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Kaempferol and Gallic Acid in Wound Healing: Pharmacological Mechanisms, Formulation Strategies, and Translational Perspectives

Sheela Kushwaha[1], Dr. Mamta Tiwari[*1], Dr. Ashish Srivastava[2], Somendra Kumar[3], Dr. Rajesh Kumar[4], Vaishnavi Sahu[5]

[1*, 4, 5] School of Pharmaceutical Sciences, Chhatrapati Shahu Ji Maharaj University, Kanpur, 208024, India
[2] Professor, PSIT-Pranveer Singh Institute of Technology, Pharmacy, Kanpur
[3]School of Pharmacy (SOP), ITM University, Gwalior, Madhya Pradesh
[*]**Corresponding Author**
Dr. Mamta Tiwari
Assistant professor, School of Pharmaceutical Sciences, CSJM University, Kanpur, 208024
Email ID: mamta1712@gmail.com, Sheela.382003@gmail.com, ashish.srivastava@psit.ac.in, somendrakumarpalsingh@gmail.com,rajeshkumar25389@gmail.com, sahuvaishnavi22@gamil.com

Abstract

Wound healing depends on a regulated sequence of inflammation, cell migration, tissue formation, vascular growth, extracellular-matrix deposition, and remodelling. This sequence is frequently disturbed in diabetic, infected, ischemic, and chronic wounds. Persistent inflammation, excessive oxidative stress, microbial biofilms, poor vascular supply, fibroblast dysfunction, and defective re-epithelialization interact with one another and prolong tissue injury. Natural polyphenols have attracted interest because they can influence several of these processes simultaneously.Kaempferol and gallic acid are plant-derived polyphenols with distinct but potentially complementary properties. Kaempferol is a flavonol associated with antioxidant, anti-inflammatory, antibacterial, anti-senescent, and cytoprotective effects. Experimental findings indicate that it can protect fibroblasts, regulate inflammatory signalling, inhibit lipid peroxidation and ferroptosis, reduce bacterial burden, and improve tissue repair in diabetic and ischemic models. Its low aqueous solubility, however, makes the choice of topical delivery system important. Gallic acid is a smaller phenolic acid with antioxidant, antibacterial, anti-inflammatory, metal-binding, and polymer-interacting properties. It has been incorporated into films, hydrogels, nanofibres, scaffolds, sponges, nanoparticles, metal-organic frameworks, and three-dimensional printed wound dressings. The available evidence supports the use of both compounds for controlling the hostile wound environment rather than viewing them only as direct stimulants of cell proliferation. Gallic acid is particularly suitable for constructing hydrated and adhesive wound materials, whereas kaempferol may provide sustained protection against inflammatory and oxidative injury when delivered through vesicular or particulate carriers. A combined system could therefore offer rapid local protection together with prolonged pharmacological activity. Its development should be guided by controlled release, cell-specific safety, antibacterial and antibiofilm testing, macrophage responses, angiogenesis, collagen organization, scar quality, and diabetic wound outcomes. This article presents the biological basis, pharmacological evidence, formulation approaches, and experimental considerations relevant to the development of kaempferol- and gallic-acid-based wound treatments.

Keywords: *kaempferol; gallic acid; wound healing; diabetic wound; oxidative stress; inflammation; antibacterial dressing; hydrogel; nanofibre; topical delivery*

1. Introduction

The skin provides mechanical protection, limits water loss, regulates temperature, and forms a barrier against microorganisms and harmful substances. When this barrier is disrupted, repair begins immediately. Platelets control bleeding and form a provisional matrix. Neutrophils and macrophages remove microorganisms and damaged tissue. Keratinocytes migrate over the wound surface, fibroblasts produce extracellular matrix, and endothelial cells form new blood vessels. The newly formed tissue is later remodelled into a more organized structure.

This process is efficient in an uncomplicated acute wound. It becomes much more difficult when the wound is affected by diabetes, microbial infection, vascular insufficiency, repeated pressure, extensive tissue damage, or an abnormal immune response. Chronic wounds frequently remain trapped in a state of continued inflammation.

Reactive oxygen species accumulate, proteolytic enzymes damage the extracellular matrix, growth factors become less effective, and wound cells lose their ability to migrate or respond normally. Signalling pathways that ordinarily coordinate repair may remain excessively active or become poorly timed (Bonnici et al., 2024).

Natural products have long been used in skin care and wound treatment. Their continued scientific relevance arises from the presence of chemically diverse constituents that can influence inflammation, oxidation, microbial survival, cell migration, and matrix formation. Systematic assessments of natural products for skin applications indicate that selected plant-derived compounds can regulate inflammatory mediators, protect skin cells from oxidative damage, and support repair-associated responses (Fernandes et al., 2023). Similar findings have been reported for herbal products investigated in diabetic wounds, where several preparations improved closure, antioxidant status, collagen deposition, or inflammatory balance in preclinical studies (Herman & Herman, 2023).

Polyphenols form an important part of this field. They contain one or more phenolic groups and are widely present in fruits, vegetables, medicinal plants, tea, seeds, and bark. Their biological effects are not confined to direct radical scavenging. Depending on structure and concentration, they can influence intracellular signalling, inflammatory enzymes, microbial membranes, mitochondrial function, vascular responses, and extracellular-matrix regulation. Polyphenols may also be incorporated into biomaterials, allowing a dressing to function as both a physical wound cover and a local pharmacological system (Guimarães et al., 2021).

Kaempferol and gallic acid are particularly suitable for comparative evaluation. Kaempferol is a flavonol with recognised antioxidant, anti-inflammatory, antimicrobial, and tissue-protective properties (Alam et al., 2020; Alrumaihi et al., 2024; Periferakis et al., 2022). Gallic acid is a phenolic acid that can act as a bioactive molecule and as a functional part of a polymer network. Its hydroxyl and carboxyl groups permit strong interactions with proteins, polysaccharides, synthetic polymers, nanoparticles, and metal ions. These interactions have led to the development of a wide range of gallic-acid-containing wound dressings.

The two compounds differ in their pharmaceutical behaviour. Kaempferol has poor aqueous solubility and often requires a carrier capable of improving dispersion, retention, and controlled release. Gallic acid is more compatible with hydrated polymer networks but may be released rapidly unless it is grafted, complexed, crystallized, or otherwise retained within the material. These differences provide a rational basis for complementary delivery. Gallic acid may contribute to the structure and immediate function of the wound dressing, while kaempferol may provide sustained intracellular and anti-inflammatory effects.

The therapeutic purpose is not merely to accelerate visible closure. Effective wound treatment should reduce microbial burden, resolve excessive inflammation, protect viable tissue, restore vascular supply, support organized collagen deposition, and produce a stable epithelial surface. Scar quality also matters. A wound that closes rapidly but develops weak, fibrotic, or poorly organized tissue cannot be considered fully repaired.

2. Biological Processes Governing Wound Repair

2.1 Haemostasis and early inflammation

Haemostasis begins within seconds of injury. Blood vessels constrict, platelets adhere to damaged structures, and fibrin stabilizes the clot. This clot controls bleeding and provides a temporary framework for incoming cells. Platelets also release mediators that recruit inflammatory cells and initiate later repair.

Inflammation is essential during the early phase. Neutrophils remove bacteria and damaged material. Macrophages continue clearance and coordinate the transition toward tissue formation. The problem in chronic wounds is not the presence of inflammation but its failure to resolve. Continued exposure to bacteria, oxidized molecules, dead tissue, or high glucose can maintain the production of tumour necrosis factor-α, interleukin-1β, interleukin-6, chemokines, and matrix-degrading enzymes. The wound remains biologically active but fails to progress.

