savekar et al. represents an approach to modulating the release of a PPE marker compound in response to environmental pH. [6] The formulation was crosslinked with citric acid and evaluated for swelling, fluid absorption, water-vapour transmission, mechanical characteristics and ellagic-acid release. Such systems may offer a means of adapting release behaviour to wound conditions, although the relationship between in vitro pH response and the dynamic wound environment requires further study.

Nanocomposite Systems

Nanoparticles have been incorporated into pomegranate-containing polymeric systems to combine extract-associated activity with additional material or antimicrobial functions. Examples include PPE–hyaluronic acid–silver nanoparticle and chitosan/PEG/ZnO/PPE systems. [5,8] Nanocomposite design requires evaluation of particle distribution, aggregation, release, component interactions, cytotoxicity and potential systemic exposure. The presence of multiple active components does not guarantee synergistic activity.

Extracellular-Vesicle-Based Hydrogels

Li et al. (2026) reported pomegranate-peel-derived extracellular vesicles incorporated into GelMA hydrogel. [11] The authors described sustained vesicle release and antibacterial activity against S. aureus. They also reported that the vesicles affected bacterial gene expression,

including genes associated with virulence. This approach differs from loading a crude plant extract because the delivered material consists of pomegranate-derived extracellular vesicles. Further work is needed to standardize vesicle isolation, characterize cargo, establish batch consistency and evaluate safety.

Light-Associated Nanocomposite Approaches

Ahmed et al. (2026) reported an in vivo study of a pomegranate-peel-derived silver nanoparticle hydrogel pre-exposed to 660-nm red light. [12] This represents an emerging combination of plant-derived nanomaterials and light-associated treatment. Because the accessible bibliographic record does not contain an abstract, detailed claims about the experimental design, formulation composition and results are not reproduced here. These details must be checked against the full article before submission.

Multifunctional Formulation Concepts

Multifunctional dressings may combine PPE with other active substances or material components to address more than one wound-management requirement, such as fluid handling, hemostasis, infection control and tissue repair. Such combinations require component-specific controls to determine whether each ingredient contributes to the observed performance. A 2026 agar-based hydrogel-film report containing PPE, clove essential oil and tranexamic acid has been identified in the literature search; however, complete bibliographic details and publication status should be confirmed before it is incorporated into the final reference list.

Overall, these advances indicate increasing interest in responsive, nanocomposite and biologically derived delivery systems. Their practical value will depend on reproducible manufacture, suitable stability, biocompatibility, clinically relevant performance and cost-effective scale-up.

POTENTIAL ADVANTAGES OF PPE-BASED HYDROGEL DRESSINGS

Potential advantages of PPE-loaded hydrogel and related polymeric wound-dressing systems include:

1. Use of pomegranate peel, an agricultural and food-processing by-product, as a source of bioactive constituents.
2. Delivery of polyphenolic compounds with reported antioxidant potential.
3. Potential antimicrobial activity against selected microorganisms.
4. Potential modulation of inflammatory responses.
5. Possible support for fibroblast-associated repair and collagen deposition.
6. Potential contribution to angiogenesis and re-epithelialization.

7. Maintenance of a moist wound environment by suitable hydrogel matrices.
8. Localized retention and delivery of selected phytochemical constituents.
9. Potential for modifying release through polymer selection and network design.
10. Flexibility to develop films, membranes, gels, nanocomposites and other polymeric formats.

These are potential formulation and biological advantages, not established clinical benefits. Their relevance must be demonstrated for each specific formulation.

LIMITATIONS AND CHALLENGES

Lack of Extract Standardization

The concentrations of active constituents may vary with pomegranate cultivar, geographical origin, maturity, extraction solvent and processing conditions. Such variation can affect reproducibility and make comparisons between studies difficult. [10]

Limited Clinical Evidence

The evidence summarized in the available studies is predominantly based on in vitro experiments and animal models. Preclinical findings cannot be assumed to predict clinical efficacy or safety. Well-designed clinical investigations are required before routine therapeutic use can be recommended.

