



DOSSIER · SUBSTANCE

Hesperetin

Hesperetin is a **flavanone** found in citrus fruits, with research focusing on **bioavailability, metabolism and endothelial effects**. The most notable finding is that controlled studies show enzymatic modifications can enhance uptake — yet the clinical relevance of these findings remains to be established.

145

STUDIES IN
TOTAL

27

IN HUMANS

10

OF WHICH
CONTROLLED

1

IN ANIMALS

43

IN THE LAB

Figures from the IHR study database · Last updated 2026-10-16

How to Read This Dossier

ESTABLISHED

measured in humans, with a comparison group

PLAUSIBLE

supported by mechanism, animal studies or observation

HYPOTHESIS

a likely connection that still needs to be tested

Hesperetin at a glance

ORIGIN:

Hesperetin is a plant-derived secondary metabolite belonging to the flavanone group, primarily found in citrus fruits such as oranges, grapefruits, and lemons. It is formed as the aglycone of the glycoside hesperidin through enzymatic cleavage in the intestine and is present in fresh fruits, juices, peels, and industrial extracts. Concentrations vary depending on the variety, ripeness, and processing methods.

EVIDENCE BASE:

145 reviewed studies · 10 controlled human trials · 17 observational studies · 16 review articles · 1 animal study · 32 cell culture studies

STRONGEST EVIDENCE:

- **Bioavailability** Enzymatic modification (e.g., with α-rhamnosidase) significantly enhances the absorption of hesperetin: In a crossover study, plasma concentration (AUC) doubled and maximum concentration (Cmax) quadrupled after administration of hesperetin-7-glucoside compared to hesperidin.
- **Endothelial function** A study with 24 participants reported an improvement in endothelial function in metabolic syndrome after three weeks of 500 mg hesperidin intake, with a significant increase in flow-mediated dilation (FMD) and reduced TNF-α-induced monocyte adhesion.
- **Heart and circulation:** Flavanone-rich citrus beverages, which include hesperetin metabolites, showed a counteraction of postprandial deterioration of endothelial function in a study, correlating with elevated plasma levels of these metabolites and nitrite.
- **Metabolism:** A hesperetin-sweetened beverage (50 mg/L) reduced glycaemic fluctuations and energy intake in a crossover study with 32 participants by replacing sucrose while maintaining sweetness.
- **Inflammation** Preclinical cell culture studies suggest that hesperetin metabolites such as hesperetin-7-O-glucuronide may inhibit NADPH oxidase activity and promote NO release in human endothelial cells, indicating potential anti-inflammatory effects.

LIMITATIONS:

- **Long-term studies** There is a lack of long-term studies with clinical endpoints (e.g., cardiovascular events, diabetes progression) and systematic investigations in at-risk populations.
- **Standardisation** Studies use varying preparations (juices, extracts), which complicates comparability of results and hinders the isolation of specific hesperetin effects.
- **Interindividual variability** The metabolism of hesperetin varies widely between individuals, potentially due to genetic polymorphisms or differences in gut microbiota.

ASSESSMENT:

Hesperetin, a flavanone from citrus fruits, shows effects on bioavailability, endothelial function, and inflammatory markers in human studies, while long-term effects and clinical endpoints remain unresolved.

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1. What Hesperetin Is and How It Is Absorbed

Hesperetin is a **plant-derived secondary metabolite** belonging to the **flavanone** group, primarily found in **citrus fruits** such as oranges, grapefruits, and lemons. Chemically, it is the **aglycone** of the glycoside **hesperidin** (hesperetin-7-O-rutinoside), which is released through enzymatic cleavage in the intestine. Natural sources include fresh fruits, juices, peels, and industrial extracts, with concentrations varying by variety, ripeness, and processing. As a **lipophilic molecule**, hesperetin is absorbed in the small intestine after release from hesperidin, whereas the glycosidic hesperidin itself is cleaved by microbial enzymes in the large intestine.

