RESEARCH PAPER

Naringenin And Zinc Oxide Nanoparticle-Loaded Polymeric Hydrogel Films for Accelerated Wound Healing: A Comprehensive Review

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ABSTRACT
Chronic and non-healing cutaneous wounds represent a significant global healthcare burden, driven by the rising prevalence of diabetes, obesity, and an ageing population. Conventional dressings often fail to sustain a moist wound environment, control bacterial colonisation, and deliver bioactive molecules in a regulated manner, which prolongs the inflammatory phase and delays tissue regeneration. Hydrogel films have emerged as an advanced class of wound dressings because of their three-dimensional hydrophilic network, high exudate absorbency, conformability, and capacity to encapsulate multiple therapeutic agents. Naringenin, a citrus-derived flavanone, exhibits pronounced antioxidant, anti-inflammatory, antimicrobial, and pro-angiogenic activities; however, its clinical translation is limited by poor aqueous solubility, extensive first-pass metabolism, and low oral bioavailability. Zinc oxide nanoparticles complement naringenin through broad-spectrum antibacterial activity, stimulation of re-epithelialisation, and reinforcement of polymeric matrices. Incorporation of these bioactives into sodium alginate, chitosan, and polyvinyl alcohol-based hydrogel films, prepared by solvent-casting with physical and chemical crosslinking, produces multifunctional dressings that combine controlled drug release, mechanical durability, haemostatic activity, and skin-friendly physicochemical properties. The present review consolidates current knowledge on the pathophysiology of chronic wounds, the rationale for topical flavonoid and metal-oxide nanoparticle therapy, the design principles of polymeric hydrogel films, and representative preclinical investigations that support clinical translation. Characterisation strategies including Fourier-transform infrared spectroscopy, differential scanning calorimetry, scanning electron microscopy, swelling analysis, in vitro drug release, and antibacterial assays are critically discussed. The synergistic naringenin–zinc oxide hydrogel film platform is positioned as a promising next-generation dressing for acute and chronic wound management.

Keywords: *Naringenin; zinc oxide nanoparticles; hydrogel film; wound healing; sodium alginate; polyvinyl alcohol; topical drug delivery*

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INTRODUCTION

The skin serves as the principal protective barrier of the human body, and any disruption of its structural integrity initiates a complex and highly regulated cascade of haemostasis, inflammation, proliferation, and remodelling that culminates in tissue restoration[1]. Although superficial injuries generally resolve spontaneously, deep and chronic wounds remain trapped in a prolonged inflammatory phase, resulting in delayed closure, infection, and patient morbidity[2]. Worldwide, chronic wounds affect approximately 40 million individuals, and annual expenditure on chronic wound care in developed economies exceeds US $25 billion[3,4]. The rising incidence of diabetes mellitus, projected to affect 552 million people globally by 2030, is expected to further escalate this clinical and economic burden[5].

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Conventional wound dressings such as gauze and cotton pads frequently adhere to the wound bed, dehydrate the tissue, and offer limited protection against microbial invasion[6]. These limitations have motivated intensive research into advanced polymeric dressings capable of maintaining a moist microenvironment, absorbing exudate, delivering bioactive agents in a controlled manner, and supporting cellular proliferation[7,8]. Among such systems, hydrogel films have attracted particular attention owing to their hydrophilic three-dimensional network, biocompatibility, tunable mechanical properties, and ease of fabrication[9].

Naringenin, a naturally occurring citrus flavanone, exerts antioxidant, anti-inflammatory, antibacterial, and pro-angiogenic effects that are directly relevant to each phase of the healing cascade[10,11]. Its clinical utility is nevertheless constrained by poor aqueous solubility, a short plasma half-life, and extensive hepatic first-pass metabolism, which together limit oral bioavailability to approximately 15 %[12]. Topical delivery through a hydrogel film bypasses the gastrointestinal tract, sustains therapeutic concentrations at the wound site, and can enhance local drug levels up to several thousand-fold compared with systemic administration[13].

Co-incorporation of zinc oxide nanoparticles (ZnO NPs) further broadens the therapeutic scope of the dressing by contributing potent antimicrobial activity, stimulation of keratinocyte migration, and reinforcement of the polymeric matrix[14,15]. The present review summarises the pathophysiology of chronic wounds, the pharmacological rationale for naringenin and ZnO NPs, the design and characterisation of polymeric hydrogel films based on sodium alginate, chitosan, and polyvinyl alcohol (PVA), and the preclinical evidence supporting their translation into next-generation wound dressings[16].

