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Review Article

Hesperidin: A Comprehensive Review of its Pharmacological Activities and Therapeutic Applications

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ABSTRACT

Hesperidin is a naturally occurring citrus bioflavonoid that has gained significant interest for its wide range of pharmacological and therapeutic activities. Found abundantly in citrus fruits, hesperidin exhibits potent anti-inflammatory, antioxidant, antihypertensive, antimicrobial, anticarcinogenic, and vasodilatory effects, making it an important bioactive compound in both pharmaceutical and nutraceutical contexts. It plays a vital role in vascular health by improving venous tone, enhancing microcirculation, and promoting the healing of venous ulcers. Clinically, hesperidin is utilized in the management of chronic venous insufficiency, hemorrhoids, and the prevention of postoperative thromboembolism. Supplementation with hesperidin has been shown to alleviate edema by reducing swelling from fluid accumulation in the lower extremities and improving overall vascular function. Furthermore, it helps address conditions such as unusual capillary leakiness, extremity pain, night leg cramps, and general weakness, thereby improving quality of life. Emerging studies also highlight its neuroprotective and anticarcinogenic potential, indicating promising applications in the treatment of neurodegenerative disorders and cancer prevention. Increasing evidence highlights the significance of hesperidin as a multifunctional compound with broad therapeutic benefits. This review aims to comprehensively examine the biological importance of hesperidin, detailing its pharmacological activities, clinical applications, and potential role in future therapeutic strategies to advance human health and disease management.

Keywords: Anti-inflammatory, Antioxidant, Citrus bioflavonoid, Neuroprotection, Nutraceuticals, Vascular health.

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INTRODUCTION

Traditional medicine is a holistic approach to health, focusing on the overall condition of the individual rather than the specific ailment or disease. It has a history of over 3000 years and is influenced by various conditions, environments, and geographic areas. Over the past 100 years, the development and mass production of chemically synthesized drugs have revolutionized health care in most parts of the world. However, large portions of the population in developing countries still depend on traditional practitioners and herbal medicines for primary care. Herbs and plants can be processed into various forms like whole herbs, teas, syrups, essential oils, ointments, rubs, capsules, and tablets. Extracts vary in solvent, temperature, and time, and components may vary significantly between batches and producers. There is no standardization (Benzie and Wachtel-Galor, 2011).

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Herbs are recognized for their medicinal value and therapeutic benefits, as they contain pharmacologically active compounds from various plant parts that can act as life-saving drugs directly or indirectly. Plants and their constituents have long been harnessed for their flavors, scents, and therapeutic properties, offering a myriad of benefits over pharmaceutical products. Plant extracts and phytoconstituents have demonstrated diverse biological activities, including antihyperlipidemic, antidiabetic, anti-inflammatory effects, and free-radical scavenging (Zhang *et al*., 2015). Nature's balanced system promotes healthy life, with plants being a valuable source for drug discovery, particularly compounds with antioxidant activity, gaining attention in recent decades of the plant kingdom, which comprises approximately 374,000 known and accepted plant species, including about 308,312 vascular plants and 295,383 flowering plants (angiosperms), the angiosperms alone represent an immense reservoir of biological and medicinal potential (Christenhusz and Byng, 2016). Plants are rich in compounds, including secondary metabolites and aromatic substances, including phenols and tannins. These compounds have antioxidant properties and are important for pharmacological research and drug development. The first pharmacologically active pure compound, morphine, was produced from opium extracted from the seed pods of the poppy *Papaver somniferum* 200 years ago. Products from plants and natural resources have contributed significantly to commercial drug preparations today. Examples include digoxin, salicylic acid, reserpine, antimalarials, and lipid-lowering agents. Over 60% of cancer therapeutics on the market or in testing are based on natural products, with over 70% based on natural products or mimetics. About 25% of drugs prescribed worldwide are derived from plants, and 121 active compounds are in use (Wachtel-Galor and Benzie, 2011). Plants contain a variety of secondary metabolites, known as phytochemicals, which have diverse structural and functional properties. These metabolites, such as alkaloids, polyphenols, flavonoids, saponins, carotenoids, and terpenes, are biologically active molecules that play a vital role in the plant's secondary metabolism and promote health and disease prevention. Phytochemicals are produced by specific cellular types and carry out important functions in plant secondary metabolism, such as insect repellents, sun blockers, and growth regulators. However, their effects can depend on the dose (Rodríguez-Negrete *et al.*, 2024). Researchers are exploring plant-based natural resources for potential drug development discoveries due to the increasing global demand for pharmaceutical substances.

Citrus fruits are one of the major sources of bioflavonoids plant secondary metabolites with potent antioxidant and pharmacological activities. These bioactive flavonoids, including hesperidin, naringin, diosmin, and tangeretin, have various pharmacological properties, including antioxidant, anti-inflammatory, cardioprotective, antimicrobial, and anticancer effects. Hesperidin, found in orange peels and pulp, has gained scientific interest for its potential role in chronic disease prevention and treatment (Barreca *et al.*, 2020). As demand for safer, natural therapeutic agents increases, citrus-derived flavonoids are becoming prominent candidates in pharmacological research and drug development. Despite growing interest and expanding literature on hesperidin, a comprehensive understanding of its pharmacological mechanisms, therapeutic range, and bioavailability challenges remains limited. Hence, the present review aims to provide a comprehensive overview of the biological significance of hesperidin, a prominent citrus bioflavonoid. It focuses on elucidating its pharmacological activities, including antioxidants, anti-inflammatory, antimicrobial, anticancer, cardioprotective, neuroprotective, and metabolic effects.

