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HESPERIDIN: A MULTIFUNCTIONAL BIOFLAVONOID IN HEALTH AND DISEASE

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ABSTRACT

Hesperidin, a naturally occurring flavanone glycoside predominantly found in citrus fruits such as oranges and lemons, has emerged as a multifunctional bioflavonoid with significant pharmacological potential. It possesses a wide range of biological activities including antioxidant, anti-inflammatory, antiapoptotic, and cardioprotective effects. Despite its abundance in nature and long history in traditional medicine, the therapeutic application of hesperidin has been limited by its poor aqueous solubility and low bioavailability. Recent advances in nanotechnology and formulation science have focused on enhancing its pharmacokinetic properties and systemic delivery. Hesperidin exerts its biological actions through multiple molecular pathways, including modulation of oxidative stress via Nrf2/ARE signaling, inhibition of NF-κB-mediated inflammation, and regulation of apoptotic proteins. Evidence from preclinical and emerging clinical studies suggests its potential role in preventing and managing chronic disorders such as cardiovascular diseases, diabetes, neurodegenerative conditions, hepatic dysfunctions, and cancers. This review provides a comprehensive analysis of hesperidin's chemistry, biosynthesis, mechanisms of action, therapeutic applications, and current advancements in drug delivery approaches. It also highlights the limitations in its clinical translation, emphasizing the need for standardized formulations and omics-based research to fully exploit its potential as a multitarget therapeutic compound in modern medicine.

1. INTRODUCTION

Flavonoids are a diverse group of naturally occurring polyphenolic compounds that contribute to the color, flavor, and pharmacological properties of many fruits, vegetables, and medicinal plants. Among them, citrus bioflavonoids constitute a prominent subclass known for their significant roles in human health due to their antioxidant, anti-inflammatory, and vasoprotective properties.[1,2] These compounds, abundantly found in oranges, lemons, grapefruits, and tangerines, have been extensively studied for their therapeutic potential in chronic diseases linked to oxidative stress and inflammation.[3]

Hesperidin (hesperetin-7-rutinoside) is one of the most abundant flavanone glycosides present in citrus peels and pulps. It was first isolated from the inner white layer (albedo) of citrus fruits in the early 19th century and has since been recognized for its multifaceted pharmacological activities.[4] Structurally, hesperidin consists of the aglycone hesperetin bound to the disaccharide rutinose, conferring unique physicochemical properties that influence its solubility, metabolism, and biological activity.[5]

From a nutritional standpoint, hesperidin contributes to the health-promoting effects of citrus fruits, often associated with improved vascular integrity, reduced capillary permeability, and enhanced antioxidant defense.[6] Historically, hesperidin-containing preparations have been used for treating hemorrhoids, venous insufficiency, and inflammatory conditions in European and Asian traditional medicine.[7]

Despite its broad biological potential, hesperidin's poor aqueous solubility and low oral bioavailability have limited its clinical efficacy.[8] Upon ingestion, hesperidin undergoes hydrolysis by intestinal microbiota to yield hesperetin, which is more readily absorbed and pharmacologically active.[9] However, variability in gut metabolism and poor systemic distribution remain major challenges to its therapeutic translation.[10]

Recent years have witnessed a resurgence of interest in natural therapeutics, driven by concerns over synthetic drug toxicity and the global push for plant-based alternatives.[11] Hesperidin stands out as a multifunctional bioactive compound targeting multiple molecular pathways, making it an attractive candidate for preventing and managing chronic disorders such as cardiovascular diseases, diabetes, neurodegeneration, and cancer.[12,14]

2. Chemistry and Biosynthesis

Hesperidin belongs to the class of flavanone glycosides, characterized by a three-ring (C6–C3–C6) structure comprising two aromatic rings (A and B) connected via a heterocyclic pyran ring (C). Structurally, hesperidin is the 7-rutinoside of hesperetin, where a disaccharide moiety—rutinose (α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranose)—is attached at the C7 hydroxyl position of the aglycone.[15] This glycosylation significantly influences its solubility, stability, and intestinal absorption.