PATHOPHYSIOLOGY OF CHRONIC WOUNDS

Chronic wounds are arbitrarily defined as those failing to achieve anatomical and functional integrity within 12 weeks of injury[2]. Impaired vascularisation, persistent hypoxia, bacterial biofilm formation, and sustained over-expression of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) collectively arrest healing at the inflammatory phase[1,17]. Overactivity of matrix metalloproteinases (MMP-2 and MMP-9) degrades newly synthesised extracellular matrix (ECM) components and prevents the transition to the proliferative phase[18]. In diabetic ulcers, hyperglycaemia additionally suppresses fibroblast proliferation, impairs angiogenesis, and promotes advanced glycation end-product accumulation, further compounding the delay in healing[19].

LIMITATIONS OF CONVENTIONAL WOUND CARE

Current management strategies rely on a combination of debridement, antiseptic irrigation, systemic antibiotics, and passive dressings; however, inconsistent diagnosis of infection and the non-specific nature of topical antimicrobials frequently compromise therapeutic outcomes[20,6]. Broad-spectrum antibiotic use is further restricted by concerns over bacterial resistance and systemic toxicity[21]. Consequently, contemporary wound-care research emphasises stimulus-responsive, patient-specific dressings that combine antimicrobial protection with controlled delivery of bioactive molecules capable of modulating oxidative stress, inflammation, and angiogenesis[22,7].

NARINGENIN: THERAPEUTIC RATIONALE FOR WOUND HEALING

Naringenin (4′,5,7-trihydroxyflavanone; $C_{15}H_{12}O_5$; M.W. 272.25 g/mol) is a Class IV flavonoid obtained principally from Citrus species[10]. It scavenges superoxide and hydroxyl radicals, upregulates endogenous antioxidant enzymes including superoxide dismutase, catalase, and glutathione peroxidase, and activates the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway on macrophages, thereby inducing heme oxygenase-1 expression and attenuating oxidative injury[11,23]. The flavanone also down-regulates pro-inflammatory mediators such as TNF-α, IL-6, and nuclear factor-κB, thereby accelerating the transition from the inflammatory to the proliferative phase[24]. In addition, naringenin displays antibacterial activity against both Gram-positive and Gram-negative pathogens and promotes angiogenesis through enhanced expression of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF)[25,26]. These multifaceted actions make naringenin a promising candidate for integration into advanced wound-dressing platforms[27].

ZINC OXIDE NANOPARTICLES IN WOUND THERAPY

Zinc oxide nanoparticles (1–100 nm) exhibit enhanced surface-to-volume ratio, superior reactivity, and well-documented antimicrobial activity compared with bulk ZnO[14]. Their bactericidal mechanism involves generation of reactive oxygen species, disruption of bacterial cell membranes, and liberation of Zn^{2+} ions that interfere with microbial enzymatic systems[15]. Zn^{2+} additionally acts as a cofactor for lysyl oxidase and several metalloenzymes critical to collagen cross-linking, tensile-strength development, and keratinocyte proliferation[28]. Incorporation of ZnO NPs within polymeric hydrogels has been shown to reinforce mechanical properties, augment antimicrobial efficacy, and promote re-epithelialisation in animal models of diabetic and burn wounds[29].

TOPICAL DRUG DELIVERY FOR WOUND MANAGEMENT

Topical administration offers direct access to the wound site, bypasses hepatic first-pass metabolism, and minimises gastrointestinal degradation of labile therapeutics[30]. Local drug concentrations achieved at the wound bed may exceed systemic levels by several orders of magnitude, thereby improving efficacy while curbing adverse effects[13]. Challenges associated with topical therapy include limited skin permeability for hydrophilic molecules, potential contact dermatitis, and the need for formulation strategies that balance local retention with controlled release[31].

HYDROGEL FILMS AS ADVANCED WOUND DRESSINGS

Hydrogels are three-dimensional, cross-linked, hydrophilic polymer networks capable of absorbing water or biological fluids up to several hundred times their dry mass without dissolving[9]. Their high water content mimics the natural ECM, while porous architecture supports cell adhesion, gaseous exchange, and sustained release of encapsulated bioactives[32]. Compared with traditional gauze dressings, hydrogel films maintain a moist wound environment, prevent eschar formation, and allow atraumatic removal[33], as summarised in **Table 1**.