ROLE OF BIOFLAVONOIDS IN DISEASE MANAGEMENT

Bioflavonoids are a class of natural benzo-γ-pyran derivatives found in fruits and vegetables. Bioflavonoids include flavonol (e.g., quercetin, myricetin), isoflavone (e.g., genistein, daidzein), flavan-3-ols (e.g., catechin, epigallocatechin), flavonone (e.g., naringenin, hesperidin), anthocyanidin (e.g., cynidin), etc. (Ghosh *et al.*, 2022). Flavonoids, a remarkable group of polyphenolic substances, comprise over 6000 different components found in almost all plants and are responsible for the vibrant pigmentation of fruits (Panche *et al.*, 2016). It is a subset of flavonoids which has been extensively utilized in alternative medicine to enhance various physiological functions (David *et al.*, 2016). Bioflavonoids have been employed in the management of a wide spectrum of conditions, angina, atherosclerosis, stress, asthma, rheumatoid arthritis, herpes, cancer, cataracts, emphysema, common cold, colitis, gingivitis, recurring ear infections, glaucoma, hemorrhoids, high cholesterol, high blood pressure, macular degeneration, lupus, menopause, and urinary tract infections (Fernandes *et al.*, 2017; Kris-Etherton *et al.*, 2002).

Bioflavonoids, with their anti-inflammatory properties, play a crucial role in human health by regulating inflammation and reducing the risk of respiratory and cardiovascular illnesses (Frei and Higdon, 2003). *In vitro* studies have demonstrated the antitumor activity of flavonoids, showcasing various anticancer abilities such as inhibiting cell growth and kinase activity, inducing apoptosis, suppressing the secretion of matrix metalloproteinases, and inhibiting tumor invasive behavior (Ren *et al.*, 2003). Importantly, dietary flavonoids have been shown to possess antitumor capabilities. Even in high concentrations, flavonoids exhibit no signs of toxic effects (Wren *et al.*, 2002).

CITRUS FLAVONOIDS

Epidemiological research has highlighted the multifaceted impact of citrus flavonoids on various activities, encompassing antioxidant, anti-carcinogenic, anti-inflammatory activities, and neuroprotective effects (Hajialyani *et al.*, 2019). They are part of the polyphenol family. Major types include flavanones (e.g., hesperidin, naringin, eriocitrin, didymin), flavones (e.g., apigenin, luteolin, diosmin), and polymethoxylated flavones (e.g., tangeretin, nobiletin). Flavanones are the most abundant in citrus. Biological activities of a few citrus flavonoids are summarized in Table 1 (Bellik *et al.*, 2012; Huwait and Mobashir, 2022; Madureira *et al.*, 2023; Mas-Capdevila *et al.*, 2020).

Chemistry of Citrus Flavonoid

Flavanones, which constitute a major and predominant class of flavonoids (Figure 1a), comprise approximately 350 aglycones and 100 glycosylated forms identified to date. Structurally, flavanones conform to the general flavonoid framework, featuring a flavan nucleus composed of aromatic rings A and B linked by a dihydropyrone ring (C). Distinguishing features of flavanones include the absence of a C2–C3 double bond, the presence of a chiral carbon atom at the C2 position, and the lack of substitution at the C3 position of the C ring. These structural distinctions differentiate flavanones (Figure 1b) from the other two classes of flavonoids found in Citrus, namely flavones and flavanols (Barreca *et al.*, 2017).

The prevalent aglycones of citrus flavonoids include hesperetin, naringenin, eriodictyol, isosakuranetin, taxifolin, poncirin, neoeriocitrin, neohesperidin, didymin, and narirutin. This group encompasses various combinations with a sugar moiety bound to the aglycone hydroxyl groups through the formation of an O-glycosidic linkage, typically found at the C-7 position (A ring). The bound saccharides are commonly rutinose or neohesperidose moieties, both L-rhamnosyl-D-glucosyl derivatives. The former presents an α-1,6 interglycosidic linkage, while the latter features an α-1,2 interglycosidic bond (Barreca *et al.*, 2016, 2017).

Flavonoids offer numerous health benefits, including antioxidants, free radical scavenging, anti-inflammatory, and cytoprotective properties. They play a crucial role in treating obesity, diabetes, and cardiovascular disease by preventing cell damage and oxidative stress. Flavonoids' chemical structure allows them to act as radical scavengers, oxygen quenchers, and hydrogen-donating antioxidants (Mahmoud *et al.*, 2019).

HESPERIDIN

Hesperidin ($C_{28}H_{34}O_{15}$) is a naturally occurring flavanone glycoside (bioflavonoid) abundant in citrus fruits. Hesperetin is the aglycone (non-glycosylated) form of hesperidin. Both hesperidin and hesperetin exhibit antioxidant and anti-inflammatory properties, but hesperidin is the most abundant form in citrus fruits. Hesperidin was first isolated in 1828 by French chemist M. Lebreton from the white inner layer of citrus peels, derived from the name "hesperidium", a fruit of a citrus plant (Tong *et al.*, 2023). It was formerly known as 'Vitamin P' (Man *et al.*, 2019). It appears as a crystalline powder that is light yellow in color, odorless and tasteless. It has a melting point of 258-262°C and a molecular weight of 610.6 g/mol. Hesperidin is highly soluble in pyridine, dimethylformamide, and sodium hydroxide solution, but slightly soluble in benzene and acetone. Its solubility in water is very low, requiring approx. 50 L of water to dissolve 1 g of hesperidin (PubChem [Internet], n.d.; Ma *et al.*, 2024). Structurally, hesperidin comprises an aglycon (hesperitin or methyl eriodictyol) linked to rutinose (Figure 2a), making it a -7-rutinoside of hesperetin (Figure 2b). Neohesperidin, an isomer of hesperidin (Figure 2c), is present in bitter oranges (*Citrus aurantium*) (Aggarwal *et al.*, 2020; Hajialyani *et al.*, 2019).

