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Velutin: A Natural Flavonoid with Emerging Potential in Wound Healing

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Abstract

Wound Although the biological process of healing is intricate and tightly controlled, chronic and non-healing wounds continue to pose a significant clinical challenge, impacting millions of patients globally and putting a significant financial strain on healthcare systems. Prolonged inflammation, poor angiogenesis, oxidative stress, microbial colonization, and dysregulated protease activity are some of the factors that lead to delayed wound healing, especially in older and diabetic populations. Because of its strong anti-inflammatory, antibacterial, antioxidant, and pro-angiogenic qualities, velutin, a naturally occurring flavonoid, has garnered more and more interest for use in wound healing applications. Poor aqueous solubility, low absorption, and insufficient retention at the wound site hinder velutin's clinical translation despite its therapeutic potential. Thermosensitive hydrogels have emerged as an advanced drug delivery platform capable of overcoming these limitations by providing in situ gelation, sustained drug release, enhanced wound residence time, and a moist, protective healing environment. This review highlights the pathophysiology of chronic wounds, the pharmacological potential of velutin in wound repair, and the advantages of thermosensitive hydrogel systems as wound dressings. Emphasis is placed on the synergistic integration of velutin with thermoresponsive hydrogels as a promising strategy to improve therapeutic efficacy, patient compliance, and overall wound healing outcomes.

Keywords

Wound healing; Chronic wounds; Velutin; Flavonoids; Thermosensitive hydrogel; Drug delivery system; Controlled release; Tissue regeneration

1. INTRODUCTION

Although wound healing is a basic biological process that is necessary to restore tissue integrity after an injury, complex and chronic wounds continue to provide major clinical practice challenges. These injuries have a significant financial impact on healthcare systems and impact millions of patients globally. The aging of the world's population, the prevalence of diabetes, and cardiovascular diseases have all significantly increased the incidence of poor wound healing. Because they don't go through the typical healing phases, chronic wounds—like diabetic foot ulcers, pressure ulcers, venous leg ulcers, and surgical site infections—are especially troublesome. They are frequently characterized by oxidative stress, excessive protease activity, prolonged inflammation, poor angiogenesis, and persistent microbial colonization, which can result in serious consequences like infection, limb amputation, and higher mortality.

Despite the availability of various wound management strategies, including conventional dressings, topical antibiotics, and growth factor-based therapies, treatment outcomes remain suboptimal for many patients with chronic wounds. These approaches frequently suffer from limitations such as inadequate drug penetration, rapid clearance from the wound site, systemic adverse effects, and the growing concern of antimicrobial resistance. Moreover, the dynamic and hostile wound microenvironment—marked by fluctuating pH, moisture, temperature, and enzymatic activity—poses significant challenges to

maintaining effective local concentrations of therapeutic agents. In order to facilitate effective tissue repair, sophisticated wound care devices that not only shield the wound bed but also gradually and carefully provide bioactive substances are desperately needed.