Table 1: Comparative attributes of hydrogel films and traditional wound dressings.

Attribute	Hydrogel film	Traditional dressing
Moisture retention	Maintains 70–90 % water content, supporting a moist wound bed	Dehydrates the wound, promoting eschar formation
Cooling and analgesia	Provides a cooling, soothing effect owing to high water content	No intrinsic cooling effect; removal may be painful
Adherence	Non-adherent; allows atraumatic removal	Adheres to the wound, causing bleeding on removal
Exudate management	Absorbs exudate while preserving moisture	Over-absorbs, leaving wound dry and fragile
Drug delivery	Enables sustained, controlled release of bioactives	Limited or no capacity for drug delivery

Preparation techniques

Hydrogel networks may be generated by physical or chemical crosslinking[34]. Physical methods include hydrogen bonding, ionic interaction (e.g., alginate with divalent Ca^{2+}), hydrophobic self-assembly, and freeze–thaw-induced crystallisation characteristic of PVA systems[35,36]. Chemical crosslinking via Schiff-base imine formation, enzymatic coupling, γ- or UV-irradiation, and dynamic covalent chemistry produces networks with superior mechanical strength and tunable degradation kinetics[37,38].

Polymeric carriers

Sodium alginate, a linear polysaccharide extracted from brown algae, exhibits high exudate absorbency, haemostatic activity, and the capacity to form robust ionic gels in the presence of divalent cations[39,40]. Chitosan, obtained by deacetylation of chitin, possesses inherent antibacterial, mucoadhesive, and haemostatic properties, and contributes to granulation-tissue formation across all phases of healing[41]. Polyvinyl alcohol (PVA) provides film-forming capability, mechanical strength, biocompatibility, and excellent water solubility, and is widely employed as a matrix component in combination with polysaccharides[42,43]. Glycerol is frequently incorporated as a plasticiser and humectant to improve flexibility, prevent cracking, and retain moisture, whereas Pluronic F-127 functions as a surfactant and thermoresponsive micelle-forming agent[44].

MULTIFUNCTIONAL MECHANISM OF NARINGENIN–ZNO HYDROGEL FILMS

The synergistic activities of naringenin and ZnO NPs within a polymeric hydrogel film translate into simultaneous modulation of the four key phases of wound healing, as illustrated in Figure 1[45].

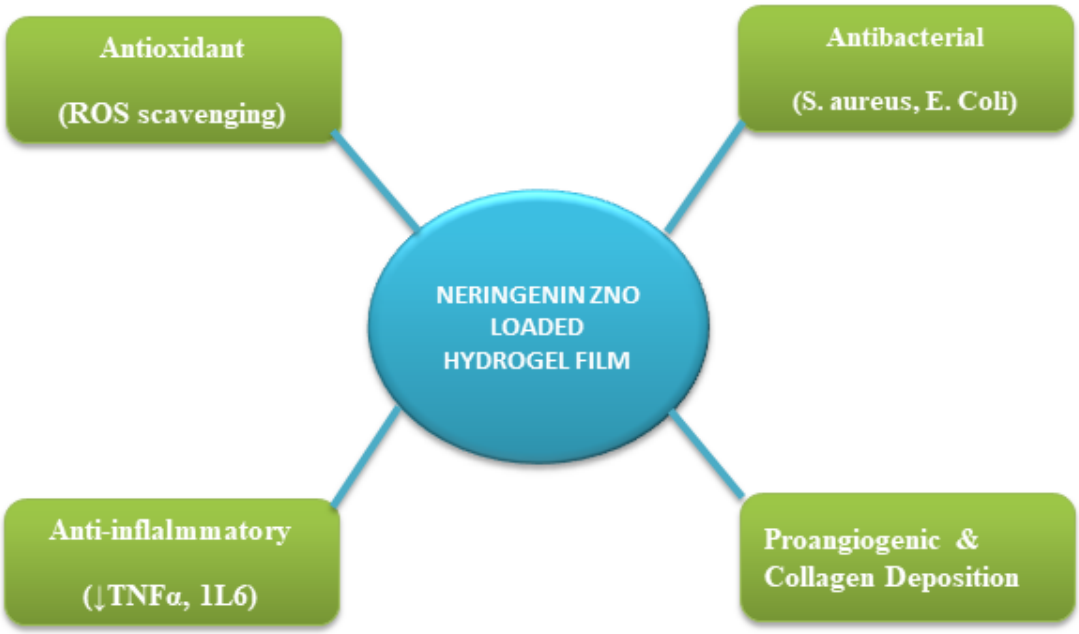

Figure 1: Multifunctional therapeutic mechanism of the naringenin–ZnO-loaded hydrogel film.

