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Flavonoids In Wound Healing

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Abstract: Flavonoids, abundant polyphenolic compounds in plants, exhibit remarkable potential in wound healing through their multifaceted actions on key phases of repair: hemostasis, inflammation, proliferation, and remodeling. Their therapeutic effects arise primarily from potent antioxidant properties neutralizing reactive oxygen species (ROS), upregulating enzymes such as SOD, CAT, and GPx, and activating the master regulator Nrf2/ARE pathway to mitigate oxidative stress alongside robust anti-inflammatory activities via inhibition of NF-κB, MAPK/ERK, COX-2, and pro-inflammatory cytokines (TNF-α, IL-6, IL-1β). Additional benefits include promotion of angiogenesis (via upregulation of VEGF, bFGF, TGF-β), re-epithelialization, collagen synthesis, extracellular matrix remodeling, and antimicrobial action against common wound pathogens. Preclinical evidence, predominantly from animal models of acute, burn, and diabetic wounds, demonstrates that prominent flavonoids (e.g., quercetin, kaempferol, curcumin, rutin) accelerate closure, enhance granulation tissue formation, and reduce scarring. However, challenges such as poor solubility and bioavailability are being addressed through advanced formulations, including hydrogels, nanoparticles, nanogels, and composite dressings, which enable sustained release, improved penetration, and superior outcomes in diabetic wound models (e.g., >90% closure in 14 days in some studies).While clinical translation remains limited, emerging data support flavonoids as safe, multi-target natural agents, particularly for managing chronic non-healing wounds dominated by persistent inflammation and oxidative stress. This review highlights underlying pathways, key compounds, formulation advances, and future directions for harnessing flavonoids in wound therapeutics.

Keywords: Flavonoids, Wound healing, pathway

Introduction:

Flavonoids, a diverse group of polyphenolic compounds abundant in plants, have gained significant attention for their multifaceted role in wound healing. Their therapeutic potential stems from potent antioxidant, anti-inflammatory, antimicrobial, pro-angiogenic, and collagen-promoting activities, which collectively modulate all major phases of wound repair: hemostasis, inflammation, proliferation, and remodeling. These properties make flavonoids particularly valuable for managing acute wounds, chronic wounds (such as diabetic ulcers), and burn injuries, often outperforming conventional treatments in preclinical models when formulated appropriately (e.g., hydrogels, nanoparticles, or ointments).

Mechanisms of Flavonoids in Wound Healing

Flavonoids exert their effects through multiple interconnected pathways:

Antioxidant activity: They neutralize reactive oxygen species (ROS), upregulate endogenous antioxidant enzymes (SOD, CAT, GPx), and activate the Nrf2/ARE pathway, thereby reducing oxidative damage that delays healing (Carvalho et al., 2021; Al-Rekabi et al., 2023).

ROS (Reactive Oxygen Species) are highly reactive oxygen-containing molecules, including superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radical (•OH). In wound healing, ROS exhibit a dual (biphasic) role (Deng et al., 2024; Li et al., 2023; Wilkinson & Hardman, 2024):

Beneficial at physiological/low-to-moderate levels (especially in the early inflammatory phase): They serve as signaling molecules to recruit immune cells, promote antimicrobial defense via respiratory burst in phagocytes, stimulate angiogenesis (e.g., via VEGF), enhance fibroblast proliferation, support collagen synthesis, and facilitate extracellular matrix remodeling (Deng et al., 2024; Li et al., 2023).

Detrimental when excessive or prolonged: Leading to oxidative stress (OS), which causes lipid peroxidation, protein oxidation, DNA damage, prolonged inflammation, impaired re-epithelialization, reduced angiogenesis, increased apoptosis, and chronic non-healing wounds (e.g., diabetic ulcers) (Wilkinson & Hardman, 2024; Ju et al., 2023).

Precise spatiotemporal regulation of ROS is essential for smooth progression through hemostasis, inflammation, proliferation, and remodeling phases.

Antioxidant Enzymes: SOD, CAT, GPx

These form the primary enzymatic antioxidant defense cascade to maintain redox homeostasis by detoxifying ROS sequentially (Deng et al., 2024; Li et al., 2023; Soares et al., 2021):

SOD (Superoxide Dismutase)*:* The frontline enzyme that dismutates superoxide: $2O_2^- + 2H^+ \rightarrow H_2O_2 + O_2$ Preventing superoxide from forming damaging species like peroxynitrite. Isoforms include Cu/Zn-SOD (cytosolic), Mn-SOD (mitochondrial, often induced in hypoxic wounds), and extracellular SOD. Activity often decreases in chronic wounds, exacerbating OS (Deng et al., 2024).

