International Journal of Research in Medical Sciences
Haridas H et al. Int J Res Med Sci. 2025 Jun;13(6):2734-2739
www.msjonline.org

pISSN 2320-6071 | eISSN 2320-6012

DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20251677

Review Article

Hesperidin in dentistry: a natural flavonoid with promising therapeutic potential: a narrative review

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Received: 22 April 2025
Revised: 14 May 2025
Accepted: 21 May 2025

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ABSTRACT

Hesperidin, a flavonoid primarily found in citrus fruits has garnered attention in biomedical research for its potential to inhibit demineralization, enhance remineralization, antimicrobial properties, anti-inflammatory effects, regenerative properties and wound healing. Flavonoids also possess collagen-crosslinking effects and dentin collagen proteolytic degradation inhibition property. Hesperetin (HS), a metabolite of hesperidin, is a polyphenolic component of citrus fruits. This ingredient has a potential role in bone strength and the osteogenic differentiation. This review aims to summarize current evidence regarding the application of hesperidin in various dental disciplines, highlighting its mechanisms of action, clinical relevance and future research prospects. More researches and studies are required in this regard to use them in our daily clinical practices.

Keywords: Antioxidants, Dentistry, Dental pulp, Flavonoids, Hesperidin, Oral health, Periodontal therapy

INTRODUCTION

Natural compounds have emerged as promising adjuncts in the prevention and treatment of oral diseases due to their biocompatibility and multi-targeted mechanisms. Among these, hesperidin, a flavanone glycoside found in citrus fruits such as oranges and lemons has shown a wide range of therapeutic potential in the realm of dentistry. Hesperidin was first isolated from the inner portion of orange peels in 1828. Hesperidin together with other similar biofavonoids was formerly called “vitamin P”.[1]

Hesperidin (3, 5, 7-trihydroxyflavanone 7-rhamnoglucoside, hesperetin-7-O-rutino-side) belongs to flavanone compounds, one of the flavonoids subclasses. It has been recently extensively evaluated for its health-promoting and pharmacological effects and is used in a treatment of type 2 diabetes, cancer and cardiovascular diseases, neurological and psychiatric disorders, as well as a radioprotector. Administrations of hesperidin can also benefit a variety of cutaneous function in both normal and diseases skin.[1] Hesperidin and its derivatives are characteristic compounds of citrus fruits (*Rutaceae* family) such as orange (*Citrus sinensis*), grapefruit (*Citrus paradise*), tangerine (*Citrus reticulata)*, lime (*Citrus aurantifolia*) and lemon (*Citrus limon*). Their content in citrus fruits depends on fruit variety, part of the fruit itself, climate and degree of maturation. Its use has been associated with a great number of health benefits, including antioxidant, antibacterial, antimicrobial, anti-inflammatory and anticarcinogenic properties. The molecular weight of hesperidin is approximately 610.6 g/mol.[2]

CHEMICAL STRUCTURE, PROPERTIES AND MECHANISM OF ACTION

Hesperidin ($C_{28}H_{34}O_{15}$) is composed of a glycone hesperetin and disaccharide rutinose. The chemical structure of hesperidin is shown in Figure 1.[2]

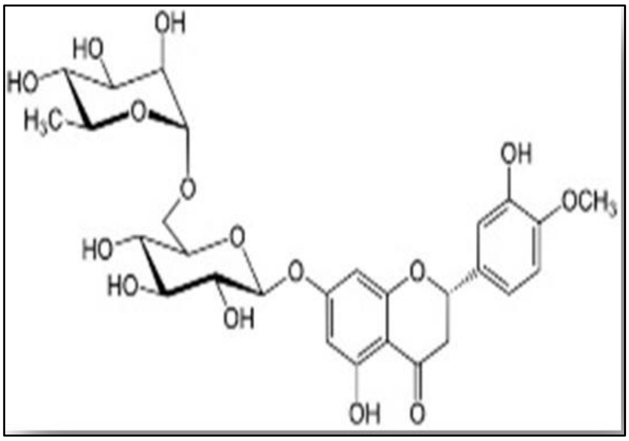

Figure 1: Chemical structure of hesperidin.

Its mechanisms of action are attributed to:

Scavenging of free radicals through upregulation of endogenous antioxidants (e.g., glutathione, superoxide dismutase). Inhibition of inflammatory mediators, including TNF-α, IL-1β, and COX-2. Antimicrobial activity against oral pathogens such as *S. mutans* and *P. gingivalis.*

Hesperidin demonstrates poor water solubility but exhibits improved bioavailability upon hydrolysis to its aglycone form, hesperetin. The pharmacological activities of hesperidin are largely attributed to its capacity to modulate oxidative stress, inflammatory pathways (notably the NF-κB and MAPK pathways) and microbial growth.[3]

APPLICATIONS IN DENTISTRY

Oral mucosal conditions

Hesperidin has demonstrated effectiveness in treating aphthous ulcers and oral lichen planus due to its mucosal healing properties and ability to modulate local immune responses. Its antioxidant action can also help in reducing oxidative stress-induced mucosal damage.