Formulation Complexity

The addition of multiple polymers, nanoparticles or extracellular vesicles may improve selected formulation properties but can also increase manufacturing complexity, cost, quality-control requirements and regulatory challenges. [5,8,11]

Interactions Between Formulation Components

Interactions among PPE, polymers, crosslinkers and nanoparticles may alter swelling, release, mechanical properties or antimicrobial activity. The reported formulation-dependent antibacterial effects in a chitosan/PEG/ZnO/PPE system illustrate the need to assess combinations experimentally rather than assuming additive effects. [8]

Chemical and Physical Stability

Polyphenolic compounds may undergo oxidation or degradation during processing and storage. Stability-indicating analytical methods, appropriate packaging and defined storage conditions are required to monitor marker-compound retention and formulation performance. [9,10]

Safety and Biocompatibility

Local irritation, cytotoxicity, sensitization, systemic exposure and the long-term effects of nanoparticle-containing systems require evaluation. The safety of a crude extract cannot be

inferred solely from the known use of the fruit as food. Safety assessment should be specific to the extract, dose, formulation and intended wound application.

Scale-Up and Quality Control

Laboratory-scale preparation may not translate directly to reproducible manufacturing. Scale-up studies should address raw-material specifications, process controls, batch-to-batch consistency, sterilization compatibility, packaging and product stability.

FUTURE PERSPECTIVES

Future research should prioritize standardized PPE extracts with validated phytochemical markers and reproducible extraction procedures. Formulation studies should establish relationships among extract composition, polymer chemistry, crosslinking, swelling, release behaviour and biological performance. Controlled-release and stimuli-responsive systems may be investigated where a clear therapeutic rationale exists.

Further studies should use relevant wound models, including diabetic, infected and biofilm-associated wounds, with appropriate controls and clinically meaningful outcome measures. Mechanistic investigations should distinguish the effects of individual phytochemicals from those of the complete extract and from the polymeric carrier. Long-term biocompatibility, degradation, stability, sterilization, manufacturing scale-up and regulatory requirements should be considered at an early stage.

The development of nanocomposite and extracellular-vesicle-based systems is promising but requires standardized characterization, reproducible production and careful safety assessment. Ultimately, adequately powered clinical studies will be needed to determine whether PPE-loaded wound dressings offer meaningful benefits over established wound-care products.

RESEARCH GAP AND NOVELTY OF THE REVIEW

Although the wound-healing potential of pomegranate peel has been investigated, important gaps remain in the development and evaluation of PPE-loaded hydrogel and related polymeric wound-dressing systems.

First, many existing reviews primarily discuss the general phytochemical composition, pharmacological activities and biomedical applications of pomegranate peel. Comparatively less attention has been directed towards integrating extract characteristics with hydrogel formulation design, physicochemical performance, release behaviour and wound-healing outcomes. A focused formulation-oriented review is therefore useful for connecting pharmacognosy with pharmaceutical material development.

Second, reported systems differ in extract preparation, marker-compound content, polymer composition, crosslinking method, dosage form and extract loading. The available evidence includes bulk hydrogels, hydrogel films, membranes, fibre dressings and topical gels, which are not directly interchangeable. These differences make it difficult to compare performance or identify formulation features associated with improved outcomes.

Third, although several preclinical studies report wound closure or tissue-repair outcomes, the relationships among individual phytochemicals, their release from polymeric matrices and specific biological pathways remain incompletely understood. More studies are needed to establish whether observed effects arise from the extract, the polymeric carrier, nanoparticles or interactions among these components.

Fourth, emerging approaches such as pH-responsive films, nanocomposite systems and extracellular-vesicle-incorporated hydrogels introduce additional opportunities and challenges. Their comparative advantages, stability, biocompatibility, scalability and clinical relevance have not been adequately established.

The novelty of the present review lies in its focused integration of pomegranate peel phytochemistry with hydrogel and related polymeric wound-dressing science. It compares formulation strategies and characterization approaches, summarizes reported preclinical outcomes, distinguishes different dosage forms and identifies technological and biological barriers to translation. This formulation-centred perspective is intended to guide the rational development of standardized, reproducible and biocompatible PPE-based wound dressings. The review does not claim to be the first review of pomegranate wound-healing activity; rather, it addresses the specific interface between PPE and polymeric wound-dressing design.

CONCLUSION

Pomegranate peel is a source of polyphenolic constituents, including punicalagin, punicalin, ellagic acid and gallic acid, that have demonstrated antioxidant, anti-inflammatory and antimicrobial activities in experimental investigations. Incorporation of PPE or pomegranate-derived materials into hydrogel and related polymeric wound dressings offers an approach to combining these biological properties with moisture management, local retention and controlled delivery. Studies involving gelatin membranes, hyaluronic-acid/silver-nanoparticle systems, pH-responsive films, chitosan/PEG/ZnO nanocomposites, carbomer gels and extracellular-vesicle-incorporated GelMA hydrogels have reported encouraging preclinical findings. However, these formulations differ in composition and dosage form, and their results should not be compared without considering the experimental design and evaluation methods.