The biosynthesis of hesperidin in citrus plants occurs through the phenylpropanoid and flavonoid pathways. It begins with the deamination of phenylalanine to cinnamic acid, catalyzed by phenylalanine ammonia-lyase (PAL). Successive hydroxylation and methylation reactions produce naringenin chalcone, which is then isomerized to naringenin. The enzyme flavanone 3′-hydroxylase catalyzes the hydroxylation of naringenin to yield eriodictyol, which is methylated by O-methyltransferase to form hesperetin. Glycosylation by UDP-rhamnosyl and glucosyl transferases finally yields hesperidin.[16,17]

For analytical identification, high-performance liquid chromatography (HPLC) and liquid chromatography–mass spectrometry (LC-MS) remain the gold-standard techniques for quantification of hesperidin in plant matrices and formulations.[18] Advanced methods such as UPLC-QTOF-MS and NMR spectroscopy provide precise structural elucidation and metabolite profiling.[19] The concentration of hesperidin varies across citrus species, with *Citrus sinensis* and *Citrus aurantium* peels being the richest sources.[20]

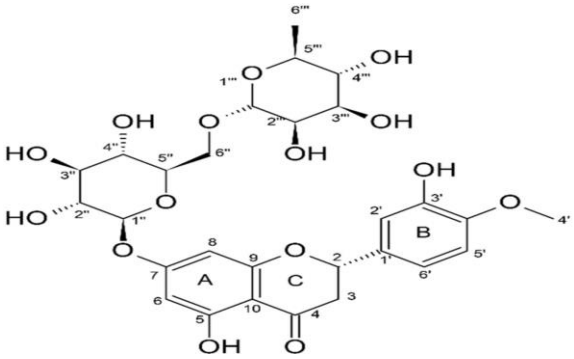

Figure 1: Chemical structure of Hesperidin.

3. Pharmacokinetics and Bioavailability

Despite its potent pharmacological potential, hesperidin's oral bioavailability remains limited due to poor water solubility (0.005 g/100 mL) and limited intestinal permeability.[21]

Following oral administration, hesperidin is hydrolyzed by colonic microbiota β-glucosidases into its aglycone form, hesperetin, which is more lipophilic and readily absorbed across the intestinal epithelium.[22] Once absorbed, hesperetin undergoes extensive phase II metabolism, producing conjugated metabolites such as hesperetin-7-O-glucuronide and hesperetin-3′-O-sulfate, which circulate systemically.[23]

The pharmacokinetic profile of hesperidin is influenced by dietary composition, gut microbiota diversity, and formulation strategy.[24] Studies have shown that plasma concentrations of hesperetin typically peak between 4–6 hours post-ingestion, with an elimination half-life of approximately 5–7 hours.

To overcome its low bioavailability, several formulation strategies have been developed, including nanoparticles, solid dispersions, micelles, phospholipid complexes, and co-crystals.[26] Hesperidin–phospholipid complexes (phytosomes) have shown improved intestinal absorption and sustained plasma levels.[27] Nanocrystal formulations enhance dissolution rate and stability, while polymeric nanoparticles (PLGA-based) increase cellular uptake and tissue distribution.[28,29] Co-crystallization with amino acids or sugars has also demonstrated improved dissolution and antioxidant activity.[30]

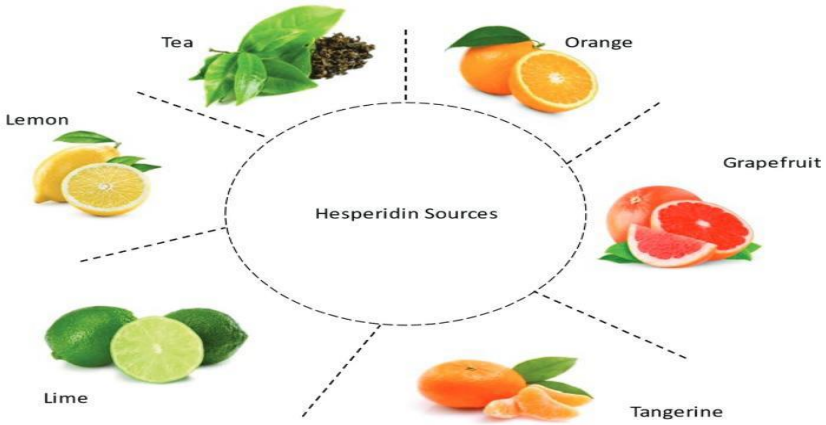

Figure 2: Sources of Hesperidin.