Hesperidin acts as a potent antioxidant and anti-inflammatory agent, which can help protect tissues from damage and reduce inflammation associated with oral ulcers. It also possesses cytoprotective effects. Studies suggest hesperidin can protect oral epithelial cells, potentially enhancing the healing process of ulcers. Hesperidin can improve the barrier function of the oral epithelium, which is crucial for preventing further damage and promoting healing.[4]

Periodontology

Hesperidin shows promising effects in the management of periodontal disease. *In vivo* studies demonstrate its ability to reduce alveolar bone loss, suppress pro-inflammatory cytokines, and enhance collagen formation. Its local application in gels or rinses may improve outcomes in nonsurgical periodontal therapy.

Oxidative stress and inflammation are key contributors to the pathogenesis of several oral diseases, including periodontitis and pulpitis. Studies have shown that hesperidin can reduce reactive oxygen species (ROS) and downregulate pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6. In experimental models of periodontal disease, hesperidin administration led to a reduction in alveolar bone loss and inflammatory markers, suggesting a protective role against periodontal breakdown.

Several animal studies have demonstrated that topical or systemic hesperidin can reduce periodontal tissue destruction and promote healing. It may work synergistically with scaling and root planning (SRP) and other mechanical debridement procedures. Furthermore, its ability to modulate bone remodeling suggests potential as an adjunct in regenerative periodontal therapies.[5]

Endodontics

The antioxidant and anti-inflammatory properties of hesperidin may be beneficial in managing pulpal inflammation and promoting pulp regeneration. It can modulate the inflammatory response of dental pulp stem cells (DPSCs), supporting their viability and differentiation. Moreover, hesperidin nanoparticles are being studied as potential intracanal medicaments. Hesperidin may also have other potential benefits, such as promoting angiogenesis (new blood vessel formation), reducing inflammation and enhancing the bioactivity of biomaterials, making it a promising candidate for regenerative endodontic applications.

It can be used as a pulp capping material. Hesperidin hydrogel has shown potential as a next-generation biomaterial for direct pulp capping, even outperforming bio dentine in sustaining VEGF release (Vascular endothelial growth factor) which is crucial for angiogenesis and pulp vitality.

Dentine bridge formation-studies suggest that hesperidin can induce good dentine bridge formation, a positive outcome in pulp capping procedures. Hesperidin exhibits antioxidant and anti-inflammatory properties, which can be beneficial in the context of pulp health and wound healing.[6]

Adhesive dentistry

Hesperidin enhances the durability of dentin bonds and improve antibacterial properties of dental adhesives. Hesperidin helps to enhance dentin bond durability. Studies have shown that incorporating hesperidin into self-etch adhesive primers can lead to significantly higher microtensile bond strength (μTBS) compared to control groups.[7]

Hesperidin helps to preserve the morphology of collagen fibrils, which are crucial for a strong and durable dentin bond. Some research suggests that hesperidin can enhance the antibacterial capabilities of dental adhesives. Hesperidin-incorporated adhesives have shown increased zones of inhibition against bacteria like *L. acidophilus, E. faecalis*, and *S. mutans*.[8]

Hesperidin can inhibit the action of matrix metalloproteinases (MMPs). MMPs are enzymes involved in the breakdown of collagen and other proteins. Hesperidin can inhibit MMPs, thus protecting the integrity of dentin and the hybrid layer.

Mechanism of hesperidin in inhibitingg the action of MMPs

Hesperidin's hydrophobic nature allows it to strongly associate with collagen fibrils, potentially improving the bonding interface. Hesperidin may also act as an antioxidant and anti-inflammatory agent, which could further contribute to its positive effects on dentin bonding and tissue health. Hesperidin interacts with type I collagen, potentially increasing the mechanical properties of dentin organic matrix (DOM) through a cross-linking action.[7]

Due to its antioxidant capabilities, hesperidin can aid in preventing oxidative stress and dentin deterioration. As a result, the link between the adhesive and the tooth structure may last longer. By reducing the inflammatory response in the dentin and surrounding tissues, hesperidin's anti-inflammatory effect can help minimise post-operative discomfort. This may result in greater patient satisfaction and comfort after adhesive restorations.