Sources of Hesperidin

Hesperidin, abundant in citrus fruits such as lemon and others, has been identified not only in Citrus species but also in diverse plant families like Fabaceae (e.g., *Cyclopia* spp.), Betulaceae (e.g., *Carpinus* spp.), Lamiaceae (e.g., *Mentha* spp.), and Papilionaceae (e.g., Pterocarpus spp.). Hesperidin has also been found in the bark of *Zanthoxylum avicennae* and *Zanthoxylum cuspidatum*, occurs predominantly as neohesperidin in *Cynara* species, and is present among the chemical constituents of the roots of *Acanthopanax setchuenensis* (Devi *et al.*, 2015).

Citrus fruits and their juices are rich sources of bioflavonoids, particularly flavanones such as hesperetin, naringenin, eriodictyol, and isosakuranetin, as well as their glycosides. These compounds occur at varying concentrations, typically ranging from approximately 180 to 740 mg/L depending on the Citrus species and cultivar, and contribute to a range of biological activities (Barreca *et al.*, 2017). Hesperidin, a prominent bioflavonoid, is commonly found in plants belonging to the Rutaceae family, including Citrus species like *Citrus sinensis, Citrus limon, Citrus aurantiifolia*, as well as in plants from the Lamiaceae family, such as *Mentha piperita*. Hesperidin is abundant in clementine, sweet orange, mandarin orange, and lemon juices (39.9-20.5 mg/100 mL juice) (Addi *et al.*, 2021). Hesperidin can constitute up to 14% of immature oranges (Johnston *et al.*, 2014). Generally, the immature citrus fruits and the citrus peel contain a higher amount of hesperidin (Man *et al.*, 2019).

BIOLOGICAL ACTIVITY

Antimicrobial

Flavonoids are secondary (non-essential) metabolites synthesized by numerous plants, where they function as defense compounds against a variety of threats, including toxins and microbial pathogens. While some flavonoids play a role in protecting the plant's roots from pathogens, they also exhibit potential health benefits for humans. Hesperetin, the aglycone of hesperidin, demonstrates antimicrobial activity (Choi and Lee, 2023). Although the exact mechanisms behind these antimicrobial properties are not fully understood, several processes, including the activation of the host immune system, interference with bacterial membranes, and disruption of microbial enzymes, have been investigated. In addition to their antimicrobial effects, hesperidin and hesperetin have been reported to offer protection against toxicity induced by various factors, with this protective capability extending to tissues and cells through their antioxidant and radical scavenging activities (Garg *et al.*, 2001). The multifaceted nature of flavonoids highlights their significance in both plant defense mechanisms and potential contributions to human health.

Anticancer

Hesperidin has been identified as a compound capable of inducing apoptotic cell death in various cancer cells through both intrinsic and extrinsic pathways (Bartoszewski *et al.*, 2014). In SNU-C4 colon cancer cells, hesperidin triggers specific intracellular death-receptor pathways, leading to DNA fragmentation and the formation of perinuclear apoptotic bodies. The apoptotic process is notably characterized by the up-regulation of Bax and Caspase-3 mRNA (Park *et al.*, 2008). Similarly, the administration of hesperidin to SNU-668 Human Gastric cells induces apoptotic changes, including chromatin condensation, apoptotic morphology of cellular bodies, modulation of Bcl-2, and activation of Caspase 3. These findings suggest the potential utility of hesperidin in patients with gastric cancer (Devi *et al.*, 2015; Deng *et al.*, 2025).). Hesperidin's ability to induce apoptosis in cancer cells highlights its promising role in cancer research and potential therapeutic applications. Hesperidin has been shown to induce apoptosis and cell cycle arrest, thereby inhibiting cancer cell proliferation and contributing to the reversal of drug resistance. In addition, evidence suggests that hesperidin may play a promising role in suppressing tumor cell metastasis, angiogenesis, and chemoresistance (Aggarwal *et al.*, 2020).

Cardioprotective Effects

In an *in vitro* experiment, hesperidin demonstrated its ability to prevent hypoxic injury in cardiomyocytes by activating the PI3K/Akt intracellular signaling pathway (Yin *et al.*, 2017). Further studies on the cardioprotective effects of hesperetin in rodents, particularly in a doxorubicin-induced oxidative stress model, revealed significant outcomes. In rats, hesperetin displayed cardioprotective effects at dose levels of 25, 50, and 100 mg/kg by reducing malondialdehyde levels and oxidative stress, while concurrently increasing glutathione levels in animals administered with doxorubicin (Trivedi *et al.*, 2011). These results highlight the potential therapeutic applications of hesperidin for cardiovascular health.