4. Mechanisms of Action

4.1. Antioxidant Mechanisms

Hesperidin exhibits strong radical scavenging activity against reactive oxygen species (ROS) such as superoxide anions, hydroxyl radicals, and peroxynitrite.[31] It enhances endogenous antioxidant defense by upregulating enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx).[32] Mechanistically, hesperidin activates the

Nrf2/ARE signaling pathway, promoting the transcription of antioxidant response genes like HO-1 and NQO1.[33] Through this mechanism, it mitigates oxidative stress-mediated cellular injury in neuronal, hepatic, and cardiac tissues.[34]

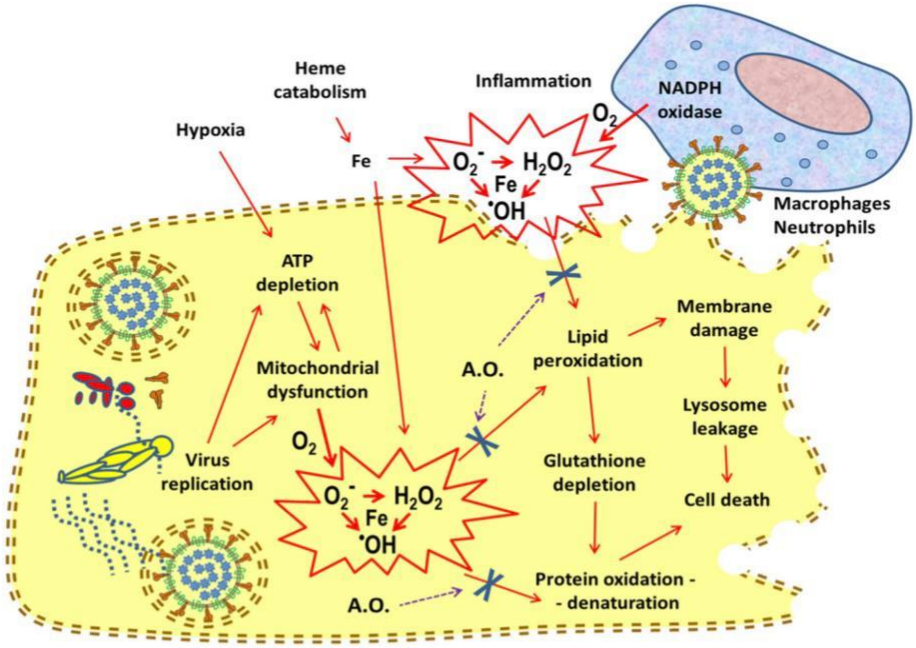

Figure 3: Schematic representation of the mechanisms of generation of oxygen free radicals in the course of Coronavirus disease 2019 (COVID-19), and assumptions about the antioxidant (A.O.) action sites, indicated with "X".

4.2. Anti-inflammatory Mechanisms

Hesperidin suppresses inflammation by inhibiting NF-κB and MAPK signaling cascades, leading to decreased expression of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6.[35] It also inhibits COX-2 and iNOS expression, reducing prostaglandin and nitric oxide production.[36] In chronic inflammatory models, hesperidin attenuates macrophage activation and endothelial dysfunction, thereby reducing vascular inflammation.[37] The compound's modulation of TLR4/MyD88 signaling further contributes to its anti-inflammatory efficacy.[38]

4.3. Antiapoptotic and Cytoprotective Effects

Hesperidin exerts antiapoptotic effects by regulating the Bcl-2/Bax ratio, inhibiting caspase-3 and caspase-9 activation, and preventing cytochrome c release from mitochondria.[39] It maintains mitochondrial integrity by stabilizing the membrane potential and reducing oxidative damage.[40] In neuronal and cardiac cells, hesperidin confers cytoprotection by activating PI3K/Akt signaling, leading to enhanced cell survival under oxidative stress.[41]

Table 1: Molecular Mechanisms and Targets of Hesperidin.