CAT (Catalase)*:* Primarily peroxisomal; decomposes H_2O_2: $2H_2O_2 \rightarrow 2H_2O + O_2$ Blocking Fenton-mediated •OH generation. Critical in high-ROS wound microenvironments to limit peroxide buildup (Soares et al., 2021; Long et al., 2019).

GPx (Glutathione Peroxidase): Selenoenzymes (e.g., GPx1–4) reduce H_2O_2 and lipid hydroperoxides using GSH: $H_2O_2 + 2GSH \rightarrow GSSG + 2H_2O$ Protecting membranes from lipid peroxidation; GSSG is recycled by glutathione reductase. Often depleted in wounds, contributing to sustained OS (Deng et al., 2024; Brigelius-Flohé & Maiorino, 2013).

These enzymes synergize: SOD produces H_2O_2, which CAT/GPx eliminate, averting oxidative cascades. Induction (e.g., via Nrf2 or flavonoids) mitigates OS, shortens inflammation, boosts granulation, collagen deposition, and accelerates closure (Soares et al., 2021; Al-Rekabi et al., 2023).

Nrf2/ARE Pathway:

The Nrf2/ARE pathway is the master regulator of adaptive antioxidant responses to oxidative/electrophilic stress (Soares et al., 2021; Long et al., 2019; Carvalho et al., 2021).

- *Nrf2* (Nuclear factor erythroid 2-related factor 2) is a Cap 'n' Collar bZIP transcription factor.
- In basal conditions, *Keap1* binds Nrf2 in the cytoplasm, promoting ubiquitination and proteasomal degradation.
- Oxidative stress (e.g., ROS) or electrophiles modify Keap1 cysteines, disrupting binding; Nrf2 accumulates, translocates to the nucleus, heterodimerizes with small Maf, and binds *ARE* (Antioxidant Response Element) sequences (e.g., 5'-RTGACNNNGC-3') in target promoters.
- This induces >1000 cytoprotective genes, including antioxidant enzymes (SOD, CAT, GPx, HO-1, NQO1), GSH synthesis (GCL), and others (ferritin) (Soares et al., 2021; Tonelli et al., 2018).

Significance in OS and Wound Healing:

Nrf2 senses wound-site ROS and activates defenses, restoring redox balance and preventing damage (Soares et al., 2021; Long et al., 2019). Promotes inflammatory-to-proliferative transition by reducing NF-κB-driven inflammation, supporting TGF-β granulation, VEGF angiogenesis, keratinocyte/fibroblast migration/proliferation, and anti-apoptosis (Wilkinson & Hardman, 2024; Zhao et al., 2016). In chronic/diabetic wounds, Nrf2 impairment sustains OS/inflammation and delays healing; Nrf2 knockout slows closure, while activation (e.g., DMF, sulforaphane) accelerates it via upregulated SOD/CAT/GPx/HO-1 (Rabbani et al., 2018; Li et al., 2022). Flavonoids (e.g., quercetin, curcumin, xanthohumol, rutin) activate Nrf2/ARE (via Keap1 modification, MAPK/PI3K/PKC, or GSK3 inhibition), enhancing enzyme expression and multi-target protection for wound healing (Al-Rekabi et al., 2023; Li et al., 2022; Carvalho et al., 2021). Targeting Nrf2/ARE (e.g., via flavonoids or activators) harnesses endogenous defenses for chronic wound therapy.

Anti-inflammatory effects: Flavonoids inhibit NF-κB, MAPK/ERK, COX-2, and pro-inflammatory cytokines (TNF-α, IL-6, IL-1β), attenuating excessive inflammation and promoting transition to the proliferative phase (Al-Rekabi et al., 2023; Carvalho et al., 2021).

NF-κB, MAPK/ERK, COX-2, and Pro-Inflammatory Cytokines (TNF-α, IL-6, IL-1β) play central roles in the inflammatory phase of wound healing. While essential for initiating repair (e.g., pathogen clearance, immune cell recruitment), their excessive or prolonged activation contributes to chronic inflammation, delayed healing, and non-healing wounds (e.g., diabetic ulcers) (Al-Rekabi et al., 2023; Deng et al., 2024; Wilkinson & Hardman, 2024).