Cytotoxicity and antibacterial activity: Research assessing the cytotoxicity and antibacterial effects of hesperidin-incorporated dentin adhesives found that the modified adhesives effectively inhibited the growth of *L. acidophilus*, *S. mutans* and *E. faecalis*, without exhibiting cytotoxic effects, suggesting their potential for clinical application in preventing recurrent caries.[8]

Antibacterial properties in adhesives: An *in vitro* study evaluated the incorporation of hesperidin into a total-etch dental adhesive system at concentrations of 0.2%, 0.5%, and 1%. The modified adhesives exhibited significant antibacterial activity against *S. mutans*, with the 0.5% concentration showing optimal results without adversely affecting the adhesive's microtensile bond strength.[9]

Bone regeneration

Recent studies explore the incorporation of hesperidin into dental biomaterials such as scaffolds for bone regeneration, resin composites with antimicrobial properties, and coatings for implant surfaces. Its role in osteoblast proliferation and angiogenesis further supports its potential in tissue engineering. Hesperidin can help reduce inflammation and fight bacteria associated with periodontitis, potentially aiding in the treatment of gingivitis and periodontal diseases. It can promote wound healing and mineralization in periodontal tissues, contributing to the restoration of damaged areas.

Hesperidin has demonstrated osteoinductive and osteoconductive properties, partly due to its ability to promote osteoblast differentiation and inhibit osteoclastogenesis. In animal models, hesperidin has enhanced the formation of new alveolar bone in extraction sockets and periodontal defects. These findings suggest its potential use in guided bone regeneration (GBR) and implantology. Nano-hesperetin can be considered an ideal option in bone and tooth tissue engineering. In addition, hesperetin nanoparticles can be applied to expand suitable scaffolds for bone, teeth and periodontium regeneration.[10]

Human periodontal ligament cells: An *in vitro* study on human periodontal ligament cells cultured under high glucose conditions revealed that hesperidin at 100 µM concentration significantly improved wound closure, alkaline phosphatase activity, and calcium release, indicating its potential to promote healing and mineralization in periodontal tissues.[11]

Enhancement of dental materials

Incorporating hesperidin into dental materials has shown promising results. Studies have reported improved mechanical properties, antibacterial effects, and biocompatibility in resin composites and endodontic sealers supplemented with hesperidin. These modifications may enhance the performance and longevity of dental restorations and root fillings. Hesperidin's natural antimicrobial properties can help prevent/combat bacterial infections in oral cavity, particularly important in endodontic treatments and around restorations. Studies have shown that hesperidin-incorporated dental materials can be well-tolerated by dental tissues, reducing the risk of adverse reactions and promoting healing. While promising, more research is needed to fully understand long-term effects and optimal concentrations of hesperidin in various dental applications.[10]

Antioxidant property

Hesperidin possesses property of upregulation of antioxidant enzymes. It enhances cellular antioxidant defense by upregulating the expression of enzymes like catalase (CAT), superoxide dismutase (SOD), and glutathione-S-transferase (GST), which are involved in scavenging free radicals and protecting cells from oxidative damage.[12]

Anti-cancer effects

Hesperidin inhibits cancer cell proliferation by inducing cell cycle arrest at specific phases (G0/G1 or G2/M) and promoting apoptosis (programmed cell death).

It possesses anti-angiogenesis and anti-metastasis, hesperidin inhibits angiogenesis (the formation of new blood vessels) and metastasis (the spread of cancer cells), which are crucial for tumor growth and spread.[13]

Mechanism

Targeting multiple cellular protein targets: Hesperidin inhibits tumor growth by targeting multiple cellular protein targets, including caspases, Bcl-2, Bax, COX-2, MMP-2, and MMP-9.

Inhibition of signalling pathways: Hesperidin inhibits various signaling pathways involved in cancer development and progression, including PI3K/Akt, NF-κB, and MAPK pathways.[14]

FORMULATIONS OF HESPERIDIN FOR BIOMEDICAL RESEARCH

For biomedical research, hesperidin formulations often aim to enhance its bioavailability and targeted delivery, using methods like nano-formulations, microemulsions, hydrogels and *in situ* gels to improve its solubility, stability and absorption.