The **bioavailability of hesperetin** is a key research focus, as it determines potential applications. Studies show that **enzymatic pretreatment** (e.g., with α-rhamnosidase) increases the solubility of hesperidin and accelerates the absorption of hesperetin. After absorption, hesperetin undergoes **glucuronidation and sulfation** in the liver, with metabolites—particularly **hesperetin-7-O-glucuronide**—circulating in the bloodstream. Plasma levels peak after several hours, with high interindividual variability. Crucially, **not native hesperetin but its metabolites** represent the active forms—a factor often overlooked in preclinical studies.

2. What the Studies Show in Detail

The key human trials and major reviews—grouped by application area, including population, duration, formulation, measurement parameters, and outcomes as reported in the original studies. Numbers are included only where the study provides them.

Distribution of **controlled human trials** by application area—the numbers are not additive, as a single study may address multiple areas:

APPLICATION AREA	CONTROLLED TRIALS
Cut and microbiome	6
Absorption and availability	6
Metabolism	4

APPLICATION AREA	CONTROLLED TRIALS
Heart and circulation	4
Inflammation	2
Oxidative stress	1
Fatigue and stress	1

Gut and Microbiome

Evidence-based: The bioavailability of hesperetin can be significantly enhanced through enzymatic modification of the glycoside hesperidin. In a randomised, double-blind crossover study with 16 healthy participants, replacing the rutinoid with hesperetin-7-glucoside (via hesperidinase-treated orange juice) doubled plasma hesperetin concentration: The area under the curve (AUC) increased from 1.16 ± 0.52 to 3.45 ± 1.27 mmol/(L·h) ($P < 0.0001$), and the maximum plasma concentration (C_{max}) quadrupled to 2.60 ± 1.07 mmol/L ¹. A further study with 16 participants investigated naringenin-7-glucoside and confirmed that enzymatic removal of rhamnose (α -rhamnosidase treatment) accelerated absorption in the small intestine (T_{max} decreased from 311 to 92 minutes) and increased AUC fourfold ($P < 0.0001$) ³.

Only 3% of the dose was recovered unchanged in perfusate, whereas hesperetin-7-rutinoside (hesperidin) remained 80% unchanged and few metabolites were detectable in blood or urine ⁴. This demonstrates that the glycoside form is critical for absorption in the small intestine. Despite the 2.4-fold higher dose in fresh oranges, excretion did not differ significantly (21.6 ± 8.0 vs. 18.3 ± 7.2 μ mol), suggesting saturation of absorption or metabolism capacity ⁵.

PLAUSIBLE The metabolism of hesperidin by gut microbiota leads to the formation of hesperetin and smaller phenolic catabolites such as 3-(3'-hydroxy-4'-methoxyphenyl)propionic acid. A study with 12 participants showed that excretion of these catabolites was inversely correlated with that of hesperetin, highlighting the role of microbiota in metabolism ⁵. Another investigation stratified participants by their ability to excrete hesperetin metabolites ("high", "medium", "low excretors"). It revealed that phase II metabolism (e.g., sulfation vs. glucuronidation) varies individually, potentially due to genetic polymorphisms in UDP-glucuronosyltransferases ⁷.

HYPOTHESIS The observed interindividual differences in metabolism may be related to the composition of the gut microbiota, even though the study by ⁷ found no correlation at the genus level. It remains unclear whether more specific microbiological analyses (e.g., at the strain level) or longer intervention periods could explain this variability. What is missing are studies that systematically record microbiome changes under hesperetin influence over weeks or months.

Inflammatory Processes

Evidence: Hesperetin improves endothelial function in patients with metabolic syndrome. In a randomised, placebo-controlled crossover study with 24 participants, daily intake of 500 mg hesperidin over three weeks led to a significant increase in flow-mediated dilation (FMD) of the brachial artery. At the cellular level, hesperetin activated phosphorylation of Src, Akt, AMP kinase and eNOS in bovine aortic endothelial cells (BAEC), leading to nitric oxide production—a process dependent on H₂O₂ formation and shown in preclinical models. Hesperetin also reduced TNF- α -induced monocyte adhesion and VCAM-1 expression in cell studies ².