During haemostasis, the hydrophilic matrix absorbs blood exudate and facilitates platelet aggregation, while Zn^{2+} ions activate intrinsic coagulation pathways[46]. In the inflammatory phase, naringenin suppresses TNF-α, IL-1β, and IL-6 production, and ZnO NPs eliminate bacterial colonisation, jointly shortening this phase[24,15]. The proliferative phase benefits from enhanced fibroblast migration, collagen deposition, and neovascularisation stimulated by both bioactives, as confirmed by increased VEGF and bFGF expression in preclinical studies[26,47]. In the remodelling phase, Zn^{2+}-mediated lysyl-oxidase activation promotes collagen cross-linking, while naringenin prevents excessive fibrosis through down-regulation of transforming growth factor-β signalling, culminating in aesthetically superior scar tissue[28,48].

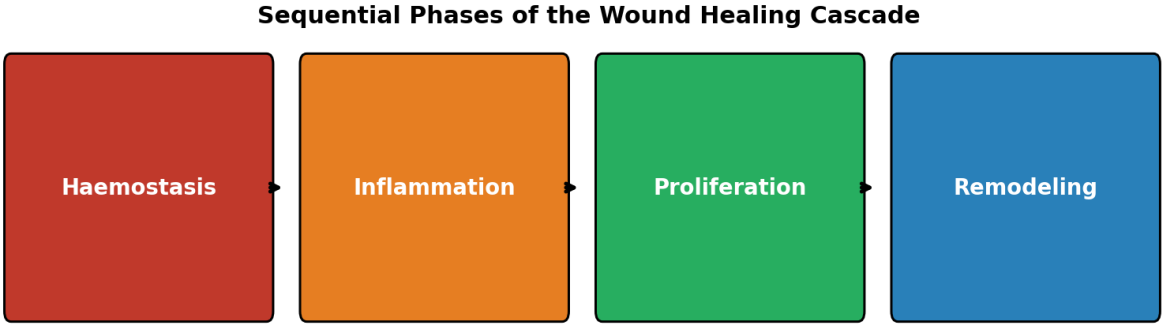

Figure 2: Sequential phases of the wound-healing cascade targeted by naringenin–ZnO hydrogel films.

REPRESENTATIVE RESEARCH INVESTIGATIONS

Diverse polysaccharide- and PVA-based hydrogels loaded with antimicrobial, antioxidant, and regenerative agents have demonstrated favourable wound-healing outcomes in preclinical models[49], as summarised in **Table 2.**

Table 2: Representative hydrogel formulations investigated for wound healing.

Polymer system	Therapeutic agent	Key findings	Reference
Oxidised dextran–gelatin (Schiff base)	Apocynin	Reduced inflammation; accelerated angiogenesis and skin regeneration	50
PEGDA/PVA/tragacanth gum	—	Non-toxic film with the strongest antibacterial activity among tested variants	51
Sodium alginate/pectin	Simvastatin	99 % wound closure in 21 days; enhanced angiogenesis and collagen synthesis	52
κ-Carrageenan/C-phycocyanin	—	Superior haemostasis; enhanced tissue regeneration	53
Alginate/chitosan	Hesperidin	Improved re-epithelialisation and collagen deposition in rat model	54
Alginate	Naringenin	Accelerated excisional wound closure; reduced oxidative stress	55
Chitosan/PVA with ZnO NPs	Flavonoid + ZnO	Synergistic antibacterial and pro-angiogenic effects; sustained release	29

CHARACTERISATION OF NARINGENIN–ZNO HYDROGEL FILMS

Spectroscopic and thermal analysis

Fourier-transform infrared spectroscopy (FTIR) confirms the retention of characteristic functional groups of naringenin (O–H stretching at ~3256 cm^{-1}; C=O stretching at ~1504 cm^{-1}), alginate (–OH at ~3364 cm^{-1}; –CH at ~2897 cm^{-1}), and PVA (–OH at ~3566 cm^{-1}), while the appearance of new absorption bands and peak broadening in composite films indicates successful physical crosslinking and molecular compatibility[56]. Differential scanning calorimetry (DSC) thermograms of drug-loaded hydrogels display characteristic endothermic transitions between 119 °C and 268 °C, reflecting polymer melting, drug dispersion, and improved thermal stability of the composite matrix[57].