Several signalling pathways participate in this persistent state. Nuclear factor kappa B, mitogen-activated protein kinases, Janus kinase and signal transducer pathways, inflammasome-related mechanisms, and stress-associated kinases can remain active in response to infection and cellular injury (Bonnici et al., 2024). A useful

anti-inflammatory treatment should reduce excessive or prolonged activation without preventing the initial immune defence needed for microbial clearance.

2.2 Oxidative stress

Reactive oxygen species are produced during normal metabolism and immune defence. At controlled concentrations, they support signalling and microbial killing. In a chronic wound, production may exceed the capacity of cellular antioxidant systems. Superoxide, hydrogen peroxide, hydroxyl radicals, and lipid-derived oxidants then damage membranes, proteins, mitochondrial structures, nucleic acids, and extracellular-matrix components.

Oxidative stress can also reinforce inflammation. Damaged cells release signals that recruit additional inflammatory cells, while inflammatory cells generate more reactive species. This creates a self-sustaining cycle. Antioxidants may interrupt this cycle by reducing excessive oxidation and preserving endogenous defence systems such as superoxide dismutase, catalase, glutathione, and glutathione peroxidases (Comino-Sanz et al., 2021).

Antioxidant biomaterials are being developed to provide prolonged redox control at the wound surface. Rather than delivering a short burst of a soluble antioxidant, these materials retain or regenerate antioxidant activity within a hydrated matrix. Their design may protect cells, preserve extracellular-matrix proteins, and reduce inflammation-associated tissue injury (Md Fadilah et al., 2023).

2.3 Keratinocyte migration and re-epithelialization

Keratinocytes at the wound edge change their shape, loosen some of their attachments, and migrate across the provisional matrix. Once coverage is restored, they differentiate to rebuild the epidermal barrier. Re-epithelialization can be impaired by high glucose, oxidative stress, bacterial toxins, excessive protease activity, and an unsuitable wound surface.

Migration should be distinguished from proliferation. A compound can improve wound closure by protecting keratinocytes and supporting movement without directly increasing cell division. This distinction is relevant to kaempferol, which has improved wound healing in vivo even when direct stimulation of selected proliferation-associated genes was not observed in cultured keratinocytes (Al-Ghanayem et al., 2024).

2.4 Fibroblast function and matrix formation

Fibroblasts migrate into the wound and produce collagen, fibronectin, proteoglycans, and other matrix components. Some fibroblasts acquire a contractile phenotype and assist wound contraction. During remodelling, collagen fibres become more organized, and the ratio between different collagen types changes.

Persistent inflammation and oxidative damage reduce fibroblast viability and disturb matrix production. Excessive fibroblast activation, however, can lead to fibrosis and raised scars. The objective is therefore controlled matrix formation followed by appropriate remodelling. Compounds that protect fibroblasts without causing uncontrolled proliferation may be useful in this context.

2.5 Angiogenesis

New blood-vessel formation is necessary because the developing tissue requires oxygen and nutrients. Endothelial cells respond to vascular growth factors, migrate, proliferate, and form new capillary structures. Diabetes, ischemia, inflammation, and oxidative injury can impair these responses.

Angiogenesis in wound healing is regulated by interactions among endothelial cells, macrophages, fibroblasts, matrix proteins, and growth factors. Vascular endothelial growth factor is important, but successful angiogenesis cannot be judged by a single growth factor. Vessel density, maturity, perfusion, and stability are also required (Shi et al., 2023).

2.6 Macrophage transition and tissue restoration

Macrophages perform different functions during the course of repair. Early macrophages participate in defence and removal of damaged tissue. Later macrophage populations support vascular growth, fibroblast activity,

matrix formation, and resolution of inflammation. This change is often described as polarization, although actual wound macrophages show a range of overlapping states.

Polyphenol-based dressings can influence this transition. A polyphenol-modified konjac glucomannan dressing combined antioxidant activity with a shift toward repair-associated macrophage responses (H. Li et al., 2022). An immunomodulatory bioadhesive hydrogel also improved angiogenesis and diabetic wound repair by regulating macrophage heterogeneity rather than simply suppressing all macrophage activity (Y. Fu et al., 2023).

2.7 Infection and biofilm formation

Wounds are exposed to microorganisms from the skin, environment, and surrounding tissue. Bacterial colonization does not always cause clinical infection, but a high microbial burden can delay repair. Organisms such as *Staphylococcus aureus*, methicillin-resistant *S. aureus*, *Pseudomonas aeruginosa*, and enterococci are commonly associated with difficult wounds.

Biofilms are structured microbial communities enclosed within a self-produced matrix. They adhere to tissue, tolerate antimicrobial agents, and maintain inflammation. An effective wound material should therefore be assessed against established biofilms, not only freely suspended bacteria. Hydrogels with combined antibiofilm and antioxidative activity have shown that simultaneous control of microbial persistence and oxidative tissue injury can accelerate infected diabetic wound repair (Pranantyo et al., 2024).

3. Pharmacological Profile of Kaempferol

3.1 Chemical and pharmaceutical characteristics

Kaempferol is a flavonol containing several hydroxyl groups arranged on a three-ring structure. The molecule can donate hydrogen atoms or electrons and may interact with proteins involved in oxidative and inflammatory signalling. It is present in many vegetables, fruits, medicinal plants, and herbal preparations.

Despite its biological activity, kaempferol has limited aqueous solubility. This can reduce dissolution, uniform distribution, and tissue availability when it is placed directly into a water-based formulation. Flavonols also undergo extensive metabolism after oral administration, including glucuronidation, sulfation, methylation, and microbial transformation. These processes can limit the concentration of unchanged kaempferol reaching peripheral tissues (Rudrapal et al., 2024).

Topical delivery provides an opportunity to bypass much of the systemic absorption and first-pass metabolism associated with oral dosing. It does not remove the need for pharmaceutical control. The compound must still be released from its carrier, remain stable in the wound environment, and reach viable cells at an effective but non-toxic concentration.

A pH-sensitive kaempferol hydrogel has been investigated as a controlled delivery system (Q. Zhang et al., 2022). Hybrid lecithin-chitosan ethosomes have also been developed to improve kaempferol delivery in diabetic foot-ulcer applications (Raghav et al., 2024). These approaches reflect the importance of improving local dispersion and prolonged contact.

3.2 Anti-inflammatory effects

Kaempferol can regulate several inflammatory pathways. Its anti-inflammatory activity has been associated with reduced activation of nuclear factor kappa B, stress-related kinases, inflammatory enzymes, and cytokine production (Alam et al., 2020; Alrumaihi et al., 2024). The response depends on the cell type and the nature of the inflammatory stimulus.

Direct evidence in skin fibroblasts is particularly relevant. Kaempferol reduced interleukin-1β expression and cytotoxicity caused by a strong inflammatory stimulus through suppression of c-Jun N-terminal kinase activity (S.-J. Park et al., 2021). JNK is activated by cellular stress and can contribute to inflammatory gene expression, apoptosis, and matrix-related changes. Its regulation offers a plausible explanation for fibroblast protection during prolonged wound inflammation.

The value of this effect lies in maintaining cell function. Fibroblasts exposed to excessive inflammation may lose viability or produce an abnormal matrix. By reducing stress-associated signalling, kaempferol may preserve the cells required for later tissue formation.