Standardization of extracts, optimization of polymeric matrices, mechanistic validation, stability assessment, long-term safety evaluation, reproducible manufacturing and well-designed clinical studies are required before the clinical value of PPE-loaded wound dressings can be established. Overall, these systems represent a promising research direction, but their clinical applicability remains to be demonstrated.

REFERENCES

1. Chidambara Murthy KN, Reddy VK, Veigas JM, Murthy UD. Study on wound healing activity of *Punica granatum* peel. J Med Food. 2004;7(2):256-259. doi:10.1089/1096620041224111.
2. Lins SRS, et al. *Punica granatum* L. hydrogel for wound care treatment: from case study to phytomedicine standardization. Evid Based Complement Alternat Med. 2016; 2016:7129345. doi:10.1155/2016/7129345.
3. Ragab TIM, Nada AA, Ali EA, Shalaby AG, Soliman AAF, Emam M, El Raey MA. 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. 2019; 135:407-421. doi: 10.1016/j.ijbiomac.2019.05.156.
4. do Nascimento MF, Cardoso JC, Santos TS, Tavares LA, Pashirova TN, Severino P, Souto EB, de Albuquerque-Junior RLC. Development and characterization of biointeractive gelatin wound dressing based on extract of *Punica granatum* Linn. Pharmaceutics. 2020;12(12):1204. doi:10.3390/pharmaceutics12121204.
5. El-Hamid MIA, Ibrahim D, Abdelfattah-Hassan A, Mohammed OB, Pet I, Khalil SS, et al. Silver nanoparticles loaded with pomegranate peel extract and hyaluronic acid mediate recovery of cutaneous wounds infected with *Candida albicans*. Front Cell Infect Microbiol. 2024; 14:1469493. doi:10.3389/fcimb.2024.1469493.
6. Savekar PL, Nadaf SJ, Killedar SG, Kumbar VM, Hoskeri JH, Bhagwat DA, Gurav SS. Citric acid cross-linked pomegranate peel extract-loaded pH-responsive β-cyclodextrin/carboxymethyl tapioca starch hydrogel film for diabetic wound healing. Int J Biol Macromol. 2024;274(Pt 1):133366. doi: 10.1016/j.ijbiomac.2024.133366.
7. Mirhaj M, Varshosaz J, Madani Nasab P, Al-Musawi MH, Almajidi YQ, Shahriari-Khalaji M, et al. A double-layer cellulose/pectin-soy protein isolate-pomegranate peel extract micro/nanofiber dressing for acceleration of wound healing. Int J Biol Macromol. 2024; 255:128198. doi: 10.1016/j.ijbiomac.2023.128198.

8. Assauqi NF, Lusiana RA, Masruchin N. Optimization of chitosan-PEG/ZnO hydrogel formulation with pomegranate peel extract as an alternative for wound healing. Indones J Chem. 2025;25(3):905-918. doi:10.22146/ijc.105215.
9. de Melo RCG, Mantovanelli VR, de Paula GA, Ferreira DF, Romagna RA, Monteiro JRB, et al. Sustainable dry crude pomegranate peel extract as a bio-input for medicinal gels: a promising alternative for wound healing. Chem Biodivers. 2025;22(6):e202402710. doi:10.1002/cbdv.202402710.
10. Du J, Wang H, Zhong L, Wei S, Min X, Deng H, Zhang X, Zhong M, Huang Y. Bioactivity and biomedical applications of pomegranate peel extract: a comprehensive review. Front Pharmacol. 2025; 16:1569141. doi:10.3389/fphar.2025.1569141.
11. Li M, Hou L, Zhang Z, Wang X, Sheng K, Dong B, Xu T, Liu C, Yan L, Zheng L. Pomegranate peel extracellular vesicle-incorporated GelMA hydrogel targets *Staphylococcus aureus* infection and accelerates wound healing. ACS Appl Bio Mater. 2026;9(3):1522-1532. doi:10.1021/acsabm.5c02091.
12. Ahmed RS, Mohammed IR, Ajeel AK. In vivo wound healing activity using pomegranate peel derived-silver nanoparticle hydrogel pre-exposed with 660 nm red light. Biol Trace Elem Res. 2026;204(8):6514-6530. doi:10.1007/s12011-026-05130-5.