Mechanism	Molecular Pathway	Key Outcome	Reference
Antioxidant	Nrf2/ARE activation	↑ SOD, CAT, GPx	[28]
Anti-inflammatory	NF-κB inhibition	↓ TNF-α, IL-6	[32]
Antiapoptotic	Bcl-2/Bax modulation	↓ Caspase-3 activation	[37]
Mitochondrial protection	PGC-1α pathway	↑ ATP, ↓ ROS	[38]

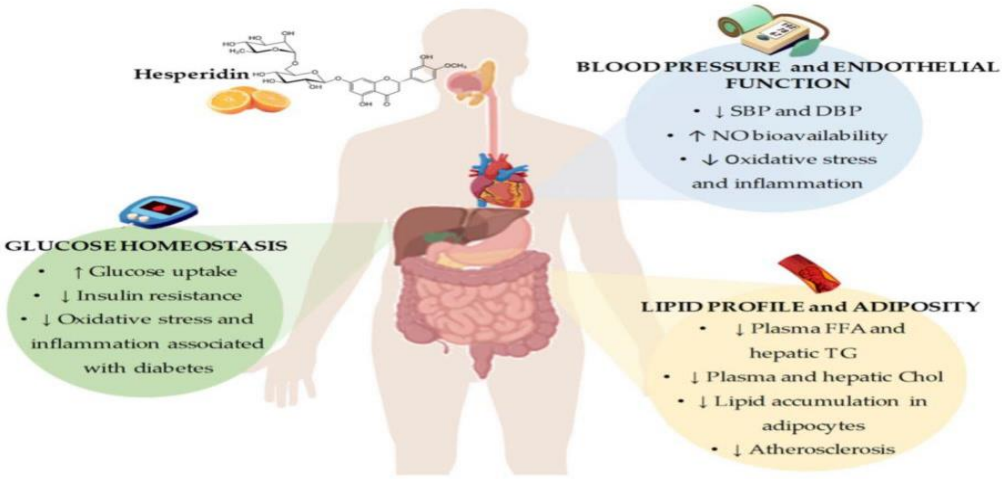

Figure 4: Summary of the most representative effects of hesperidin consumption and its derivatives on cardiovascular risk factors, including glucose homeostasis, blood pressure and endothelial function, and lipid profile and adiposity. SBP: systolic blood pressure; DBP: diastolic blood pressure; NO: nitric oxide; FFA: free fatty acids; TG: triglycerides; Chol: cholesterol.

5. Therapeutic Applications in Disease Models

5.1. Neuroprotective Effects

Numerous studies have demonstrated the neuroprotective role of hesperidin in Alzheimer's disease, Parkinson's disease, and cerebral ischemia.[42] In Alzheimer's models, hesperidin reduces amyloid-β aggregation, suppresses acetylcholinesterase activity, and mitigates oxidative damage.[43] It inhibits microglial activation and neuroinflammation via NF-κB and MAPK inhibition.[44] In cerebral ischemia, hesperidin improves neurological scores and reduces infarct volume by upregulating Nrf2 and HO-1 expression.[45]

5.2. Cardioprotective and Vascular Effects

Hesperidin has demonstrated cardioprotective properties through modulation of lipid metabolism, enhancement of endothelial function, and attenuation of oxidative stress.[46] It improves endothelial nitric oxide synthase (eNOS) activity, leading to vasodilation and improved blood pressure regulation.[47] In hyperlipidemic models, hesperidin lowers serum

LDL and triglyceride levels while elevating HDL cholesterol.[48] The compound also reduces myocardial apoptosis and inflammatory cytokines, thereby protecting cardiac tissue from ischemia-reperfusion injury.[49]

Table 2: Cardioprotective Effects of Hesperidin.