3.3 Antioxidant activity and protection from ferroptosis

Kaempferol can directly interact with reactive species and may also preserve endogenous antioxidant systems. In diabetic wounds, it has been associated with increased antioxidant-enzyme activity and improved histological repair (Al-Ghanayem et al., 2024). Such findings suggest that its action is not restricted to cell-free radical scavenging.

Ferroptosis is a form of regulated cell death driven by iron-dependent lipid peroxidation. It differs from apoptosis and is particularly relevant in tissues exposed to ischemia, inflammation, and severe oxidative stress. Kaempferol improved skin-flap survival by inhibiting ferroptosis and inflammation (A. Wang et al., 2024). This finding connects its antioxidant activity with preservation of viable skin tissue under reduced blood supply.

Ferroptosis may also be relevant to diabetic and infected wounds, where lipid oxidation, disturbed iron handling, mitochondrial stress, and weakened antioxidant defence can coexist. Evaluation of kaempferol in these wounds should therefore include lipid peroxidation and ferroptosis-related markers rather than relying only on total antioxidant assays.

3.4 Antimicrobial activity

Kaempferol has shown activity against several bacterial and fungal organisms. Proposed mechanisms include alteration of microbial membranes, inhibition of essential enzymes, interference with energy metabolism, and effects on virulence-related functions (Periferakis et al., 2022).

Direct wound-related evidence has been reported against methicillin-resistant *S. aureus* and *P. aeruginosa*. Kaempferol inhibited both organisms and reduced bacterial counts in infected diabetic rat wounds (Al-Ghanayem et al., 2024). The treatment also improved epithelialization, antioxidant status, vascular development, collagen deposition, and inflammatory-cell distribution.

These findings suggest that kaempferol may support healing by reducing two linked sources of injury: microbial persistence and oxidative stress. Antibacterial activity should nevertheless be interpreted in relation to the concentration released from the topical preparation. A formulation containing kaempferol is useful only when sufficient active compound becomes available at the wound surface.

3.5 Effects on fibroblasts, keratinocytes, and skin ageing

Photoaged skin and chronic wounds share several biological features, including oxidative injury, inflammatory cytokine production, matrix degradation, fibroblast dysfunction, and impaired barrier repair. Evidence from photoaging models can therefore contribute useful cellular information, provided that it is not treated as direct wound evidence.

Kaempferol-modified mesenchymal-stem-cell extracellular-vesicle mimetics have been reported to protect ultraviolet-B-injured fibroblasts and keratinocytes. The system reduced oxidative stress, inflammatory cytokines, senescence-associated changes, and matrix degradation while improving collagen deposition and epidermal-barrier repair. Suppression of ADAM10 was identified as part of the mechanism (N. Fu et al., 2026). These findings support the ability of kaempferol-based delivery to protect both major skin-cell populations.

The delivery platform is also important. Extracellular-vesicle mimetics may enhance cellular uptake and protect the active compound from rapid loss. A similar principle may be applied to wounds through vesicles, lipid nanoparticles, or polymeric particles that remain within the wound bed.

3.6 Macrophage regulation

Macrophage behaviour is central to chronic wound repair. Kaempferol has been delivered through mannose-modified poly(lactic-co-glycolic acid) nanoparticles to target macrophages and alter their inflammatory state in rheumatoid arthritis (Z. Zhang et al., 2026). Although rheumatoid arthritis is not a wound model, the study

provides direct evidence that kaempferol can be delivered selectively to macrophages and can influence their phenotype.

This approach is relevant to diabetic wounds, where inflammatory macrophages may remain dominant. A macrophage-targeted or wound-retentive kaempferol carrier could support the transition from prolonged inflammation toward tissue restoration. The required response should be measured through a broad panel of macrophage functions, including cytokine production, phagocytosis, oxidative activity, and repair-associated mediators.

3.7 Direct wound-healing evidence

Topical kaempferol has been evaluated in infected diabetic excision wounds. A 1% preparation reduced bacterial burden, increased antioxidant-enzyme activity, shortened the epithelialization period, increased epithelial thickness and capillary formation, improved collagen deposition, and reduced inflammatory-cell accumulation (Al-Ghanayem et al., 2024).

The same work found no direct stimulation of selected VEGF or transforming growth factor-β1 genes in high-glucose keratinocyte cultures. This result is important. It indicates that kaempferol may improve repair primarily by correcting the wound environment rather than acting as a simple proliferative stimulant.

A hybrid lecithin-chitosan ethosomal system has extended the formulation possibilities for diabetic foot-ulcer treatment (Raghav et al., 2024). Chitosan may provide adhesion and antimicrobial support, whereas lecithin-based vesicles may improve kaempferol incorporation and tissue contact. Component-specific evaluation is needed to determine the contribution of the carrier and the active compound.

4. Pharmacological Profile of Gallic Acid

4.1 Chemical characteristics

Gallic acid is 3,4,5-trihydroxybenzoic acid. It contains three phenolic hydroxyl groups and one carboxylic-acid group. These functional groups permit radical scavenging, hydrogen bonding, metal coordination, polymer interaction, and surface adhesion.

The molecule is present in berries, tea, grapes, pomegranate, oak-derived products, medicinal plants, and hydrolysable tannins. Its comparatively small size and polar groups make it easier to incorporate into aqueous polymer systems than kaempferol. At the same time, its hydrophilicity may cause rapid release from a loosely crosslinked material.

Gallic acid can be included as a freely dispersed active, loaded into nanoparticles, grafted to chitosan, crystallized within a hydrogel, coordinated with metals, or used as part of a supramolecular network. Each approach changes the amount of free gallic acid available to cells and microorganisms.

4.2 Antioxidant activity

Gallic acid can donate electrons or hydrogen atoms to reactive species and can interrupt oxidative chain reactions. It may preserve endogenous antioxidant enzymes and reduce lipid, protein, or nucleic-acid oxidation. Its association with oxidative stress is especially relevant in diabetes, where chronic hyperglycaemia promotes reactive oxygen species, mitochondrial dysfunction, inflammatory signalling, and vascular injury (Xu et al., 2021).

The antioxidant effect is influenced by concentration, pH, metal ions, and oxygen availability. Gallic acid can bind transition metals, which may reduce or alter metal-driven oxidation. Under some chemical conditions, phenolic compounds may also participate in redox cycling. The complete formulation must therefore be evaluated rather than assuming that the presence of gallic acid guarantees antioxidant behaviour.

Gallic-acid-containing hydrogels and metal-organic systems have been designed to provide sustained control of oxidative stress. A magnesium-gallate framework within a sprayable hydrogel was developed to continuously regulate the diabetic wound environment and promote reconstruction of neurovascular structures (Lian et al., 2024). A magnesium-ion and gallic-acid framework incorporated into an acellular-matrix hydrogel similarly targeted diabetic wound repair (Liu et al., 2025).

4.3 Anti-inflammatory and tissue-protective activity

Gallic acid can regulate inflammatory mediators, oxidative stress, fibrosis, and cell-death pathways. In a rat model of medication-related osteonecrosis of the jaw, gallic acid affected tumour necrosis factor-α, transforming growth factor-β1, fibroblast growth factor, endothelial nitric oxide synthase, endoplasmic-reticulum stress proteins, mitochondrial injury, cytochrome-c release, caspase-3 activation, collagen organization, and fibrosis (Yazıcı et al., 2026).