Hesperidin is also help in normalizing the blood glucose levels via hepatic glucose-regulating enzyme activities, serum insulin and adiponectin levels, as well as serum and hepatic lipid levels (Akiyama *et al.*, 2009). Hesperidin exhibits lipid-lowering effects by reducing plasma levels of total cholesterol, low-density lipoprotein-cholesterol, very-low-density lipoprotein-cholesterol, triglycerides, free fatty acids and phospholipids, and increasing levels of high-density lipoprotein-cholesterol. It also possesses antiplatelet activity, helps in vasodilation as well and helps in lowering the leukocyte activation (Zanwar *et al.*, 2014).

Anti-inflammatory

Hesperidin shows significant anti-inflammatory activity against carrageenan and dextran-induced rat paw edema and carrageenan pleurisy without causing side effects (Guardia *et al.*, 2001). Diosmin and hesperidin, used in combination (90% diosmin and 10% hesperidin), are employed for the management of chronic venous insufficiency. This combination has been reported to inhibit the inflammatory process in hyperpermeability induced by ischemia, a characteristic of

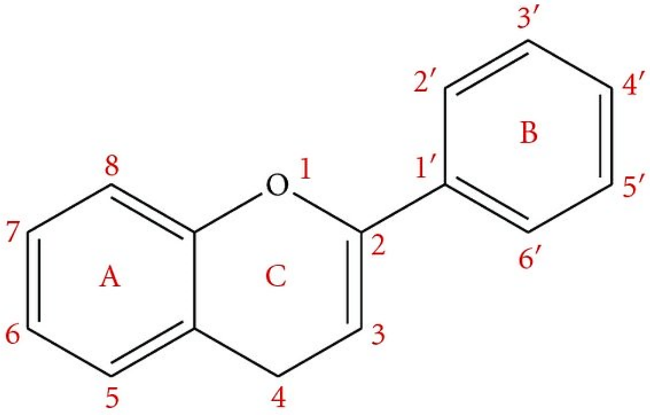

Figure 1(a): Common flavonoid carbon skeleton structure.

Table 1: Biological activities of citrus flavonoids.

Effect	Mechanism	Example
Antioxidant	Scavenges free radicals, protects lipids and DNA from oxidative stress	Hesperidin, Naringin (Madureira *et al.*, 2023)
Anti-inflammatory	Reduces cytokine production (e.g., TNF-α, IL-6) and inhibits NF-κB signaling	Nobiletin, Luteolin (Bellik *et al.*, 2012)
Cardioprotective	Improves lipid metabolism, reduces LDL oxidation, and enhances endothelial function	Hesperidin, Diosmin (Huwait and Mobashir, 2022; Mas-Capdevila *et al.*, 2020)
Anticancer	Induces apoptosis and inhibits tumour growth in cell studies	Nobiletin, Tangeretin (Morley *et al.*, 2007)
Antidiabetic	Enhances insulin sensitivity and glucose uptake	Naringin (Den Hartogh and Tsiani, 2019)
Neuroprotective	Protects against neuroinflammation and oxidative stress in brain tissues	Hesperidin, Nobiletin (Ho and Kuo, 2014)
Hepatoprotective	Reduces liver lipid accumulation and inflammation	Naringenin (Márquez-Quiroga *et al.*, 2025)

venous stasis. The protective effects of these flavonoids against inflammatory disorders have been demonstrated in both *in vivo* and *in vitro* studies, potentially through mechanisms such as mechanisms that include the inhibition of eicosanoid synthesis and/or antioxidant-mediated free radical scavenging. Diosmin and hesperidin appear to inhibit leukocyte attachment to the endothelial wall and subsequent migration of these cells into the interstitium (Awad *et al*., 2024; Gerges *et al*., 2022; Rutkowska *et al*., 2024). It was found that hesperidin has anti-inflammatory activity in the non-neuronal system due to the reduction of inflammatory mediators *via* reductions in proinflammatory cytokines through the nuclear factor kappa-light-chain-enhancer of activated B cell (NF-κβ) pathway (Kim *et al*., 2019; Tejada *et al*., 2019).

Oxidative stress and inflammation are major contributors to numerous life-threatening diseases and are mitigated by the biological activities of hesperidin and hesperetin, particularly their antioxidant and anti-inflammatory effects. The antioxidant activity of these compounds extends beyond radical scavenging to enhance cellular protection through the ERK/Nrf2 signaling pathway. *In vivo* and *in vitro* studies have demonstrated the potential of hesperidin, its metabolites, and derivatives in reducing inflammatory targets and molecular markers associated with chronic inflammation (Parhiz *et al*., 2015). Hesperidin supplementation has been shown to alleviate edema, reducing swelling due to fluid accumulation in the lower extremities, and is associated with improved vascular health (Chen *et al*., 2010). Additionally, it helps address issues such as unusual capillary leakiness, pain in the extremities, causing aches, night leg cramps, and weakness (Y. Li *et al*., 2019; Parhiz *et al*., 2015).

Antioxidant Properties

Hesperidin has demonstrated significant antioxidant properties in both chemical and biological assays (Wilmsen *et al*., 2005). Hesperidin also acts as an antioxidant by restoring the deficits in the activity of antioxidant enzymes, including Glutathione Peroxidase (GPx), glutathione reductase, catalase, and Superoxide Dismutase (SOD), which are downregulated (Kim *et al*., 2019). Hesperidin exhibits strong antioxidant properties that play a vital role in protecting biological systems from oxidative stress. Oxidative stress results from an imbalance between the production of Reactive Oxygen Species (ROS) and the body's antioxidant defense mechanisms, leading to cellular damage and the development of chronic diseases such as cardiovascular disorders, diabetes, cancer, and neurodegenerative conditions. Hesperidin exerts its antioxidant effects through multiple mechanisms (Table 2).