PLAUSIBLE The anti-inflammatory effect of hesperetin is mediated by its metabolites, particularly phase II conjugates such as hesperetin-7-O-glucuronide (Hp7GA). In vitro, Hp7GA showed similar inhibition of NADPH oxidase activity to hesperetin itself, promoting NO release in human umbilical vein endothelial cells (HUVEC) ¹¹. An observational study involving orange juice consumption over several weeks reported a reduction in inflammatory markers such as CRP, IL-6, and TNF- α , reflecting changes in surrogate parameters rather than clinical anti-inflammatory outcomes.

PLAUSIBLE The intestinal metabolism of hesperidin by the microbiota leads to the formation of hesperetin and smaller phenolic compounds with anti-inflammatory effects. A review summarises that these metabolites strengthen the gut barrier and reduce the expression of pro-inflammatory cytokines, which may be particularly relevant in chronic inflammatory bowel diseases ²². A preclinical study using self-assembled nanoparticles of berberine and hesperetin (BBR-HST NPs) *in combination* showed reduced inflammation and repaired gut barrier function in a colitis model, suggesting a potential synergistic effect ²³.

HYPOTHESIS The observed effects on inflammatory markers may partly be due to modulation of the microbiota, as hesperetin and its metabolites influence the composition of gut bacteria. It remains unclear whether these effects are dose-dependent and whether they can be reproduced in clinical studies over longer periods. What is missing are controlled human studies systematically investigating the anti-inflammatory effect of hesperetin in specific patient groups (e.g., with rheumatoid arthritis or ulcerative colitis).

Heart and Circulation

PLAUSIBLE The intake of flavanone-rich citrus beverages counteracts postprandial deterioration of endothelial function. The effects correlated with the peak of naringenin and hesperetin metabolites in plasma and increased nitrite levels ⁶.

PLAUSIBLE Water-dispersed hesperetin (150 mg) reached a maximum plasma concentration (C_{max}) of 10.2 ± 1.2 μ M within one hour in healthy participants. The main metabolites in plasma were hesperetin-7-O-glucuronide (Hp7GA), hesperetin-3'-O-glucuronide (Hp3'GA), and hesperetin sulfate. In vitro, Hp7GA showed a similar effect to hesperetin itself: it promoted NO release by inhibiting NADPH oxidase in HUVEC. A pilot study in women with cold sensitivity *provided preliminary evidence* for a potential improvement in peripheral vasodilation after a single dose ¹¹.

PLAUSIBLE The vasoprotective effects of hesperetin and its metabolites may be based on an improvement in the NO/ET-1 balance. In preclinical studies using EA.hy926 endothelial cells under oxidative stress (induced by highly oxidised LDL), hesperetin-7-O-glucuronide upregulated the expression of *NOS3*, *HMOX1* and *GCLC* and inhibited *EDN1* by modulating miR-660-5p and miR-21-5p ⁸. These findings are preliminary, derived from cell culture studies, and do not yet demonstrate effects in humans.

What is missing are long-term studies investigating the cardiovascular effects of hesperetin in at-risk populations (e.g., patients with hypertension or metabolic syndrome) over months, capturing both functional endpoints (e.g., FMD) and clinical outcomes (e.g., cardiovascular events).

Metabolism

PROVEN Reducing sucrose while maintaining sweetness by adding hesperetin (50 mg/L) showed a reduction in glycaemic fluctuations and energy intake in healthy men. In a randomised crossover study with 32 participants, a 7% sucrose solution with hesperetin, compared to an isosweet 10% sucrose solution, led to a less pronounced drop in blood glucose levels and reduced energy intake in the subsequent meal. The study provides a hint that hesperetin may improve postprandial glucose regulation as a taste modulator.

What is missing are studies investigating the long-term effects of hesperetin on glucose metabolism in individuals with prediabetes or type 2 diabetes, particularly with regard to HbA1c values and insulin resistance.

Oxidative Stress

PLAUSIBLE Hesperetin and its metabolites may act as antioxidants by upregulating enzymes such as heme oxygenase-1 (*HMOX1*) and the catalytic subunit of glutamate-cysteine ligase (*GCLC*). In preclinical studies using EA.hy926 endothelial cells under oxidative stress (highly oxidised LDL), hesperetin-7-O-glucuronide improved the NO/ET-1 balance and reduced oxidative stress by modulating microRNAs (miR-660-5p↑, miR-21-5p↓) ⁸.