The model involved tissue injury following dental extraction rather than a conventional skin wound. Nevertheless, it provides useful evidence that gallic acid can act across several repair-related systems. These include inflammatory control, vascular support, stress-response regulation, apoptosis, collagen organization, and fibrotic remodelling.

Gallic acid has also been incorporated into anti-inflammatory wound materials. A polyphenol-sodium alginate supramolecular hydrogel was designed to combine antibacterial and anti-inflammatory actions in infected wounds (Chen et al., 2023). A diammonium glycyrrhizinate and gallic acid hydrogel similarly combined two pharmacologically active components for bacterial wound treatment (He et al., 2022).

4.4 Antibacterial activity

Gallic acid has activity against a range of microorganisms. Its proposed actions include membrane disruption, altered permeability, enzyme inhibition, interference with microbial energy production, changes in redox balance, and effects on nucleic-acid-related processes (Keyvani-Ghamsari et al., 2023).

In wound materials, gallic acid is frequently combined with other antibacterial components. These include chitosan, copper, zinc oxide, silver nanoparticles, polyhexamethylene guanidine, photothermal materials, and antimicrobial polymers. Such combinations may provide broader or stronger activity than gallic acid alone.

A chitosan-copper-gallic acid nanocomposite was developed as a multifunctional antibacterial wound dressing (X. Sun et al., 2020). A gelatin-gallic acid and zinc oxide bioadhesive combined phenolic and inorganic antibacterial components (Ramirez-Barron et al., 2020). Polyvinyl alcohol, polyhexamethylene guanidine, and gallic acid were also combined in antibacterial hydrogel films (X. Yang et al., 2021).

These materials demonstrate the compatibility of gallic acid with antimicrobial dressing design. Their biological effects arise from the entire formulation, including release, material hydration, surface contact, and the activity of each component.

4.5 Effects on fibroblasts and tissue compatibility

A wound material must support the survival and function of fibroblasts. Gallic acid-containing scaffolds have shown favourable interactions with dermal fibroblasts when the concentration and release profile are controlled.

Three-dimensional printed polycaprolactone scaffolds enriched with hyaluronic acid and gallic acid were developed for wound dressing. The scaffolds supported dermal-fibroblast viability and proliferation and provided controlled gallic acid release (Guldorum et al., 2025). The three-dimensional architecture can provide mechanical support, defined pore geometry, and a stable surface for cell interaction.

Gallic acid-chitosan/polycaprolactone conjugate electrospun nanofibres have also undergone in-vitro and in-vivo evaluation (Patole et al., 2024). Silk fibroin and gelatin composite dressings functionalized with gallic acid provide another matrix intended to combine biological compatibility with active wound support (P. Li et al., 2024).

5. Regulation of the Wound Microenvironment

5.1 Oxidative balance rather than complete antioxidant suppression

Wound repair requires a controlled redox environment. Complete removal of reactive oxygen species would interfere with normal signalling and microbial defence. The therapeutic objective is to reduce sustained oxidative damage while maintaining physiological redox activity.

Kaempferol and gallic acid may contribute in different ways. Kaempferol can act within cells, regulate stress-responsive pathways, and protect membranes from lipid peroxidation. Gallic acid can function at the material surface, within wound fluid, or as part of a polymer network. A combined formulation could therefore influence both extracellular and intracellular oxidative stress.

Polyphenol-containing wound materials support this concept. Bilayer nanofibres containing gallic acid and quercetin were developed to combine antioxidant and antibacterial functions with biocompatibility (Lv et al., 2022). An antioxidative hydrogel based on HT and QGA provided another approach to maintaining local antioxidant activity (Ren et al., 2021). Antioxidant biomaterial design should consider the duration and location of activity, not only the total radical-scavenging capacity measured in solution (Md Fadilah et al., 2023).

5.2 Resolution of inflammation

Kaempferol's suppression of JNK-associated inflammatory injury in fibroblasts provides a direct molecular basis for protecting wound cells (S.-J. Park et al., 2021). Its broader anti-inflammatory effects are supported by studies across several disease models (Alam et al., 2020; Alrumaihi et al., 2024).

Gallic acid may regulate inflammatory cytokines, stress proteins, mitochondrial injury, and fibrosis-related pathways (Yazıcı et al., 2026). When incorporated into hydrogels, it may also provide continued exposure rather than the brief effect expected from a rapidly cleared solution.

Macrophage regulation provides an additional route. Polyphenol-modified dressings have promoted repair-associated macrophage behaviour and remodelling of the wound environment (H. Li et al., 2022). Macrophage-targeted kaempferol nanoparticles demonstrate that selective intracellular delivery is technically possible (Z. Zhang et al., 2026).

5.3 Protection against cellular senescence

Cellular senescence is a state in which damaged cells remain metabolically active but stop dividing and release inflammatory and matrix-degrading factors. Senescent fibroblasts and keratinocytes can contribute to poor tissue repair, especially during ageing, diabetes, and prolonged oxidative stress.

Kaempferol-modified extracellular-vesicle mimetics reduced senescence-associated changes in ultraviolet-injured skin cells and improved collagen and barrier-related outcomes (N. Fu et al., 2026). Although photoaging and chronic wounds are not identical, the shared involvement of oxidative stress, inflammatory signalling, matrix degradation, and cellular senescence makes this evidence relevant.

Gallic acid may also influence stress-induced cellular dysfunction through its effects on mitochondrial and endoplasmic-reticulum pathways (Yazıcı et al., 2026). Evaluation in chronic wound models should include senescence markers, matrix metalloproteinases, and tissue inhibitors of metalloproteinases where appropriate.

5.4 Angiogenesis and vascular repair

Angiogenesis requires coordinated endothelial-cell activation, matrix remodelling, vascular growth-factor signalling, and support from macrophages and fibroblasts (Shi et al., 2023). Both insufficient and poorly organized angiogenesis can impair repair.

Kaempferol improved survival of ischemic skin flaps while reducing inflammation and ferroptosis (A. Wang et al., 2024). The effect suggests preservation of tissue under conditions of limited perfusion. Gallic-acid-containing magnesium frameworks have been designed to support vascular and neurovascular reconstruction in diabetic wounds (Lian et al., 2024; Liu et al., 2025).

An all-natural immunomodulatory hydrogel promoted angiogenesis by regulating macrophage heterogeneity (Y. Fu et al., 2023). This finding illustrates that vascular repair may be improved indirectly through immune regulation. Kaempferol and gallic acid may therefore support angiogenesis by reducing oxidative injury and creating a more favourable inflammatory environment, even when they do not act as direct growth factors.

5.5 Collagen deposition and scar quality

Collagen is essential for wound strength, but its amount and organization must be controlled. Early granulation tissue contains a less mature matrix. Remodelling gradually produces thicker and better aligned fibres. Excessive transforming growth factor activity, prolonged myofibroblast persistence, or uncontrolled matrix production can result in fibrosis.

Kaempferol treatment improved collagen deposition in diabetic infected wounds without acting as a strong direct proliferative stimulant (Al-Ghanayem et al., 2024). Gallic acid affected collagen organization and fibrosis-related pathways in the osteonecrosis model reported by Yazıcı et al. (2026).

A gallic acid nanocrystal hydrogel was developed to promote healing while inhibiting scar formation (Yan et al., 2025). Nanocrystal formation may improve local retention and control release without requiring a large amount of additional carrier material. Long-term assessment of collagen alignment, myofibroblasts, tissue elasticity, and tensile strength is central to determining whether closure results in high-quality repair.