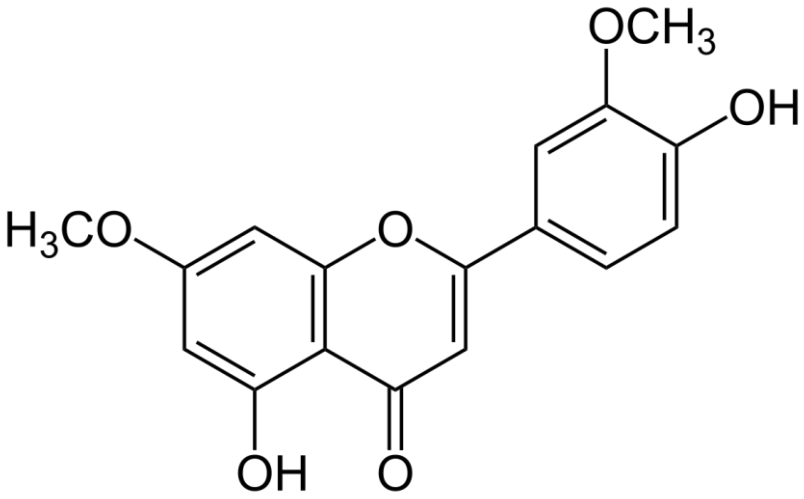
Natural Because of their wide range of pharmacological actions and advantageous safety profiles, bioactive chemicals have drawn more and more attention in the study of wound healing. Among these, velutin—a naturally occurring flavonoid obtained from a variety of plant sources—has shown promise as a wound treatment agent. By inhibiting important inflammatory mediators such nuclear factor-kappa B (NF-κB), cyclooxygenase-2 (COX-2), and pro-inflammatory cytokines like tumor necrosis factor-α and interleukin-1β, velutin demonstrates strong anti-inflammatory actions. Velutin also exhibits potent antioxidant qualities that shield healing tissues from oxidative damage and broad-spectrum antibacterial activity against common wound infections.

Its potential function in hastening wound closure and tissue regeneration is further highlighted by its capacity to promote angiogenesis through the activation of vascular endothelial growth factor and to increase collagen formation. However, velutin's poor aqueous solubility, low bioavailability, fast degradation, and inadequate retention at the wound site severely restrict its therapeutic use despite these advantageous biological characteristics.

Advanced drug delivery methods have been investigated to address these issues; thermosensitive hydrogels have shown particular promise as a platform for wound dressing applications. Thermosensitive hydrogels are clever polymeric systems that respond to temperature changes by going through a reversible sol–gel transition. This allows for simple liquid application and in situ gelation at physiological temperature. In addition to facilitating gas exchange and serving as a physical barrier against microbial invasion, these hydrogels offer a moist and protective wound environment that permits localized and prolonged medication release. By minimizing the need for frequent dressing changes, the rk structure of these hydrogels enables adjustment of release kinetics and improved patient compliance.

The pathogenesis of chronic wounds, the therapeutic potential of velutin in wound healing, and the function of thermosensitive hydrogels as cutting-edge wound dressing systems are all covered in detail in this paper. This analysis highlights a viable approach to overcome present wound care limitations and enhancing healing outcomes in both acute and chronic wound diseases by emphasizing the synergistic integration of velutin with thermoresponsive hydrogel technology.

Velutin	
Synonym	5,7-Dihydroxy-3',4'-dimethoxyflavone; 3',4'-Dimethoxyflavone-5,7-diol; Velutin hydrate
Background	Velutin is a naturally occurring flavonoid compound found in various plant species, particularly in members of the Asteraceae family. It has been isolated from traditional medicinal plants and has gained attention for its potential therapeutic properties including anti-inflammatory, antimicrobial, and wound healing activities. As a research compound, velutin represents a promising bioactive molecule for pharmaceutical development, particularly in topical and dermatological applications.
IUPAC Name	5,7-dihydroxy-2-(3,4-dimethoxyphenyl)-4H-chromen-4-one
Description	Velutin appears as a yellowish to pale yellow crystalline powder with characteristic flavonoid properties. It exhibits limited water solubility and demonstrates photosensitivity under UV light exposure. The compound shows typical flavonoid spectroscopic characteristics with distinctive UV absorption patterns.
Molecular Formula	$C_{17}H_{14}O_6$
Molecular Weight	314.29 g/mol