NF-κB Pathway

NF-κB (Nuclear Factor Kappa B) is a key transcription factor family that acts as a master regulator of inflammation. In response to injury signals (e.g., ROS, cytokines, PAMPs), NF-κB translocates to the nucleus, binding promoters of pro-inflammatory genes (Soares et al., 2021; Al-Rekabi et al., 2023).

Role in wound healing: Early activation drives cytokine/chemokine production (TNF-α, IL-1β, IL-6), adhesion molecules, and enzymes (e.g., COX-2, iNOS) to amplify inflammation, recruit neutrophils/macrophages, and promote transition to proliferation (Deng et al., 2024; Li et al., 2023). In chronic wounds, sustained NF-κB activity perpetuates M1 macrophage polarization, excessive cytokine release, impaired angiogenesis, and fibrosis (Al-Rekabi et al., 2023; Zhao et al., 2016).

Significance: Dysregulated NF-κB delays the inflammatory-to-proliferative shift, reducing growth factor expression (e.g., VEGF, TGF-β) and tissue regeneration.

MAPK/ERK Pathway

MAPK (Mitogen-Activated Protein Kinase) pathways, including **ERK** (Extracellular Signal-Regulated Kinase), **p38**, and **JNK**, are serine/threonine kinases activated by upstream signals (e.g., growth factors, stress, cytokines) (Wilkinson & Hardman, 2024; Long et al., 2019).

ERK subfamily: Promotes cell proliferation, migration (keratinocytes/fibroblasts), and re-epithelialization; ERK activation supports wound closure but can be dysregulated in chronic settings (Al-Rekabi et al., 2023).

Role in inflammation: MAPK/ERK crosstalk with NF-κB; phosphorylation cascades amplify pro-inflammatory gene expression (e.g., via AP-1 transcription factor) and cytokine production (TNF-α, IL-6) (Deng et al., 2024; Ju et al., 2023).

Significance: In wounds, balanced MAPK activity aids repair; excessive activation sustains inflammation, while inhibition (e.g., by natural compounds) promotes M2 macrophage polarization and resolution (Soares et al., 2021).

COX-2

COX-2 (Cyclooxygenase-2) is an inducible enzyme that catalyzes prostaglandin synthesis (e.g., PGE_2) from arachidonic acid.

Role in wound healing: Upregulated early by NF-κB/MAPK in response to cytokines/injury; PGE_2 promotes vasodilation, leukocyte recruitment, and pain/inflammation signaling (Al-Rekabi et al., 2023; Deng et al., 2024).

Significance: Transient COX-2 aids acute inflammation; persistent elevation in chronic wounds exacerbates edema, prolongs neutrophil influx, and delays resolution (Wilkinson & Hardman, 2024).

Pro-Inflammatory Cytokines: TNF-α, IL-6, IL-1β

These cytokines are rapidly released by neutrophils, macrophages, and keratinocytes post-injury. *TNF-α* (Tumor Necrosis Factor-α): Amplifies inflammation via NF-κB activation, induces adhesion molecules, promotes MMP production, and recruits immune cells; excessive levels cause tissue damage and chronicity (Deng et al., 2024; Li et al., 2023). *IL-6* (Interleukin-6): Dual role—early: drives acute inflammation and immune recruitment; later: supports transition to repair (e.g., fibroblast activation); sustained high levels correlate with poor healing (Al-Rekabi et al., 2023). *IL-1β* (Interleukin-1 Beta): Stimulates neutrophil influx, fever, and further cytokine cascades; overproduction sustains M1 macrophages and inhibits resolution (Wilkinson & Hardman, 2024). These mediators interconnect: Cytokines activate NF-κB/MAPK, which upregulate more cytokines and COX-2 in a feed-forward loop (Soares et al., 2021; Carvalho et al., 2021).