HYPOTHESIS The antioxidant effects of hesperetin observed in preclinical models (e.g., cell cultures and the single animal study) may suggest relevance for human tissues, such as the brain, where oxidative stress contributes to neurodegenerative diseases. However, this effect has not been investigated in humans.

What is missing are clinical studies directly measuring the antioxidant effect of hesperetin in humans, e.g., using biomarkers such as malondialdehyde or superoxide dismutase activity.

Viral Infections

PLAUSIBLE Hesperetin and related flavonoids influence the composition of the gut microbiota. In an *in vitro* fermentation study using human stool, hesperetin-7-O-glucoside, prunin, and isoquercitrin increased the relative abundance of *Bifidobacterium* and *Lactobacillus*, while reducing potentially pathogenic bacteria such as *Lachnospirillum* and *Bifidophila* ¹⁰. Whether this modulation translates into improved immune function or antiviral effects remains to be investigated in human studies.

What is missing are studies directly investigating the effect of hesperetin on viral infections (e.g., influenza or SARS-CoV-2), both *in vitro* and in clinical settings.

Cognition and Psyche

HYPOTHESIS Hesperetin and hesperidin may exert neuroprotective effects by crossing the blood-brain barrier and reducing oxidative stress and neuroinflammation.

What is missing are clinical studies investigating the neuroprotective effects of hesperetin in humans, e.g., through cognitive tests or biomarkers of neurodegeneration; existing findings are limited to preclinical evidence.

Overall Picture

Hesperetin shows effects in controlled human studies on bioavailability, endothelial function, and inflammatory markers, with enzymatic modification of the glycoside (e.g., to hesperetin-7-glucoside) significantly enhancing absorption. The available evidence pertains to cardiovascular effects, particularly improvements in flow-mediated dilation (FMD) and reductions in postprandial endothelial dysfunction. Anti-inflammatory effects have also been observed in human studies involving metabolic syndrome, while cellular models provide supporting mechanistic insights.

Evidence on long-term effects on metabolism, microbiota, and neurodegenerative diseases is primarily derived from preclinical studies or *in-vitro* models. Controlled human studies with clinical endpoints (e.g., HbA1c, cognitive function) are still pending. Interindividual variability in hesperetin metabolism remains an open question, requiring more systematic investigations into the role of gut microbiota and genetic polymorphisms.

Methodology of the evidence base

[‘The available studies on hesperetin are predominantly acute or short-term intervention trials (duration: 1–3 weeks) involving healthy volunteers or small patient groups (e.g., metabolic syndrome). Typical endpoints include pharmacokinetic parameters (AUC, Cmax), functional markers (FMD, NO production), and inflammatory biomarkers (CRP, IL-6). Long-term studies with clinical outcomes (e.g., cardiovascular events, diabetes progression) and studies in specific risk populations (e.g., older adults, patients with chronic inflammatory diseases) are systematically lacking. Most studies also rely on oral intake via orange juice or extracts; standardised, isolated administration of hesperetin or its metabolites would improve comparability.’]

Hesperetin: bioavailability as the bottleneck of its effects

THE BIOAVAILABILITY OF HESPERETIN

is the **decisive limiting factor** for its potential effects—and simultaneously the best-studied aspect. Controlled studies show that a **substantial portion of ingested hesperidin** is either excreted unchanged or degraded by gut microbiota in the colon. **Enzymatic modifications** (e.g., cleavage of the rutinoside) can improve absorption, yet even then **plasma levels rarely reach concentrations** considered effective in cell cultures. This raises the question of whether **effects**

observed *in vitro* are physiologically relevant.

A FURTHER ISSUE IS THE DISCREPANCY BETWEEN METABOLITES AND NATIVE HESPERETIN

. Most preclinical studies test **unmodified hesperetin**, whereas in the human body, **glucuronidated and sulfated derivatives** circulate almost exclusively. These metabolites exhibit **altered chemical properties** and may therefore **target different biological pathways**. The **most-cited human study** (on endothelial function) does show **significant effects**, yet it remains unclear whether these stem from hesperetin itself or its metabolites. Moreover, **dose-response studies** clarifying whether higher plasma levels yield stronger effects are lacking.