Chemical Structure	
Solubility	Poorly soluble in water (<0.1 mg/mL); soluble in organic solvents such as DMSO, ethanol, methanol; moderately soluble in aqueous alkaline solutions; enhanced solubility in presence of cyclodextrins or surfactants
pH	pKa values approximately 6.8-7.2 for phenolic hydroxyl groups; exhibits pH-dependent stability with optimal stability in slightly acidic to neutral conditions
Boiling Point	Decomposes before boiling; estimated >400°C under atmospheric pressure
Melting Point	268-272°C (may vary depending on hydration state and purity)
Viscosity	Not applicable for solid compound; solutions show Newtonian behavior at low concentrations
Handling Precautions	Handle with appropriate PPE; avoid direct skin and eye contact; use in well-ventilated areas; protect from light and moisture; avoid inhalation of powder; store away from strong oxidizing agents
Pharmacology	Exhibits multiple pharmacological activities including anti-inflammatory, antimicrobial, antioxidant, and tissue regeneration properties. Shows potential for wound healing applications through modulation of inflammatory pathways and promotion of cellular proliferation.
Pharmacodynamics	Demonstrates dose-dependent biological effects with optimal activity in micromolar concentrations. Shows synergistic effects when combined with other bioactive compounds. Exhibits time-dependent accumulation in target tissues with sustained biological activity.
Metabolism	Undergoes phase I metabolism primarily through hydroxylation and demethylation by cytochrome P450 enzymes; phase II conjugation with glucuronic acid and sulfate; metabolites retain some biological activity
Elimination	Primarily eliminated through hepatic metabolism and renal excretion; biliary excretion may contribute to elimination; metabolites excreted in urine and feces
Half-life	Estimated 2-4 hours for systemic circulation (limited data available); tissue half-life may be prolonged in formulated systems
Functional Category	Research compound; Potential pharmaceutical active ingredient; Natural product derivative; Flavonoid therapeutic agent
Stability and Storage Conditions	Store in tight, light-resistant containers at 2-8°C; protect from moisture and oxidation; stable for 24 months under proper storage conditions; avoid exposure to alkaline conditions and UV light

Incompatibilities	Incompatible with strong oxidizing agents, heavy metals (iron, copper), and alkaline conditions; may form complexes with metal ions; avoid contact with reducing sugars at elevated temperatures
Applications	Wound healing formulations; Anti-inflammatory topical preparations; Antimicrobial research; Cosmetic applications; Potential pharmaceutical ingredient for dermatological conditions; Research tool for studying flavonoid biology
Adverse Effects	Limited toxicity data available; potential for mild skin irritation in sensitive individuals; possible photosensitization with prolonged UV exposure; no significant systemic toxicity reported at therapeutic doses
Safety	Generally regarded as safe based on natural occurrence and limited toxicity studies; requires further safety evaluation for pharmaceutical use; follow standard laboratory safety protocols; monitor for allergic reactions in sensitive populations

2. Limitations of Current Wound Healing Agents

Even while wound care has advanced significantly, the present crop of wound-healing agents has a number of drawbacks that limit their clinical efficacy, especially in complex and chronic wounds.

3. Limited Efficacy in Chronic Wounds

Chronic wounds including diabetic ulcers, pressure sores, and venous leg ulcers frequently may not respond well to conventional wound-healing treatments. Persistent inflammation, poor angiogenesis, oxidative stress, and microbial colonization are characteristics of these wounds that many current agents are unable to effectively address.

3.1 Excessive Inflammatory Response

Many wound-healing medications do not adequately control chronic inflammation; instead, they mainly target infection prevention or moisture retention. Chronic inflammatory reactions can cause collagen production to be disrupted, fibroblast function to be impaired, and wound closure to be delayed, ultimately resulting in non-healing or delayed wounds.

3.2 Limited Antioxidant Protection

Because it damages extracellular matrix proteins and cellular components, oxidative stress is a major factor in delayed wound healing. However, the majority of traditional wound-healing medicines are inadequate in preventing tissue damage caused by reactive oxygen species because they lack inherent antioxidant qualities.

3.3 Risk of Infection and Antimicrobial Resistance

Although topical antibiotics and antiseptics are frequently used to treat wounds, improper or extended usage can cause local cytotoxicity, antimicrobial resistance, and disruption of the natural skin microbiome. These restrictions present serious difficulties, especially when it comes to long-term wound care.