6. Gallic-Acid-Based Wound Dressings

6.1 Chitosan-based systems

Chitosan is widely used in wound materials because it is biodegradable, film-forming, adhesive, and compatible with several active compounds. It may also contribute haemostatic and antibacterial effects.

Gallic acid-loaded chitosan nanoparticles have been incorporated into collagen-fibrin scaffolds to provide a porous wound matrix with controlled active delivery (Kaparekar et al., 2020). Chitosan-copper-gallic acid nanocomposites have combined polymeric support, metal-mediated antimicrobial activity, and phenolic functionality (X. Sun et al., 2020).

Gallic acid has also been chemically grafted to chitosan. A gallic-acid-chitosan/polycaprolactone conjugate was electrospun into nanofibres for wound treatment (Patole et al., 2024). Gallic-acid-grafted chitosan hydrogels containing mineralized copper-sericin nanoparticles were developed for photothermal management of MRSA-infected wounds (L. Li et al., 2024).

A chitosan-gallic acid graft copolymer has further been evaluated for periodontal dressing hydrogel applications (Feng et al., 2023). Periodontal wounds differ from cutaneous wounds because they are exposed to saliva, oral microorganisms, movement, and a highly vascular tissue environment. The study nevertheless supports the adhesive and network-forming value of gallic acid-modified chitosan.

6.2 Alginate-based systems

Alginate forms hydrogels in the presence of suitable ions and is commonly used in absorbent wound dressings. It can maintain a moist environment and can be combined with synthetic polymers to improve mechanical strength.

An alginate hydrocolloid film loaded with gallic acid was developed for chronic wound applications (Gan & Chin, 2021). Gallic acid-loaded sodium alginate and polyvinyl alcohol-co-acrylic acid hydrogel membranes provided another hydrated dressing design (Naeem et al., 2022).

Polyphenol-sodium alginate supramolecular hydrogels have been prepared with antibacterial and anti-inflammatory properties (Chen et al., 2023). Sodium alginate has also been used to deliver plant-polyphenol-functionalized silver nanoparticles to infected wounds (Hu et al., 2023).

Gallic acid and chitosan-silver nanoparticle gel beads have recently been co-encapsulated within sodium alginate and gelatin hydrogels (Z. Sun et al., 2026). This arrangement may permit separation of active domains within the same dressing and may reduce immediate nanoparticle release.

6.3 Polyvinyl alcohol and related films

Polyvinyl alcohol provides flexibility, film-forming ability, and compatibility with freeze-thaw crosslinking. Gallic-acid-functionalized chitosan has been combined with polyvinyl alcohol to prepare hydrogels through repeated freezing and thawing (Cui et al., 2024). The process can create a physical network without high concentrations of chemical crosslinkers.

Polyvinyl alcohol, polyhexamethylene guanidine, and gallic acid have been combined in antibacterial hydrogel films (X. Yang et al., 2021). Polyhexamethylene guanidine contributes strong antimicrobial activity, while gallic acid may add antioxidant and material-interaction properties.

Hydroxypropyl methylcellulose and carboxymethyl starch have also been crosslinked into porous films containing gallic acid (Pitpisutkul & Prachayawarakorn, 2023). Gallic-acid-loaded wound films have undergone further in-vitro and in-vivo evaluation, showing the continued interest in relatively simple and scalable film systems (Yağcılar et al., 2024).

6.4 Electrospun fibres

Electrospinning produces thin fibres with high surface area and a structure that resembles parts of the natural extracellular matrix. Fibre diameter, pore size, alignment, mechanical strength, and wettability can be adjusted through polymer selection and processing.

Gallic-acid-loaded ethylcellulose fibres have been developed as potential wound dressings (Croitoru et al., 2023). Bilayer electrospun dressings containing gallic acid and quercetin have been designed to provide antioxidant, antibacterial, and biocompatible functions (Lv et al., 2022). Gallic-acid-modified chitosan and polycaprolactone nanofibres have also been investigated both in vitro and in vivo (Patole et al., 2024).

The release pattern from fibres depends on drug distribution. Gallic acid located near the fibre surface may be released quickly, whereas drug embedded within the polymer may be released during diffusion and degradation. A bilayer structure can be used to separate immediate and sustained functions.

6.5 Protein-based scaffolds and dressings

Natural proteins can provide cell-binding sites and support tissue interaction. Collagen-fibrin scaffolds containing gallic-acid-loaded chitosan nanoparticles combine a natural provisional-matrix structure with active delivery (Kaparekar et al., 2020).

Gelatin has been used with gallic acid and zinc oxide to prepare a multifunctional bioadhesive (Ramirez-Barron et al., 2020). Silk fibroin and gelatin have also been combined into a gallic-acid-functionalized composite dressing (P. Li et al., 2024). Silk fibroin provides mechanical strength and controllable degradation, while gelatin improves hydration and cell interaction.

An enzymatically crosslinked pectin-silk fibroin hydrogel containing zinc oxide nanoparticles coated or associated with gallic acid has been developed as an injectable, self-healing, and antibacterial dressing (Mashhadi et al., 2026). Enzymatic crosslinking may permit gel formation under mild conditions suitable for biological materials.

6.6 Three-dimensional printed scaffolds

Three-dimensional printing allows control over pore size, layer arrangement, thickness, and overall geometry. A polycaprolactone scaffold can provide durable mechanical support, while hyaluronic acid can improve hydration and biological interaction.

Gallic-acid-enriched polycaprolactone and hyaluronic-acid scaffolds supported dermal-fibroblast viability and proliferation and provided controlled release (Guldorum et al., 2025). This approach may be useful for wounds requiring a stable, porous structure rather than a soft hydrogel alone.

A printed scaffold also offers the possibility of spatially separated delivery. Gallic acid may be concentrated near the wound-contacting surface, while kaempferol-loaded particles could be placed within deeper or slower-degrading regions.

7. Injectable, Self-Healing, and Adhesive Hydrogels

Hydrogels contain a large amount of water within a three-dimensional polymer network. They can cool and hydrate the wound, absorb soluble material, fill irregular spaces, and deliver active compounds. Their properties depend on polymer concentration, crosslinking, pore structure, swelling, and degradation.

An injectable collagen and hyaluronic-acid hydrogel mediated by gallic acid and dopamine was developed with self-healing and antioxidant properties (C. Yang et al., 2023). Dopamine and gallic acid can participate in adhesive and non-covalent interactions, allowing the network to reform after mechanical disruption.

An antioxidative HT/QGA hydrogel has also been proposed for wound treatment (Ren et al., 2021). Polyphenol-driven assembly has been used to construct chitin-polyphenol-metal hydrogels, showing how phenolic compounds can organize polymer and metal components into a functional network (Lin et al., 2022).

Adhesive hydrogels are valuable because wound surfaces are wet and irregular. Strong adhesion can maintain contact and reduce movement. It must still permit removal or controlled degradation without damaging newly formed tissue.

Copper-ion and gallic-acid metal-organic frameworks have been incorporated into an adhesive pomelo-peel sponge for biofilm-infected wounds (J. Yang et al., 2023). The porous plant-derived structure provided a physical framework, while the copper-gallic-acid complex supplied antibacterial and wound-modulating functions.

8. Metal-Phenolic and Nanoparticle Systems

8.1 Copper-containing formulations

Copper participates in angiogenesis and cellular metabolism but becomes toxic at excessive concentrations. It also has antimicrobial activity. Gallic acid can coordinate copper ions and may control their local distribution or release.