3. How Robust Is the Research?

Research on hesperetin spans **three main areas**: **bioavailability and pharmacokinetics**, **endothelial and cardiometabolic effects**, and **gut health and metabolism**. Most controlled human studies examine **short-term effects** following single or multi-day dosing, with **orange juice and modified extracts** as the most common administration forms. The field includes a substantial number of preclinical studies (cell cultures, animal models), which often test **native forms** rather than the metabolites circulating in the body, limiting their direct relevance to human outcomes.

Methodologically, the field is **heterogeneous**: While some controlled human studies are **randomised and double-blind**, **long-term studies** and **clinical endpoints** are missing. The **most-cited controlled trials** report **significant effects on surrogate parameters** such as **NO production or inflammatory markers**, yet **transferability to clinical outcomes** remains unproven. Another issue is the **lack of standardisation** in the tested preparations: studies use **fresh juices, pasteurised products, or isolated extracts**, whose composition and bioavailability vary widely. Moreover, **hesperetin is often studied in combination with other flavonoids**, complicating the **isolation of its specific effects**.

4. What Is Often Claimed—and What the Data Support

CLAIM	EVIDENCE BASE
Hesperetin acts as an antioxidant and anti-inflammatory agent	Evidence: Cell culture and animal studies demonstrate antioxidant and anti-inflammatory effects. In humans, controlled studies on inflammatory markers
Hesperetin improves vascular function	Plausible: Controlled studies show improvements in surrogate parameters such as NO production and endothelial function. Unresolved is whether this t
Hesperetin has been investigated in relation to neurodegenerative diseases	Hypothesis: Review articles and cell studies suggest neuroprotective effects. In humans, this has not yet been investigated in controlled studies.
Hesperetin supports gut health	Evidence: Observational studies show associations between citrus flavonoids and the gut microbiome. Controlled trials, however, investigate only short

5. Profile: Molecule and Charge

Hesperetin is not a single molecule but a **mixture**—there is no single molecular formula or fixed molecular mass. What can be described are functional groups, charge behaviour, and redox properties; these are the focus of the next section.

6. Charge, Electrons, Radicals

Hesperetin exhibits electrochemical properties that manifest in interactions with reactive oxygen species (ROS) and redox processes. This is associated with modulation of mitochondrial functions: hesperetin restores fatty acid oxidation (FAO), increases NADH and FADH₂ levels, and raises intracellular acetyl-CoA, while protecting against collapse of the mitochondrial membrane potential^{19 19}. It also influences mitochondrial respiration and calcium flux in platelets, measured after one-hour exposure at 20 μM¹⁸. Its antioxidant action is linked to regulation of pathways such as Nrf2/HO-1/ARE, PI3K/mTOR/Akt, and MAPK, which are critical for cellular redox balance^{12 20}.

PROVEN The radical-scavenging and ROS-reducing capacity of hesperetin has been directly measured in human cells and tissues, as have its effects on mitochondrial parameters (NADH, FADH₂, membrane potential)^{19 19}. **Plausible:** Observed effects on ATPases, cell-cycle proteins, and pathways such as Nrf2 or PI3K suggest involvement in electron-transfer processes and redox regulation, though the precise electrochemical mechanisms (e.g., cation

exchange or direct electron transfer) have not yet been quantified in humans ^{12 20}. In cell cultures, hesperetin showed higher radical-scavenging activity than related flavonoids ²¹, and there is evidence of chelation with metal ions such as Cu²⁺ and Zn²⁺. Next, it should be examined whether these properties correlate *in vivo* with specific redox potentials or charge distributions.

7. Interactions with Other Substances

With which other substances on this platform have **hesperetin** been studied or discussed together in human trials and reviews—whether in combination, comparison, or shared mechanisms. The number indicates papers in which both appear.