3.4 Delayed Re-epithelialization and Poor Tissue Regeneration

Many of the medications on the market today encourage wound closure mainly by contraction as opposed to actual tissue regeneration. Insufficient stimulation of angiogenesis, fibroblast proliferation, and keratinocyte migration frequently leads to poorer quality of healed tissue and delayed re-epithelialization.

3.5 Adverse Effects and Safety Concerns

Adverse effects including local irritation, allergic responses, excessive granulation tissue formation, and an increased risk of aberrant scarring are linked to some wound-healing medications, such as growth factors and synthetic compounds. Furthermore, there is still a lack of long-term safety data for several cutting-edge treatments.

3.6 High Cost and Limited Accessibility

Advanced wound-healing treatments, such as recombinant growth factors and bioengineered skin substitutes, are frequently costly and need specific administration and storage. Their broad usage is restricted by these constraints, especially in countries with low and moderate incomes.

3.7 Poor Patient Compliance

Poor patient compliance is a result of extended treatment, painful application, foul odor, and frequent dressing changes. This raises the overall cost of wound care and has a detrimental effect on therapeutic results.

3.8 Lack of Multifunctional Activity

The majority of wound-healing products on the market today are made to focus on just one area of wound healing, including moisture retention or antibacterial activity. However, many current treatments are unable to simultaneously modulate inflammation, oxidative stress, angiogenesis, and tissue remodeling, which is necessary for optimal wound healing.

4. Mechanism of Action of Velutin

Velutin is a naturally occurring flavonoid with a wide range of biological actions, mostly due to its ability to modify intracellular signaling pathways that are important in cell survival, inflammation, and oxidative stress.

5. Structure–Activity Relationship (SAR) of Velutin

The structural characteristics of velutin, a polymethoxylated flavone, include a flavone backbone (C6–C3–C6 skeleton) with particular hydroxyl and methoxy substitutions that support its biological action. The functional roles of velutin's flavone core, hydroxyl groups, and methoxy substituents can be used to understand its SAR.

5.1 Flavone Core Structure

Velutin's biological action depends on its flavone scaffold, which is a planar conjugated system with a C2=C3 double bond and a 4-oxo functional group in the C ring. This structural characteristic allows for efficient interaction with intracellular signaling proteins, such as kinases and transcription factors involved in oxidative stress and inflammatory processes, and enhances electron delocalization.

5.2 Hydroxyl Substitutions

A hydroxyl group located at the C5 position of the A ring in velutin is essential to its anti-inflammatory and antioxidant properties. This hydroxyl group's presence improves the ability to donate hydrogen and aids in the scavenging of free radicals. Furthermore, intramolecular hydrogen bonding between the 5-hydroxyl and 4-oxo groups can stabilize the flavone structure and increase its binding affinity to molecular targets including signaling proteins linked to NF-κB.

5.3 Methoxy Groups and Lipophilicity

Velutin has several methoxy substituents, especially at the C7, C3′, and C4′ locations, which set it apart from similarly related flavonoids. These methoxy groups make the molecule more lipophilic, which could enhance cellular absorption and membrane permeability. Compared to polyhydroxylated flavonoids, enhanced lipophilicity is also linked to higher metabolic stability, which may extend biological activity in vivo.The B ring's methylation is particularly crucial for controlling inflammatory signals. The suppression of NF-κB and MAPK pathways is linked to substituents at the C3′ and C4′ locations, most likely as a result of enhanced interaction with regulatory proteins and upstream kinases.

5.4 Balance Between Methoxylation and Hydroxylation

Velutin's SAR emphasizes how crucial a balanced pattern of hydroxylation and methoxylation is. Excessive hydroxylation can lower bioavailability because of poor membrane permeability, even though hydroxyl groups are necessary for antioxidant action. On the other hand, methoxy groups improve pharmacokinetic characteristics but may lessen the ability to scavenge radicals. The particular substitution pattern of velutin seems to maximize its physicochemical characteristics as well as its biological potency.