Model / Study	Dose	Duration	Key Findings
Rodent myocardial ischemia	50 mg/kg	14 days	Reduced infarct size, improved cardiac output
Human clinical trial	500 mg/day	8 weeks	Improved endothelial function, lowered BP
LDL oxidation study	800 mg/day	6 weeks	Decreased LDL oxidation, improved HDL

5.3. Antidiabetic and Metabolic Effects

Hesperidin improves insulin sensitivity, enhances glucose uptake, and modulates lipid metabolism.[50] It activates AMPK signaling, resulting in reduced gluconeogenesis and lipid accumulation.[51] In diabetic rats, hesperidin supplementation decreases serum glucose, HbA1c, and oxidative stress markers, while restoring pancreatic β-cell function.[52] Furthermore, it attenuates obesity-induced inflammation by downregulating TNF-α and leptin signaling.[53]

5.4. Hepatoprotective and Gastrointestinal Effects

Hesperidin protects hepatic tissue against toxin-induced injury (CCl_4, paracetamol, and ethanol models) by enhancing antioxidant enzyme activities and reducing lipid peroxidation.[54] It stabilizes hepatic membranes, restores mitochondrial function, and prevents hepatic apoptosis.[55] In gastrointestinal disorders, hesperidin ameliorates colitis and gastric ulcers through suppression of inflammatory mediators and reinforcement of mucosal antioxidant defense.[56]

5.5. Anti-Cancer Potential

Hesperidin exhibits cytotoxic and antiproliferative effects in various cancer cell lines, including breast, colon, lung, and hepatic carcinomas.[57] It induces apoptosis via mitochondrial pathways, inhibits angiogenesis by downregulating VEGF expression, and suppresses oncogenic signaling pathways such as PI3K/Akt and STAT3.[58,59] Hesperidin also sensitizes tumor cells to chemotherapeutic agents like doxorubicin and cisplatin, suggesting synergistic potential.[60]

5.6. Immunomodulatory and Antiviral Roles

Hesperidin enhances immune cell function, promotes macrophage phagocytosis, and regulates cytokine release.[61] During viral infections, including COVID-19, computational docking and in vitro studies have shown that hesperidin can bind to SARS-CoV-2 main protease (Mpro) and spike receptor-binding domains, potentially inhibiting viral entry.[62,63] It also modulates immune responses, reducing cytokine storms by balancing Th1/Th2 cytokine expression.[64]

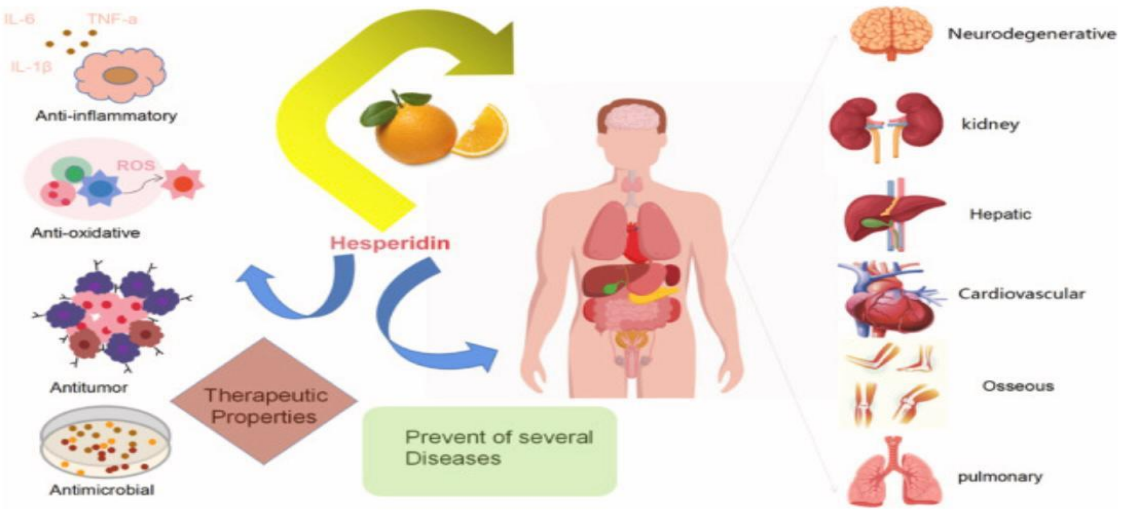

Figure 5: Biological activity of Hsd and Hst and its impact on diseases.

Table 3: Summary of Disease Models and Observed Therapeutic Effects of Hesperidin.