Neuroprotective Effects

Neurodegeneration is implicated in various neurological disorders, including Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis. Factors such as the accumulation of abnormal proteins, mitochondrial dysfunction, neuroinflammation, and oxidative stress contribute to the pathophysiology of neurodegenerative diseases (E. J. Choi and Ahn, 2008). Hesperetin exhibits significant neuroprotective effects through its antioxidant, anti-inflammatory, and anti-apoptotic mechanisms. It effectively scavenges ROS and enhances endogenous antioxidant defenses such as SOD, catalase, and GPx, thereby reducing lipid peroxidation and oxidative neuronal damage (Wang *et al*., 2013). Hesperetin also exerts anti-inflammatory actions by suppressing the secretion of TNF-α, IL-6, and IL-1β; reducing inducible iNOS and COX-2 gene expression; inhibiting NF-κB phosphorylation; and blocking IκBα phosphorylation and degradation (Li *et al*., 2023; Ren *et al*., 2016). Hesperidin has demonstrated neuroprotective effects against neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, and cadmium-induced neurodegeneration. In Alzheimer's disease models, hesperidin reduced oxidative stress and cognitive impairment by alleviating neuroinflammation mediated by TLR4. In Parkinson's disease models, hesperidin was effective in mitigating neuroinflammatory reactions and dopaminergic denervation, suggesting a significant potential as a neuroprotective agent. Hesperidin also aids in counteracting cadmium-induced neurotoxicity by activating antioxidant defenses without inducing apoptosis. Additionally, it exhibits antidepressant-like effects by modulating neuroinflammation associated with depressive behaviors, enhancing serotonergic activity, and increasing levels of BDNF (Li *et al*., 2023). Hesperetin also improves emotional memory and hippocampal long-term potentiation by enhancing AMPAR trafficking and balancing oxidants and antioxidants (Luo *et al*., 2021). Overall, hesperidin's multifaceted roles in neuroprotection and antidepressant activity

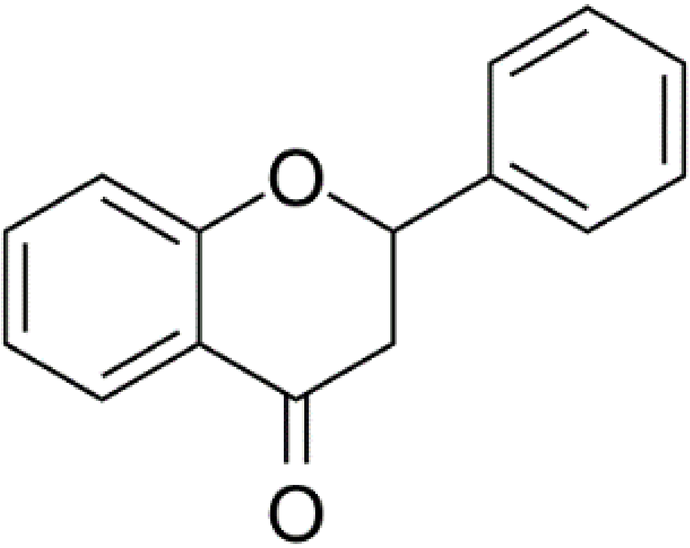

Figure 1(b): Flavanone.

Table 2: Antioxidant effects of hesperidin.

Mechanism	Description	Biological Impact
Free radical scavenging	Hesperidin donates hydrogen atoms or electrons to neutralize reactive oxygen species (ROS) and reactive nitrogen species (RNS), including superoxide anions, hydroxyl radicals, and peroxynitrite.	Protects biomolecules from oxidative damage and cellular injury (Liu *et al.*, 2023; Slika *et al.*, 2022).
Metal ion chelation	Binds with transition metal ions such as Fe^{2+} and Cu^{2+}, preventing their participation in Fenton-type reactions that generate free radicals.	Reduces metal-catalysed oxidative stress and lipid peroxidation (Abdullah *et al.*, 2025; Famurewa *et al.*, 2022).
Enhancement of antioxidant enzymes	Upregulates endogenous antioxidant enzymes such as SOD, CAT, and GPx.	Strengthens cellular antioxidant defense and detoxification capacity (Alizadeh *et al.*, 2025; Jomova *et al.*, 2024).
Inhibition of lipid peroxidation	Prevents peroxidative degradation of membrane lipids by scavenging lipid radicals.	Maintains cell membrane stability and integrity (Martínez-Noguera *et al.*, 2019).
Regulation of signaling pathways	Modulates redox-sensitive transcription factors, especially the Nrf2/ARE pathway, enhancing the expression of antioxidant and cytoprotective genes.	Promotes long-term antioxidant defense and reduces oxidative-induced inflammation (Martínez-Noguera *et al.*, 2021; Zhu *et al.*, 2020).

warrant further investigation into its mechanisms and therapeutic applications.