5.5 Comparison with Related Flavonoids

Velutin's higher degree of methoxylation has been linked to its stronger anti-inflammatory properties when compared to structurally comparable flavones like luteolin or apigenin. This alteration helps to maintain the suppression of pro-inflammatory mediators and lessens vulnerability to fast phase II metabolism.

5.6 Chemical Properties

A yellow powder, velutin (5-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-7-methoxychromen-4-one) is poorly soluble in water but highly soluble in organic solvents such as acetone, dichloromethane, ethyl acetate, chloroform, and DMSO. Although velutin itself has no known intrinsic thermosensitive phase transition or lower critical solution temperature (LCST), flavonoids like it exhibit temperature-dependent solubility influenced by conformational angles (e.g., ~40° torsion enhances solubility); these characteristics appear in polymer formulations. Its stability in hydrogel matrices for prolonged release is supported by its melting point and fusion enthalpy.

6. Pharmacological Profile

Velutin effectively reduces inflammation at low micromolar levels by blocking the NF-κB and MAPK (p38/JNK) pathways that cause LPS-induced TNF-α and IL-6. By modifying HIF-1α/NF-κB, it inhibits osteoclastogenesis, preserves cartilage, and exhibits anti-melanogenic properties by reducing melanocyte activity. Antioxidant scavenging, anti-allergic reactions, antiviral potential, and tumor cell death promotion are further functions.

6.1 Anti-inflammatory Mechanisms

Velutin's primary mode of action is the inhibition of inflammatory signaling pathways. By limiting the phosphorylation and degradation of inhibitor κBα (IκBα), velutin prevents the nuclear translocation of the NF-κB p65 subunit, which in turn prevents activation of the nuclear factor-κB (NF-κB) pathway. Reduced nitric oxide and prostaglandin production follows from the downregulation of NF-κB-dependent transcription of pro-inflammatory mediators, such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), interleukin-1β (IL-1β), inducible nitric oxide synthase (iNOS), and cyclooxygenase-2 (COX-2).

6.2 Modulation of MAPK Signaling

Additionally, velutin inhibits the signaling cascades of mitogen-activated protein kinase (MAPK). It reduces downstream inflammatory and stress-responsive gene expression by blocking the phosphorylation of p38 MAPK, c-Jun N-terminal kinase (JNK), and extracellular signal-regulated kinase (ERK).

6.3 Antioxidant Activity

By scavenging reactive oxygen species (ROS) and lowering oxidative stress at the cellular level, velutin exhibits antioxidant qualities. Furthermore, in some experimental models, velutin has been shown to activate nuclear factor erythroid 2–related factor 2 (Nrf2) signaling, which may improve endogenous antioxidant defense systems.

6.4 Anticancer and Antiproliferative Effects

Velutin shows antiproliferative effect against a variety of cancer cell lines in preclinical investigations. The stimulation of cell-cycle arrest and apoptosis, which is typified by the activation of caspase-dependent apoptotic pathways, an increase in the Bax/Bcl-2 ratio, and modification of B-cell lymphoma-

2 (Bcl-2) family proteins, mediates these effects. The inhibition of cancer cell survival caused by velutin has also been linked to the phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) signaling pathway.

6.5 Immunomodulatory and Anti-allergic Effects

immunoglobulin E (IgE)-mediated signaling and the inhibition of mast cell degranulation. This contributes to its anti-allergic action by lowering the release of pro-inflammatory cytokines and histamine.

7. Wound Healing Relevance

Velutin's antioxidant and anti-inflammatory qualities promote angiogenesis, collagen synthesis, and re-epithelialization. This makes it perfect for thermosensitive hydrogel loading, where regulated release is made possible by body-temperature gelation. In skin models, preclinical findings show improved healing and decreased proinflammatory cytokines.

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