Disease Model	Mechanism of Benefit	Key Findings	Reference
Alzheimer's	↓ Amyloid-β, ↑ BDNF	Improved memory, reduced oxidative stress	[40]
Parkinson's	↑ Dopamine levels	Neuroprotection, reduced apoptosis	[41]
Myocardial infarction	↓ TNF-α, ↑ NO	Improved cardiac function	[49]
Diabetes	↑ GLUT-4, ↓ insulin resistance	Better glucose tolerance	[51]
Liver injury	↓ ALT, AST	Hepatocyte regeneration	[54]
Colon cancer	↓ STAT3, VEGF	Tumor growth inhibition	[59]

6. Emerging Areas

Recent advances in formulation science have enabled the development of nanoformulations of hesperidin, including liposomes, solid lipid nanoparticles, nanoemulsions, and polymeric systems, to overcome bioavailability limitations.[65] These carriers enhance solubility, protect against degradation, and achieve sustained release.[66] Hesperidin phytosomes have shown improved pharmacokinetics and efficacy in animal models of oxidative stress.[67]

Synergistic effects have been observed when hesperidin is combined with curcumin, quercetin, or vitamin C, leading to enhanced antioxidant and anti-inflammatory activities.[68] Moreover, growing evidence indicates that hesperidin modulates the gut microbiota, increasing beneficial bacterial populations such as *Lactobacillus* and *Bifidobacterium*, which in turn enhance systemic metabolic health.[69]

In the cosmeceutical domain, hesperidin demonstrates potential as a skin-protective and anti-aging agent, promoting collagen synthesis, reducing UV-induced oxidative damage, and improving dermal microcirculation.[70]

Table 4: Novel Formulations and Delivery Systems for Hesperidin.

Formulation	Carrier Type	Improvement Observed	Reference
Nanoemulsion	Lipid-based	3×higher bioavailability	[65]
Phytosome	Phosphatidylcholine	Enhanced absorption, stability	[67]
Solid lipid nanoparticles	Stearic acid	Improved sustained release	[66]
Co-crystals	Nicotinamide	Faster dissolution rate	[79]
Nanofibers	PVA matrix	Topical cosmeceutical use	[70]

7. Clinical Evidence

Clinical studies have validated several preclinical findings regarding hesperidin's benefits. Supplementation with hesperidin-rich citrus extract (500–1000 mg/day) has been shown to improve endothelial function, reduce blood pressure, and lower oxidative markers in hypertensive and metabolic syndrome patients.[71,72] In diabetic subjects, hesperidin administration improved glycemic control and lipid profiles.[73] A randomized trial demonstrated significant improvement in vascular reactivity and reduction in C-reactive protein after 12 weeks of hesperidin supplementation.[74]

The compound is generally safe and well-tolerated, with no major adverse effects reported at doses up to 1000 mg/day.[75] However, clinical heterogeneity in dose, formulation, and population warrants further standardization.[76]

8. Challenges and Future Perspectives

Despite its wide-ranging pharmacological effects, hesperidin faces challenges in clinical translation, primarily due to poor solubility, low absorption, and metabolic instability.[77] There is an urgent need for standardized formulations and validated biomarkers to assess its systemic bioactivity.[78] Nanoformulations, co-crystals, and phospholipid complexes present promising solutions for enhanced therapeutic efficacy.[79]

Future research should focus on omics-based approaches—transcriptomics, proteomics, and metabolomics—to elucidate hesperidin's multitarget interactions.[80] Well-designed clinical trials are essential to confirm efficacy, safety, and pharmacokinetic profiles in diverse populations. Integration of hesperidin into nutraceuticals, functional foods, and pharmaceuticals holds substantial promise for preventive and therapeutic healthcare.[81]

9. CONCLUSION

Hesperidin represents a multifunctional bioflavonoid with broad-spectrum pharmacological activities including antioxidant, anti-inflammatory, cardioprotective, neuroprotective, and anticancer effects. Its ability to modulate multiple signaling pathways underscores its potential as a multitarget therapeutic agent in complex chronic diseases. While challenges in bioavailability and standardization persist, emerging nanotechnological and formulation strategies have begun to bridge the gap between preclinical efficacy and clinical application. Future research integrating systems biology and translational medicine will be crucial in establishing hesperidin as a cornerstone molecule in the development of next-generation phytopharmaceuticals.

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