Neurobehavioral Effects

Preclinical evaluation of hesperidin in Sprague Dawley rats demonstrates a favorable neurobehavioral and safety profile. Repeated oral administration of hesperidin (25-100 mg/kg) for 28 days produced no significant effects on locomotor activity, grip strength, memory performance, or body weight. However, higher doses were associated with improved anxiety-related behavior, indicating a potential anxiolytic effect. Importantly, key biochemical markers of hepatic and renal function, including AST, ALT, ALP, bilirubin, urea, and creatinine, remain unaltered (Selvam *et al.*, 2023). Additionally, hesperidin has been shown to mitigate neurobehavioral deficits induced by environmental toxins, such as fluoride, including motor and memory impairments and depression-like behavior. Its protective effects are associated with improvements in brain biochemical markers and are suggested to involve PPAR-γ-mediated pathways, as inhibition of this receptor reduces hesperidin's efficacy (Jaiswal *et al.*, 2020). These findings suggest that hesperidin may enhance alertness and reduce anxiety without exerting adverse effects on systemic biochemical or organ function parameters, supporting its safety in preclinical models.

Antidiabetic Activity

Studies have demonstrated that hesperidin administration in diabetic models significantly reduces fasting blood glucose levels and food intake, while increasing serum and pancreatic insulin levels, pancreatic-duodenal homeobox-1 protein expression, and body weight (Hanchang *et al.*, 2019). Hesperidin also exerts protective effects on pancreatic β-cells by enhancing the activities of antioxidant enzymes, including SOD and GPx, while reducing nitrotyrosine and malondialdehyde levels (Mallik *et al.*, 2024; Mirzaei *et al.*, 2023). Additionally, hesperidin treatment decreases the concentration of TNF-α and the expression of endoplasmic reticulum stress markers GRP78 and CHOP proteins in the pancreas of diabetic rats. Furthermore, hesperidin regulates the expressions of apoptosis-regulatory proteins, upregulating anti-apoptotic Bcl-xL while downregulating pro-apoptotic Bax and cleaved caspase-3, and inhibiting the activation of the DNA repair protein poly (ADP-ribose) Polymerase (PARP) (Hanchang *et al.*, 2019). Hesperetin has also shown efficacy against hyperlipidemia and hyperglycemia and prevents diabetes-induced histological changes in the liver and kidney (Jayaraman *et al.*, 2018). Furthermore, it effectively reduces blood glucose levels and normalizes hepatic and renal biochemical markers (Parasuraman and Thinagaran, 2023). Mechanisms of antidiabetic activity of hesperidin are summarized in Table 3.

Dermatological Effect

Studies suggested that hesperidin supports proper cutaneous function, including wound healing, UV protection, anti-skin cancer effects, and skin lightening. It contributes to the homeostasis of epidermal permeability barrier through its antioxidant properties, inhibition of MAPK-dependent signaling pathways, and stimulation of epidermal proliferation, differentiation, and lipid production (Man *et al.*, 2019).

Hepatoprotective Effect

Hesperidin can protect the liver from injury, which is caused by drugs such as diclofenac *via* antioxidant, anti-inflammatory, and antiapoptotic actions (Hassan *et al.*, 2021). Hesperidin and neohesperidin dihydrochalcone have been found to reduce the

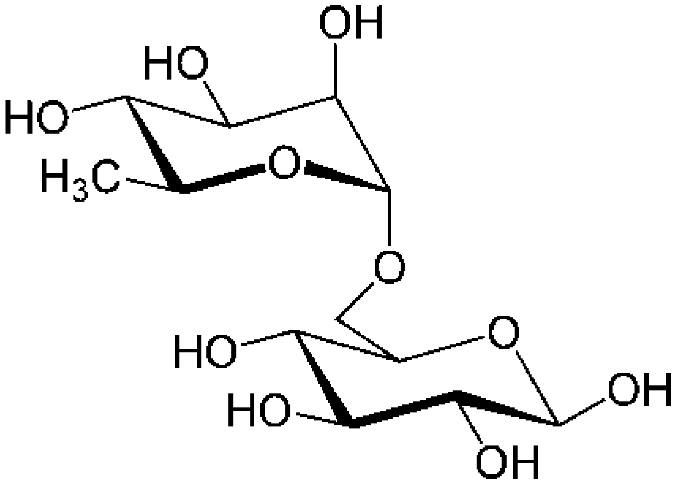

Figure 2(a): Structure of rutinose.

formation of ulcers in cold-restraint ulcers, suggesting that the amount of gastric mucus is not involved in their antiulcer activity (Suárez *et al.*, 1996). Both hesperidin and neohesperidin from bittersweet orange peels have been found to aggravate gastric damage caused by indomethacin administration, suggesting that they have proinflammatory properties in ulcerogenic stomach lining (Hamdan *et al.*, 2014).

Gastroprotective Effects

The combination of lycopene and hesperidin has been shown to protect experimentally induced ulcers in laboratory rats. Lycopene, a carotenoid found in vegetables and fruits, showed substantial improvement in ulcer conditions when pretreated with both hesperidin and lycopene. However, a combination of lycopene and hesperidin showed more significant restoration of gastric function compared to sham-operated rats (Jain and Katti, 2015). Hesperidin has also been found to protect against stress-induced gastric ulcer in diabetic rats through the regulation of peroxisome proliferator-activated receptor gamma (Elshazly *et al.*, 2018). In rats with chronic gastric ulcers induced by acetic acid, hesperidin accelerates the gastric healing process by stimulating the enzymatic activity of Glutathione-S-transferase in the gastric mucosa tissue by 35%, reducing the prevalence and severity of gastric ulcers. Hesperidin also normalises superoxide dismutase and catalase activities at similar levels compared to those in the non-ulcerated group (Silva *et al.*, 2019).