Morphology, swelling, and drug release

Scanning electron microscopy reveals a homogeneous, moderately porous surface that facilitates oxygen exchange, retains wound moisture, and supports sustained drug release while restricting bacterial ingress[58]. Swelling studies in phosphate-buffered saline (pH 7.4) demonstrate equilibrium uptake governed by hydrogen bonding between PVA hydroxyl groups and alginate carboxylate anions, with optimised formulations exhibiting rapid yet controlled hydration[59]. In vitro release profiles through cellulose-acetate membranes in Franz diffusion cells typically display an initial burst followed by a sustained diffusion-controlled phase, with approximately 79–83 % of encapsulated naringenin released over 24 h, thereby minimising the need for frequent dressing changes[60].

Antibacterial performance

Zone-of-inhibition assays consistently indicate superior antibacterial activity of naringenin–ZnO hydrogel films

against Staphylococcus aureus and Escherichia coli compared with blank hydrogels and commercial dressings, with Gram-positive strains typically more susceptible than Gram-negative strains owing to differences in outer-membrane architecture[61].

IN SILICO VALIDATION AND MOLECULAR RATIONALE

Molecular-docking studies against the catalytic domain of MMP-9 (PDB ID: 4WZV) have demonstrated that naringenin adopts a low-energy conformation within the active site, forming hydrogen bonds with ALA189 and LEU188 and π–π stacking with HIS226[62]. Naringenin yielded a docking score of –7.664, surpassing that of the reference inhibitor doxycycline (–5.942), thereby supporting its selection as an MMP-9 modulator capable of restraining excessive extracellular-matrix degradation in chronic wounds[63].

SAFETY, STABILITY, AND TRANSLATIONAL PERSPECTIVES

Stability studies over six months at accelerated conditions have shown no appreciable physical deterioration or drug-content loss in optimised formulations, suggesting acceptable shelf-life for clinical deployment[64]. In vivo investigations in rodent models of excisional, burn, and diabetic wounds have consistently reported wound-closure rates exceeding 95 %, accompanied by reduced TNF-α and IL-6 levels, increased hydroxyproline content, and organised collagen deposition without observable skin irritation[55,65]. These results, together with the favourable biocompatibility of naringenin and the established safety of ZnO in topical preparations, support further clinical evaluation of such hydrogel films for chronic wound management[66].

FUTURE PERSPECTIVES

Future research should focus on stimuli-responsive naringenin–ZnO hydrogel films capable of adapting their release profile to wound pH, temperature, or reactive oxygen species concentration, thereby matching therapeutic intensity to the evolving wound microenvironment[67]. Integration with nanocarriers such as nanoemulsions, solid-lipid nanoparticles, or electrospun fibres may further enhance solubility, skin penetration, and spatial control of delivery[68]. Scale-up using solvent-casting and 3D-printing technologies, alongside rigorous regulatory-grade toxicological evaluation, will be essential to translate laboratory-scale formulations into clinically viable dressings[69].

CONCLUSION

Naringenin and ZnO nanoparticle co-loaded polymeric hydrogel films represent a multifunctional platform that simultaneously addresses the principal challenges of chronic wound management, namely persistent inflammation, oxidative stress, bacterial colonisation, impaired angiogenesis, and disorganised extracellular-matrix remodelling[70]. Sodium alginate, chitosan, and PVA provide a biocompatible and mechanically robust matrix, while naringenin and ZnO nanoparticles contribute complementary antioxidant, anti-inflammatory, antibacterial, and regenerative activities[71]. Continued interdisciplinary research combining materials science, pharmacology, and clinical wound-care expertise is expected to translate these advanced dressings into effective, cost-efficient therapies for acute and chronic wounds[72].

AUTHOR CONTRIBUTIONS

Antil K: Literature review and Writing - Original Draft; Kumar C: Conceptualisation, Methodology, Writing - Review & Editing; Redhu R: Writing - Review & Editing, Validation; Dhounchak R: literature retrieval and formatting of tables and figures; Jangra K: Supervision, Writing - Review & Editing.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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