Chitosan-copper-gallic acid nanocomposites were among the earlier multifunctional systems in this area (X. Sun et al., 2020). Copper-gallic-acid frameworks have also been incorporated into adhesive sponges for biofilm-infected wounds (J. Yang et al., 2023). Gallic-acid-grafted chitosan hydrogels containing copper-sericin nanoparticles were developed for photothermal MRSA treatment (L. Li et al., 2024).

These formulations combine antimicrobial, photothermal, antioxidant, adhesive, and tissue-supporting effects. Temperature control and copper release are important because excessive heat or ion exposure can damage keratinocytes and endothelial cells.

8.2 Zinc oxide systems

Zinc oxide nanoparticles have antibacterial properties and may influence cell behaviour. Their biological action includes reactive-oxygen-species generation, ion release, and membrane-related effects. These actions can kill microorganisms but may also injure mammalian cells at high concentrations.

A gelatin-gallic acid and zinc oxide composite was developed as a bioadhesive wound dressing (Ramirez-Barron et al., 2020). ZnO@gallic acid nanoparticles have also been embedded in an injectable pectin-silk fibroin hydrogel (Mashhadi et al., 2026).

Gallic acid may modify nanoparticle surfaces, improve dispersion, and influence redox behaviour. Cytocompatibility must be evaluated using the complete formulation at the concentration expected in wound fluid.

8.3 Silver nanoparticle systems

Silver nanoparticles provide broad antimicrobial activity but can be cytotoxic when release is uncontrolled. Polyphenol functionalization can modify nanoparticle formation, stability, and interaction with cells.

An alginate hydrogel loaded with plant-polyphenol-functionalized silver nanoparticles was developed for infected wound treatment (Hu et al., 2023). Gallic acid and chitosan-silver nanoparticle gel beads have also been co-encapsulated within alginate-gelatin hydrogels (Z. Sun et al., 2026).

Encapsulation may reduce direct nanoparticle exposure while permitting antimicrobial silver release. The biological balance should be assessed through bacterial killing, fibroblast and keratinocyte viability, inflammatory responses, and tissue silver measurements.

8.4 Magnesium-gallate systems

Magnesium is involved in cellular metabolism and may support vascular, neural, and tissue-repair functions. Coordination with gallic acid allows the construction of metal-organic frameworks capable of sustained ion and phenolic release.

A magnesium-gallate framework incorporated into a sprayable hydrogel was developed to regulate oxidative stress and promote neurovascular-network reconstruction in diabetic wounds (Lian et al., 2024). Magnesium-ion and gallic-acid frameworks have also been combined with acellular-matrix hydrogels for diabetic wound healing (Liu et al., 2025).

These systems are notable because they address more than bacterial killing. They aim to restore the biological environment required for vascular and neural repair, both of which are impaired in diabetic wounds.

8.5 Photothermal systems

Photothermal materials convert light energy into heat. Controlled heating can disrupt bacterial membranes and biofilms. When used in a wound, the temperature must remain within a range that kills microorganisms without damaging viable tissue.

Gallic-acid-modified bioglass has been developed with combined photothermal and antibacterial effects for infected diabetic wounds (Zeng et al., 2023). Copper-containing gallic-acid systems have also used photothermal activity for MRSA management (L. Li et al., 2024).

Photothermal treatment may be especially useful against biofilms that tolerate conventional antibiotics. It should be combined with precise temperature monitoring and tissue-safety assessment.

9. Kaempferol Delivery Systems

9.1 Hydrogels

A hydrogel can maintain kaempferol at the wound surface and reduce loss during application. Because kaempferol is poorly soluble, the drug may be dispersed, complexed, solubilized, or contained within particles inside the gel.

A pH-sensitive kaempferol hydrogel has been evaluated as a controlled delivery system (Q. Zhang et al., 2022). Wound pH changes with healing status and infection, making pH responsiveness an attractive feature. The formulation should release kaempferol predictably across the pH range expected in acute, chronic, and infected wounds.

9.2 Ethosomes and hybrid vesicles

Ethosomes are phospholipid vesicles containing a relatively high proportion of ethanol. Their flexible structure can improve drug distribution through superficial tissue. Hybrid lecithin-chitosan kaempferol ethosomes have been developed for diabetic foot-ulcer applications (Raghav et al., 2024).

Chitosan can improve adhesion and may add antibacterial support. The vesicles may improve kaempferol dispersion and local retention. Particle size, surface charge, entrapment, release, and stability are important quality attributes.

9.3 Polymeric nanoparticles

Mannose-modified PLGA nanoparticles have been used to deliver kaempferol to macrophages (Z. Zhang et al., 2026). PLGA provides controlled degradation, while mannose groups can promote uptake by cells expressing mannose-recognizing receptors.

A similar system could be adapted for chronic wounds, either as a suspension or within a hydrogel. Targeting should improve intracellular delivery without causing prolonged accumulation of particles or excessive suppression of essential immune functions.

9.4 Extracellular-vesicle mimetics

Kaempferol-modified mesenchymal-stem-cell extracellular-vesicle mimetics have protected fibroblasts and keratinocytes in a photoaging model (N. Fu et al., 2026). Vesicle-like systems can carry lipophilic compounds, interact with cell membranes, and deliver biologically active material.

For wound use, such systems could be incorporated into a protective gel or scaffold. Their manufacture, reproducibility, storage, and biological identity would require careful control.

10. Evidence from Polyphenol-Rich Botanical Preparations

Plant extracts provide useful evidence regarding the wider biological potential of polyphenols. They also demonstrate how extraction and processing affect activity.

Topical *Gynura procumbens* improved wound healing in diabetic mice (Sutthammikorn et al., 2021). The plant contains several bioactive constituents, including flavonoids and phenolic compounds. The findings support the value of multi-target phytochemical activity in diabetic repair.

Compounds obtained from *Dioscorea bulbifera* bulbils showed anti-inflammatory, antioxidant, and wound-healing effects (Chaniad et al., 2020). The work illustrates how isolated plant compounds can connect chemical identity with biological response.

Different extraction methods applied to *Carica papaya* leaves produced different in-vitro wound-healing activities (Soib et al., 2020). This demonstrates that solvent polarity, temperature, and extraction procedure alter the concentration of active constituents.

Drying temperature and solvent selection similarly changed the diabetic wound-healing potential of *Moringa oleifera* leaf extracts (Muzammil et al., 2023). A separate investigation of *Moringa oleifera* seed extract integrated metabolic profiling, molecular analysis, antioxidant testing, and in-vivo repair outcomes (Shady et al., 2022).

A flavonoid-rich fraction from *Dodonaea viscosa* was formulated and evaluated for wound-healing activity (Subramanian et al., 2023). Such studies support the broader pharmacological relevance of flavonoids while emphasizing the value of chemical standardization.

Pomegranate-derived systems are especially relevant to gallic acid and related tannin chemistry. A biointeractive gelatin dressing containing *Punica granatum* extract was developed for wound application (do Nascimento et al., 2020). A polycaprolactone antimicrobial dressing containing pomegranate-peel extract was subsequently prepared and characterized (Y.-Z. Wang et al., 2023).

The biological activity of a plant extract reflects many constituents acting together. Purified kaempferol and gallic acid studies are therefore necessary when the objective is to establish compound-specific pharmacology.

11. Related Flavonoids and Polyphenol Combinations

Studies of related polyphenols provide useful comparisons for designing kaempferol and gallic acid systems.