Gonadoprotective Effects

Hesperidin has demonstrated significant protective effects against $AlCl_3$-induced testicular toxicity in experimental animal models (Parasuraman *et al.*, 2024; Yan *et al.*, 2024). In a study conducted on male Sprague-Dawley rats, exposure to $AlCl_3$ resulted in marked reproductive dysfunction, including oligospermia, structural alterations of the seminiferous tubules, and impaired testicular morphology. These adverse effects were accompanied by significant disturbances in liver and kidney function, indicating systemic toxicity. Administration of hesperidin at doses of 100 mg/kg and 200 mg/kg effectively mitigated $AlCl_3$-induced biochemical, hematological, and histopathological alterations. Hesperidin treatment preserved normal testicular architecture, maintained seminiferous tubule integrity, and exhibited notable nephroprotective effects. The protective actions of hesperidin are largely attributed to its antioxidant properties, which counteract oxidative stress and cellular damage induced by aluminum exposure (Parasuraman *et al.*, 2024).

Table 3: Antidiabetic activity of hesperidin.

Pathway	Effect of hesperidin
Glucose metabolism and enzyme regulation	Increase the activity of hexokinase and glucose-6-phosphate dehydrogenase (Sundaram *et al.*, 2019). Decrease the activity of gluconeogenic enzymes like glucose-6-phosphatase and PEPCK (Mirzaei *et al.*, 2023; Peng *et al.*, 2021). Decrease glucose-6-phosphatase and fructose-1,6-bisphosphatase (Sundaram *et al.*, 2019).
Insulin receptor signalling/insulin sensitivity	Enhancing the activity of glucokinase, inducing the phosphorylation of insulin receptor and phosphoinositide-dependent kinase 1 in the liver (Peng *et al.*, 2021). Decreasing the activity of glucose-6-phosphatase and phosphoenolpyruvate carboxykinase in the liver (Peng *et al.*, 2021). Restore the functioning of hepatic glucose metabolic enzymes (Mirzaei *et al.*, 2023).
Glucose uptake in peripheral tissues	Enhancement of glucose uptake in primary rat adipocytes and in skeletal muscle cell line (Peng *et al.*, 2021) (Dhanya and Jayamurthy, 2020).
Antioxidant / anti-inflammatory effects	Increases the levels of antioxidant enzymes both in the bloodstream and the pancreas (Mirzaei *et al.*, 2023). Reduces reactive oxygen species (ROS), increases antioxidant enzyme activities (SOD, CAT, glutathione, etc.) (Mahmoud *et al.*, 2012). Decreases markers of inflammation (e.g. TNF-α, IL-6) (Mahmoud *et al.*, 2012).
Inhibition of postprandial hyperglycemia	Inhibits α-glucosidase enzyme (Kaliaperumal *et al.*, 2023).

Safety profile

In acute oral toxicity studies, hesperidin exhibited low toxicity, causing only 10% mortality at a high dose of 5000 mg/kg in Sprague-Dawley rats, with a calculated median lethal dose of 4837.5 mg/kg. Sub-chronic toxicity evaluation revealed that hesperidin administered orally at doses of 250 and 500 mg/kg did not produce any adverse effects on body weight, food intake, clinical signs, ophthalmological and neurological parameters, urinalysis, hematology, clinical biochemistry, organ weights, or gross pathology. However, at 1000 mg/kg, significant alterations were observed in body and organ weights, hematological and biochemical parameters, and tissue histopathology. Based on these findings, the LOAEL for hesperidin is determined to be 1000 mg/kg for both male and female rats, indicating a favorable safety profile at lower doses (Li *et al.*, 2019).

Clinical Effectiveness of Hesperidin

Hesperidin has been the subject of numerous clinical trials investigating its effects across metabolic, cardiovascular, bone, cognitive, and immune-related conditions. In metabolic disorders, hesperidin has been shown to improve insulin sensitivity and glucose metabolism in patients with metabolic syndrome and prediabetes (NCT02610491, NCT03737422), with additional benefits observed when combined with flaxseed in non-alcoholic fatty liver disease and prediabetes (Maurer Sost *et al.*, 2023; Yari *et al.*, 2021). Cardiovascular and vascular studies indicate that diosmin/hesperidin combinations can reduce symptoms of chronic venous insufficiency, varicose veins, and support post-operative rehabilitation (NCT03471910, NCT06753448), while orange juice-derived hesperidin has been reported to enhance vascular compliance and endothelial function (NCT04731987, NCT04234100) (Bioavailability of Hesperidine and Narirutin From Orange Juice to Identify Metabotypes in Hypertension (FLAVOTIP); NCT No: NCT04234100, 2022; Girgin and Duman, 2025; Steinbruch *et al.*, 2020; Verny *et al.*, 2021). In postmenopausal women, hesperidin supplementation positively influences bone biomarkers and mineral density, suggesting potential benefits for osteoporosis management (NCT00330096) (Loukas *et al.*, 2024). Hesperidin also appears to enhance exercise performance and endurance in athletes (NCT04597983) and may support cognitive function in the elderly when used alongside dietary supplements (NCT06352099) (Giovannini *et al.*, 2026; Martínez Noguera *et al.*, 2021; Martínez-Noguera *et al.*, 2021). Safety and bioavailability studies indicate that hesperidin is generally well-tolerated, though its clinical efficacy can vary depending on the formulation and co-administration with other flavonoids (NCT05158192, NCT04234100) (Bioavailability of Hesperidine and Narirutin From Orange Juice to Identify Metabotypes in Hypertension (FLAVOTIP); NCT No: NCT04234100, 2022) (Bioavailability of Diosmin/Hesperidin