Preparation of hesperidin hydrogel

According to a recent invitro study conducted by Geervani et al the hydrogel formulation is as follows-about 1.0% grams of carbopol was dispersed in 100 mL of water by stirring for 30 minutes using an overhead stirrer at around 500 RPM. Then, approximately 100 mg of hesperidin (Otto Chemie Pvt. Ltd., Mumbai, India) was gradually added to the vessel containing carbopol. To enhance the antibacterial properties of the hydrogel, 0.6 mg of eugenol per 100 g of gel was incorporated. This concentration was chosen to minimize bacterial contamination while ensuring biocompatibility. The pH was adjusted to 6.7 using 0.1 N NaOH. The translucent gel was then placed in a plastic container and stored in a refrigerator. The prepared hydrogel is shown in Figure 2.[6]

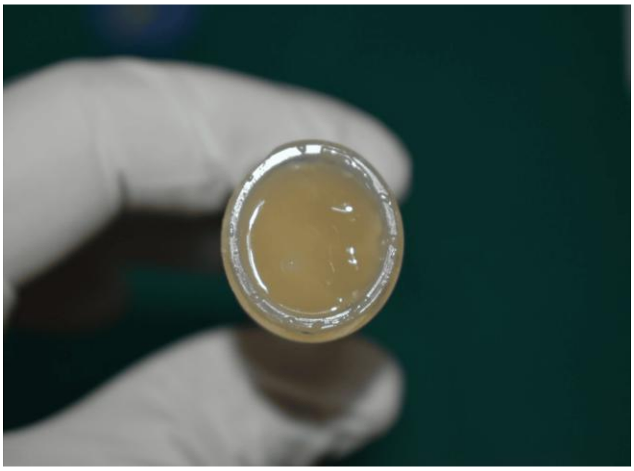

Figure 2: Hesperidin hydrogel.

ADVANTAGES OVER SYNTHETIC AGENTS

Hesperidin, as a natural compound, offers several advantages: Since it is a natural product, it possesses low toxicity, therefore minimal side effects. It is biodegradable. It is economical and cost-effective. These benefits make it a strong candidate for adjunctive therapies in both clinical and home-care settings.[15]

LIMITATIONS AND FUTURE DIRECTIONS OF HESPERIDIN

Despite promising findings, human clinical trials are limited. Most data are derived from *in vitro* and animal models, necessitating robust clinical research to confirm its safety and efficacy. Future directions should focus on optimizing delivery systems (e.g., nanoparticles, gels, mouth rinses). The dosing protocols should be standardized. More studies should be conducted to explore the action of hesperidin and its synergistic effects with conventional therapies.[16]

Drug formulation and delivery systems

Improving hesperidin's bioavailability through nanoparticle formulations, liposomes, or prodrug strategies is a key focus. Encapsulation techniques using polymers or nano carriers can enhance absorption and therapeutic efficacy.

Synergistic therapies

Investigating combinations of hesperidin with other drugs or flavonoids to enhance outcomes in diseases like cancer, diabetes, hypertension and many oral diseases.[17]

ADVANCED DRUG DELIVERY SYSTEMS

Nano-formulations

Development of nanoparticles**,** liposomes or hydrogels to enhance hesperidin's bioavailability and targeted delivery in the oral cavity. Sustained-release systems could be used in periodontal pockets or post-surgical sites for controlled, long-term anti-inflammatory or antimicrobial effects.[18]

ANTI-VIRAL AND ANTI-MICROBIAL APPLICATIONS

Emerging infectious diseases

Hesperidin has shown potential against viruses such as SARS-CoV-2 in computational and *in vitro* models. Further exploration in antiviral therapies is warranted.

Microbiome modulation

Investigating how hesperidin influences gut microbiota and how this relates to systemic health benefits.[19]

NATURAL THERAPEUTICS IN PREVENTIVE DENTISTRY

Formulating natural mouthwashes, toothpastes or gels with hesperidin for daily use, offering antioxidant and antimicrobial benefits without harsh chemicals.[20]

CONCLUSION

Hesperidin, a citrus-derived flavonoid, demonstrates significant potential in the field of dentistry due to its well-documented antioxidant, anti-inflammatory, and antimicrobial properties. Current evidence suggests promising applications in periodontology, endodontics, preventive care and dental material enhancement. As a natural therapeutic agent, hesperidin aligns with the growing interest in biocompatible and plant-based alternatives in oral healthcare.

As research continues to evolve, hesperidin may emerge as a valuable natural adjunct in both preventive and therapeutic dental care. However, clinical translation will require robust evidence from human studies and innovative drug delivery systems to harness its full potential. Future research should focus on well-designed, large-scale clinical trials and the development of hesperidin-based dental products.

Despite encouraging *in vitro* and *in vivo* results, clinical validation remains limited. Challenges such as poor bioavailability, lack of standardized formulations, and insufficient human trials hinder its routine use in dental practice. Future research should focus on developing advanced delivery systems, exploring synergistic formulations, and conducting rigorous clinical studies to confirm its efficacy and safety.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Haridas H, Varadharajan V, Kumanan S, Mohamed SK. Hesperidin in dentistry: a natural flavonoid with promising therapeutic potential: a narrative review. Int J Res Med Sci 2025;13:2734-9.