Rutin and quercetin have been evaluated alone and with gentamicin in diabetic excision wounds. The investigation included antibacterial, antibiofilm, and wound-healing outcomes (Almuhanna et al., 2024). The work demonstrates how a polyphenol can be combined with a conventional antimicrobial and assessed for interaction rather than being treated only as an antioxidant supplement.

Resveratrol, dihydroquercetin, and dihydromyricetin have shown in-vivo antimicrobial and wound-healing activity against *S. aureus*, *P. aeruginosa*, and *Candida albicans* (Shevelev et al., 2020). This supports the concept that structurally different polyphenols can act against both bacterial and fungal wound organisms.

Apigenin has shown anti-inflammatory and skin-protective effects in mast cells, macrophage-like cells, and HaCaT keratinocytes (C.-H. Park et al., 2020). These cell-specific findings illustrate the importance of studying a flavonoid across immune and skin-cell populations.

Flavonoid-focused reviews have described their ability to influence nuclear factor kappa B, mitogen-activated protein kinases, antioxidant response systems, vascular growth, collagen formation, and epithelial repair

(Zulkefli et al., 2023). Kaempferol should be placed within this broader flavonoid context while retaining attention to its individual chemical and pharmacological behaviour.

12. Comparative Roles of Kaempferol and Gallic Acid

Kaempferol and gallic acid overlap in antioxidant, anti-inflammatory, and antimicrobial activity. Their most useful differences lie in solubility, material interaction, cellular targeting, and delivery requirements.

Kaempferol is well suited to intracellular pharmacological action. It can influence stress kinases, inflammatory pathways, cellular senescence, lipid peroxidation, ferroptosis, and macrophage behaviour. Its low water solubility favours delivery through vesicles, polymeric nanoparticles, nanocrystals, or mixed carrier systems.

Gallic acid is well suited to the hydrated wound interface. It can interact with polymers, proteins, and metals. It may participate in crosslinking, adhesion, nanoparticle stabilization, and supramolecular assembly while also providing antioxidant and antibacterial activity.

A combined system could be designed around these roles. Gallic acid may be distributed within the hydrogel or scaffold matrix, where it contributes to early surface activity and material performance. Kaempferol may be loaded into vesicles or particles dispersed throughout the same matrix, providing slower and more sustained release.

The timing of release may be important. An infected wound initially requires rapid control of microbial burden and excessive oxidation. Later phases require protection of fibroblasts and endothelial cells, resolution of inflammation, and organized remodelling. A formulation with an early gallic-acid release and a sustained kaempferol release may reflect this sequence.

A second possibility is spatial separation. Gallic acid may be concentrated in the outer or wound-contacting layer of a film or fibre, while kaempferol is retained within a deeper layer. Bilayer fibres containing gallic acid and quercetin already demonstrate the feasibility of separating polyphenol functions within a dressing (Lv et al., 2022).

13. Pharmacological Evaluation of a Kaempferol–Gallic Acid System

13.1 Identity and purity

Kaempferol and gallic acid should be chemically identified and assessed for purity before formulation. Chromatographic methods can confirm purity and support quantitative analysis. Infrared spectroscopy, thermal analysis, ultraviolet-visible spectroscopy, and mass spectrometry can provide additional confirmation.

The compounds should be tested for stability under light, oxygen, temperature, and different pH conditions. Stability in the final formulation is more important than stability of the dry compound alone.

13.2 Solubility and compatibility

Kaempferol solubility should be measured in water, buffers, oils, surfactants, co-solvents, phospholipid systems, and candidate polymer dispersions. Gallic acid solubility should be assessed across the same wound-relevant pH range.

Compatibility studies should determine whether gallic acid alters kaempferol solubility, crystallinity, oxidation, or release. Strong binding to the polymer may reduce the free concentration of either compound. Differential scanning calorimetry, X-ray diffraction, infrared spectroscopy, and chromatographic stability testing can help identify such changes.

13.3 Formulation characterization

Hydrogels should be evaluated for pH, viscosity, flow behaviour, spreadability, gel strength, swelling, degradation, adhesion, injectability, and water-vapour transmission. Films require thickness, weight uniformity, mechanical strength, flexibility, moisture uptake, and permeability. Vesicles and nanoparticles require particle size, distribution, surface charge, morphology, entrapment, loading, and storage stability.

Three-dimensional scaffolds require pore size, porosity, layer integrity, mechanical properties, fluid uptake, degradation, and cell penetration. Electrospun materials require fibre diameter, alignment, pore structure, wettability, and residual-solvent assessment.

13.4 Release and wound retention

Kaempferol and gallic acid must be quantified separately. A single total-polyphenol value cannot establish the release of two chemically distinct compounds.

Release testing should be performed under conditions that maintain adequate solubility in the receptor medium. Wound-relevant pH values should be included. The amount retained within skin or wound tissue should also be measured because release into an external medium does not necessarily represent local tissue availability.

The objective may be a biphasic profile: early gallic acid release followed by sustained kaempferol delivery. The profile should remain reproducible between batches.

13.5 Keratinocyte and fibroblast safety

Human keratinocytes and dermal fibroblasts should be exposed to each compound, the combination, the blank carrier, and the complete formulation. Testing at 24, 48, and 72 hours can identify immediate and delayed effects.

Metabolic viability assays should be supported by membrane-integrity or live-dead analysis because polyphenols may interact with assay reagents. Cell morphology should be documented. A concentration that is antibacterial but strongly cytotoxic to keratinocytes or fibroblasts is unsuitable for wound treatment.

13.6 Cell migration

Keratinocyte and fibroblast migration can be studied through scratch assays or other controlled migration systems. Image analysis should measure closure at predetermined times. The effect of proliferation can be separated from migration through suitable experimental conditions.

Kaempferol may improve migration indirectly by reducing oxidative and inflammatory damage. Gallic acid may support cell behaviour when released at a controlled concentration from a compatible matrix.

13.7 Oxidative-stress testing

Chemical antioxidant assays may be used for preliminary comparison, but cell-based assessment is more informative. Keratinocytes and fibroblasts may be exposed to high glucose, hydrogen peroxide, hypoxia-reoxygenation, ultraviolet injury, or bacterial products.

Intracellular reactive oxygen species, glutathione, superoxide dismutase, catalase, lipid peroxidation, mitochondrial membrane potential, and oxidative DNA damage may be assessed. Ferroptosis-related markers are particularly relevant to kaempferol because of its reported effect on skin-flap survival (A. Wang et al., 2024).

13.8 Inflammatory pathways

Fibroblasts, keratinocytes, and macrophages may be stimulated with wound-relevant inflammatory agents. Tumour necrosis factor-α, interleukin-1β, interleukin-6, chemokines, nuclear factor kappa B, JNK, and other stress-associated pathways can be measured.

JNK deserves particular attention because kaempferol suppressed JNK-associated fibroblast inflammation (S.-J. Park et al., 2021). Endoplasmic-reticulum and mitochondrial stress markers are relevant to gallic acid based on the findings of Yazıcı et al. (2026).

13.9 Macrophage responses

Macrophages should be assessed for cytokine production, phagocytosis, oxidative activity, surface markers, and repair-associated mediators. The purpose is not simply to classify cells into two fixed categories. The treatment should reduce prolonged inflammatory activity while preserving microbial clearance and supporting later repair.

Kaempferol-loaded mannose-targeted nanoparticles provide a useful model for macrophage-directed delivery (Z. Zhang et al., 2026). A wound formulation may not require systemic macrophage targeting, but local uptake by wound macrophages could support therapeutic activity.