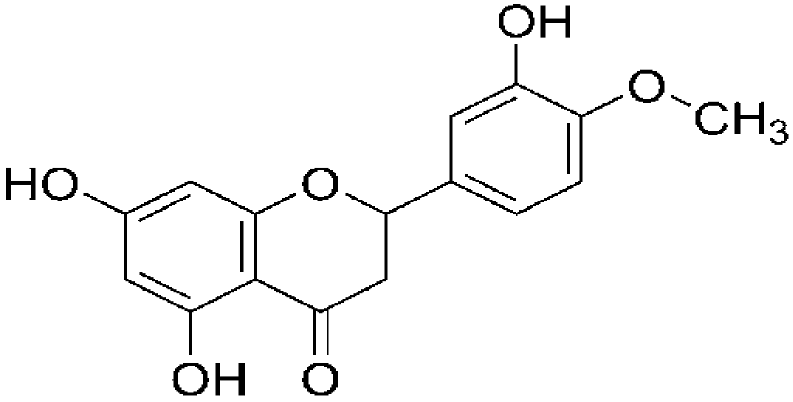

Figure 2(b): Structure of Hesperetin.

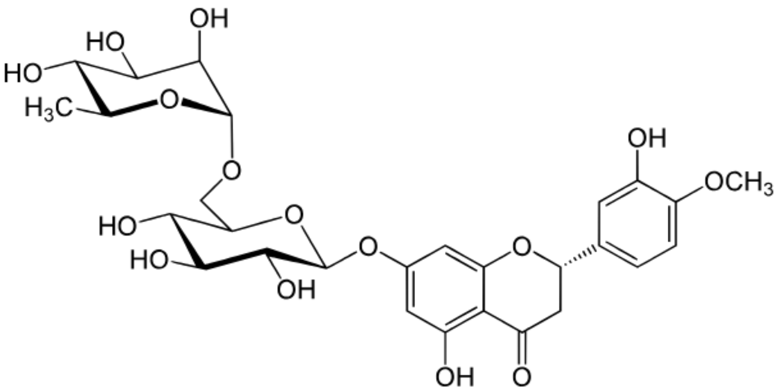

Figure 2(c): Structure of Hesperidin.

(90/10) 500 Mg Tablets With Regards to Reference Product; NCT No: NCT05158192, 2022). Additionally, hesperidin has been explored in COVID-19 therapy in combination with diosmin, although results are largely unknown (NCT04452799), and in other conditions such as rheumatoid arthritis (*Hesperidin and Diosmin for Treatment of COVID-19; NCT No: NCT04452799*, 2020), Helicobacter pylori infection, hyperglycemia control, and dental pulp treatment. These findings highlight the multiple beneficial effects of hesperidin and support the need for further large-scale, controlled trials to clarify its therapeutic potential.

CONCLUSION

Hesperidin, a prominent citrus bioflavonoid, exhibits a broad spectrum of biological activities, including anti-inflammatory, antioxidant, antihypertensive, antimicrobial, anticarcinogenic, and vasodilator properties. It is used as a marketed drug and nutraceutical and has potential therapeutic applications in neurodegenerative disorders. The compound has been found to improve venous tone, enhance microcirculation, assist in the healing of venous ulcers, and is employed in the management of chronic venous insufficiency, haemorrhoids, and the prevention of postoperative thromboembolism. Its supplementation is associated with addressing issues like unusual capillary leakiness, pain in the extremities, causing aches, night leg cramps, and weakness. Collectively, these multifaceted benefits affirm hesperidin as a bioactive compound of considerable pharmacological and clinical relevance.

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ABBREVIATIONS

$AlCl_3$: Aluminum Chloride; **ALP:** Alkaline Phosphatase; **ALT:** Alanine Aminotransferase; **AMPAR:** α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic Acid Receptor; **AST:** Aspartate Aminotransferase; **Bax:** Bcl-2-associated X protein; **BDNF:** Brain-Derived Neurotrophic Factor; **CAT:** Catalase; **COX-2:** Cyclooxygenase-2; **DNA:** Deoxyribonucleic Acid; **GPx:** Glutathione Peroxidase; **IL:** Interleukin; **iNOS:** Inducible Nitric Oxide Synthase; **LDL:** Low-Density Lipoprotein; **LOAEL:** Low Observed Adverse Effect Level; **MAPK:** Mitogen-Activated Protein Kinase; **mRNA:** Messenger Ribonucleic Acid; **NF-κB:** Nuclear Factor kappa-light-chain-enhancer of activated B cells; **PEPCK:** Phosphoenolpyruvate Carboxykinase; **PPAR-γ:** Peroxisome Proliferator-Activated Receptor Gamma; **RNS:** Reactive Nitrogen Species; **ROS:** Reactive Oxygen Species; **SOD:** Superoxide Dismutase; **TLR4:** Toll-Like Receptor 4; **TNF-α:** Tumor Necrosis Factor-alpha; **UV:** Ultraviolet.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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