Modulation by Flavonoids in Wound Healing

Flavonoids (e.g., quercetin, kaempferol, curcumin) inhibit these pathways, attenuating excessive inflammation:

Suppress NF-κB activation (via IκB stabilization, reduced p65 translocation) → ↓ TNF-α, IL-6, IL-1β, COX-2 (Al-Rekabi et al., 2023; Carvalho et al., 2021). Inhibit MAPK/ERK phosphorylation (p38, JNK, ERK) → reduced cytokine/mediator production and promoted M2 polarization (Lodhi et al., 2023). Downregulate COX-2 expression and PGE_2 → lessened vascular permeability and chronic inflammation (Al-Rekabi et al., 2023). This multi-target suppression shortens inflammation, enhances proliferation (angiogenesis, collagen synthesis), and accelerates closure in models of acute/chronic wounds (Al-Rekabi et al., 2023; Li et al., 2022). Like that Angiogenesis and GFS, Re-epithelialization, collagen synthesis and Antimicrobial action of flavonoids play crucial role in wound healing. Angiogenesis and growth factor stimulation: They upregulate VEGF, bFGF, TGF-β, and COL3A expression, enhancing new blood vessel formation, fibroblast migration, and collagen deposition (Al-Rekabi et al., 2023; Lodhi et al., 2023). Re-epithelialization and collagen synthesis: Flavonoids promote keratinocyte and fibroblast proliferation/migration, increase hydroxyproline content, and modulate MMPs/TIMPs balance for balanced extracellular matrix remodeling (Lodhi et al., 2023; Carvalho et al., 2021). Antimicrobial action: Many flavonoids (especially in combination) inhibit common wound pathogens like *S. aureus* and *P. aeruginosa*, reducing infection risk (Suntres et al., 2022; Al-Rekabi et al., 2023).

These mechanisms often involve crosstalk among pathways such as PI3K/Akt, Wnt/β-catenin, TGF-β/Smad, JNK, and Hedgehog signaling (Al-Rekabi et al., 2023; Carvalho et al., 2021).

Prominent Flavonoids and Their Evidence in Wound Healing

Quercetin: Widely studied flavonol; accelerates wound closure in diabetic models via enhanced angiogenesis, reduced oxidative stress, and fibroblast proliferation. Nano-formulations significantly improve bioavailability and efficacy (Hegde et al., 2022; Wang et al., 2022; Al-Rekabi et al., 2023).

Kaempferol — Promotes collagen synthesis, VEGF/bFGF expression, and rapid epithelialization; shows strong effects in excision and diabetic wound models (Lodhi et al., 2023; Al-Rekabi et al., 2023).

Curcumin: Exhibits synergistic effects with quercetin; reduces inflammation, stimulates migration, and combats infection. Often used in combination formulations for enhanced wound contraction (Suntres et al., 2022; Wang et al., 2022).

Rutin: Supports re-epithelialization and tensile strength; effective in burn and excision models, often combined with quercetin (Al-Rekabi et al., 2023).

Other notable flavonoids: Hesperidin, naringenin, luteolin, apigenin, and myricetin show promising anti-inflammatory, antioxidant, and pro-regenerative effects, frequently incorporated into advanced delivery systems (Lodhi et al., 2023; Carvalho et al., 2021).

Advanced Formulations Enhancing Flavonoid Delivery

Poor solubility and bioavailability limit the clinical translation of flavonoids. Recent advances focus on:

Hydrogels: Self-healing, antioxidant, and thermo-sensitive hydrogels loaded with flavonoids (or combinations like quercetin + curcumin) promote sustained release, hydration, and full-thickness regeneration in diabetic wounds (Zeng et al., 2025; Lodhi et al., 2023).

Nanoparticles and nanogels: Flavonoid-loaded nanoparticles (e.g., ZIF-8, silver, or collagen-based) enhance penetration, targeted delivery, and antimicrobial activity while accelerating granulation tissue formation (Kusnadi et al., 2024; Al-Rekabi et al., 2023).

Composite dressings: Flavonoid-rich fractions in ethyl acetate extracts or combined with polymers show superior wound contraction, collagen deposition, and upregulation of COL3A/VEGF/bFGF compared to controls (Lodhi et al., 2023).

Preclinical studies (mostly animal excision, incision, and diabetic wound models) consistently demonstrate faster closure rates (often 80–93% within 14 days), improved histopathology, and reduced scarring (Zeng et al., 2025; Lodhi et al., 2023). Clinical evidence remains limited but emerging, with promising results in topical flavonoid applications for chronic wounds.

Conclusion

Flavonoids represent a safe, multi-target, natural strategy for wound healing, particularly in chronic and diabetic cases where inflammation and oxidative stress predominate. Ongoing research into optimized nano- and hydrogel-based formulations is bridging the gap toward clinical translation, offering potential alternatives or adjuncts to existing therapies.

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