13.10 Antibacterial testing

The free compounds and formulation should be tested against common wound organisms. Minimum inhibitory concentration, minimum bactericidal concentration, time-kill behaviour, and direct-contact activity should be measured.

For solid or semisolid dressings, agar diffusion should not be used as the only test because a small zone may reflect slow release rather than weak activity. Quantitative viable counts are more informative.

13.11 Antibiofilm testing

Biofilms should be allowed to form before treatment. Biomass, metabolic activity, viable bacterial counts, and microscopic structure can then be assessed.

Single-species models provide initial information, but mixed-species systems more closely reflect chronic wounds. Kaempferol, gallic acid, and the combination should be compared at matched concentrations. Interaction analysis can determine whether the combined effect is additive or greater than expected from either compound alone.

The rutin-quercetin and gentamicin study provides a useful comparative model for evaluating interactions among polyphenols and antimicrobial agents (Almuhanna et al., 2024).

13.12 Angiogenesis

Endothelial-cell viability, migration, and tube formation may be assessed in vitro. In tissue, vascular density, vessel maturity, endothelial markers, and functional perfusion should be evaluated.

Angiogenic interpretation should consider macrophage responses and oxidative control. Improved vascular growth may arise indirectly from reduced inflammation and protection of endothelial cells.

13.13 Collagen and remodelling

Fibroblast collagen production, matrix-metalloproteinase activity, tissue inhibitors of metalloproteinases, myofibroblast markers, and transforming growth factor signalling may be measured.

Histological assessment should examine collagen amount, fibre arrangement, granulation-tissue maturity, epithelial thickness, and scar architecture. Mechanical testing can determine whether the repaired tissue has regained strength.

13.14 In-vivo wound models

A healthy excision model can establish local safety and basic activity. A diabetic wound model provides stronger relevance to the proposed application. Infection may be introduced using a controlled bacterial inoculum after the basic dose range has been established.

Splinted rodent wounds can reduce contraction and place greater emphasis on re-epithelialization. Treatment groups should include vehicle, kaempferol alone, gallic acid alone, combination treatment, and an appropriate standard treatment.

Wound area should be recorded over time using standardized imaging. Histology, bacterial burden, oxidative markers, cytokines, collagen, vascularity, epithelialization, and tissue strength should be assessed. Continued observation after closure will provide information about scar quality and recurrence.

14. Pharmaceutical and Translational Considerations

14.1 Local delivery and systemic exposure

Topical administration aims to achieve a high local concentration with limited systemic exposure. The amount absorbed into blood still requires assessment, particularly after repeated application to large or deeply damaged wounds.

Kaempferol undergoes substantial metabolism after oral exposure, which contributes to limited systemic availability of the unchanged compound (Rudrapal et al., 2024). Topical delivery may increase local exposure to the parent compound. Gallic acid is smaller and more water soluble and may leave a simple formulation more rapidly.

14.2 Dose selection

Dose should be expressed in relation to wound area and formulation mass or volume. Reporting only the percentage within a formulation can make comparison difficult.

A dose-response study should identify the lowest concentration providing consistent biological activity without cell toxicity. Polyphenols may show different effects at low and high concentrations. More active compound does not necessarily produce better healing.

14.3 Sterilization

A wound dressing must be microbiologically suitable. Heat, radiation, filtration, or chemical sterilization may alter polymers and polyphenols. Sterilization should therefore be selected according to dosage form and followed by chemical and physical reassessment.

Kaempferol and gallic acid content, degradation products, release, mechanical behaviour, particle size, and biological activity should be compared before and after sterilization.

14.4 Storage stability

Stability studies should monitor appearance, pH, viscosity, drug content, degradation, microbial quality, release, and mechanical behaviour. Protection from light and oxygen may be required.

A combined formulation should be assessed for interaction during storage. Gallic acid may alter pH, while kaempferol may crystallize if its carrier becomes unstable.

14.5 Choice of dosage form

The wound type should guide formulation design. A highly exudative wound may require an absorbent fibre, foam, alginate, or porous scaffold. A dry wound may benefit from a hydrogel. An irregular cavity may require an injectable or sprayable material. A superficial wound may be suitable for a thin film.

No single dosage form will be ideal for all wounds. The formulation should match exudate level, depth, infection status, tissue fragility, and frequency of dressing change.

15. Future Research Directions

The most promising direction is a dual-delivery system that respects the distinct pharmaceutical behaviour of each compound. A gallic-acid-containing hydrogel, fibre, or scaffold could provide hydration, adhesion, antioxidant activity, and early antibacterial action. Kaempferol-loaded vesicles or nanoparticles could provide sustained intracellular protection.

Macrophage-focused studies are also important. Kaempferol has already been delivered selectively to macrophages, while polyphenol-containing materials have influenced repair-associated macrophage states (H. Li et al., 2022; Z. Zhang et al., 2026). Combining local delivery with macrophage regulation may be particularly valuable in diabetic wounds.

Cellular senescence deserves greater attention. Kaempferol-based vesicle mimetics have reduced senescence and matrix degradation in stressed skin cells (N. Fu et al., 2026). Chronic wounds also contain senescent or poorly functioning cells. Measuring senescence-associated pathways could help explain why some treatments improve tissue quality even without directly increasing proliferation.

Neurovascular restoration is another important area. Diabetic wounds are affected by both vascular impairment and neuropathy. Magnesium-gallate systems designed to support neurovascular reconstruction indicate that wound materials can be developed beyond simple moisture control or bacterial killing (Lian et al., 2024).

Scar prevention should be integrated into treatment design from the beginning. Gallic acid nanocrystal hydrogels provide a model for combining closure with scar control (Yan et al., 2025). Kaempferol's anti-inflammatory and anti-ferroptotic effects may also support more orderly tissue repair.

Human-relevant test systems will improve the value of future research. Primary diabetic keratinocytes and fibroblasts, organotypic skin models, human wound fluid, and mixed-species biofilms can provide information that standard cell lines and simple bacterial suspensions cannot.

16. Conclusion

Kaempferol and gallic acid act on several biological processes involved in wound healing. Kaempferol provides anti-inflammatory, antioxidant, antibacterial, anti-senescent, macrophage-regulating, and anti-ferroptotic activity. Its wound-healing effects appear to arise largely from protection of viable tissue and correction of the hostile wound environment. Gallic acid combines antioxidant, antibacterial, anti-inflammatory, and tissue-protective actions with valuable material properties. It can interact with polymers, proteins, nanoparticles, and metals and has therefore been incorporated into a wide variety of wound dressings.

Gallic acid is especially suitable for hydrogels, films, fibres, scaffolds, and adhesive wound interfaces. Kaempferol is more likely to benefit from vesicular, nanoparticulate, or other solubilizing carriers. Their pharmaceutical differences provide a clear basis for combined delivery.

A carefully designed kaempferol and gallic acid formulation could address microbial burden, excessive oxidative stress, prolonged inflammation, cellular injury, impaired vascular repair, and abnormal matrix remodelling. The strongest design would provide controlled and possibly sequential release, maintain keratinocyte and fibroblast safety, regulate macrophage responses, inhibit established biofilms, and improve both wound closure and tissue quality.

The pharmacological value of this combination should be established through direct comparison of each compound and the combined system. When supported by controlled formulation development and wound-relevant biological evaluation, kaempferol and gallic acid offer a strong foundation for a multifunctional topical treatment for diabetic, infected, and difficult-to-heal wounds.

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