SUBSTANCE	JOINT STUDIES	THEREOF CONTROLLED IN HUMANS
Hesperidin	30	8
Chronic inflammation	26	2
Naringenin	11	4
Stress, cortisol and inflammation	10	1
Quercetin	6	0
Resveratrol	5	2
Gut microbiome	4	1
Anthocyanins (berries)	4	0
Fisetin	3	0
Kaempferol	3	0

The bioavailability of hesperetin is influenced by its chemical form and the site of absorption in the intestine. Studies show that enzymatic conversion of hesperidin (hesperetin-rutinoside) to hesperetin-7-glucoside shifts absorption from the colon to the small intestine, thereby improving the bioavailability of the aglycone hesperetin ^{1 1}. Similar effects have been observed for structurally related flavanones such as naringenin, although the conjugation profiles of metabolites in urine remained unchanged ³. This modulation of absorption could influence interactions with other substances absorbed in the small intestine, particularly when co-administered with nutrients or drugs sharing similar absorption mechanisms. The interaction with the gut microbiota and its role in the metabolism of hesperidin and hesperetin has also been described, with potential effects on intestinal barrier function and inflammatory processes ²².

Hesperetin shows potential interactions with drugs, particularly in oncology and cardiology. A synergistic anti-inflammatory effect has been observed in combination with berberine, attributed to regulation of the immune microenvironment and repair of the intestinal barrier ²³. There is also evidence of synergistic effects with chemotherapeutic agents, with hesperetin potentially overcoming multidrug resistance in tumour cells and enhancing therapy efficacy ^{9 9}. Concurrent administration with chemotherapeutics has been associated with a protective effect on cardiac function, maintaining nearly normal cardiac parameters ^{24 24}. Targeted studies on enzyme induction or inhibition by hesperetin are still lacking.

8. Overdose, Tolerability, Limits

Adverse effects and toxicity of hesperetin – Evidence-based findings: Hesperetin, a flavonoid from citrus fruits, shows no direct toxic effects in humans when administered in conventional forms, according to systematic investigations. Conventional applications of hesperetin (and its glycoside hesperidin) are considered safe, as they act via antioxidant, anti-inflammatory and anti-apoptotic mechanisms—such as modulation of pathways like Nrf2/HO-1/ARE or PI3K/mTOR/Akt ^{12 12}. However, nanomedical formulations (e.g., *BBR-HST nanoparticles*) carry unpredictable safety risks, despite being described as biocompatible and biosafe in preclinical studies ^{23 23}. Clinical use of such formulations remains limited due to high costs and a lack of long-term data.

Contraindications and interactions: Current studies primarily position hesperetin as a *protective* agent—e.g., against heavy metal toxicity or chemotherapy-induced cardiotoxicity—rather than as a trigger of adverse effects ^{12 24}. Since heavy metals (e.g., lead, cadmium) cause tissue damage and disrupt signalling pathways, hesperetin is attributed a modulating role without reports of its own toxicity ^{12 12}. In chemotherapy patients, hesperetin may reduce cardiac stress as an adjunct therapy, but human dose-response studies quantifying upper limits or interactions with cytostatics are lacking ²⁴.

Overdose and dose limits – State of research: Specific data on overdose symptoms or lethal doses of hesperetin *in humans* are not available. Animal and cell studies suggest that hesperetin does not induce acute toxicity even at high concentrations, yet systematic dose-finding studies in humans are missing ^{12 12}.

Open questions: It remains unclear whether hesperetin shows dose-dependent interactions with chemotherapeutics (e.g., anthracyclines) that could either exacerbate or mitigate cardiotoxicity. Additionally, it is unknown whether nanomedical formulations (e.g., *HST nanoparticles*) may develop cumulative effects with chronic use. Next, it should be examined whether standardised human dose-response studies can define safety limits for hesperetin as a single agent and in combination with other drugs.

9. The Most Robust Studies

Ranked by evidence strength, not by prominence. The full evaluation includes significantly more studies; here, the most reliable are presented.

Controlled Human Studies

- ¹ Bioavailability is improved by enzymatic modification of the citrus flavonoid hesperidin in humans: a randomized, double-blind, crossover trial (2006)
- ² Citrus polyphenol hesperidin stimulates production of nitric oxide in endothelial cells while improving endothelial function and reducing inflammatory (2011)
- ³ Absorption, conjugation and excretion of the flavanones, naringenin and hesperetin from alpha-rhamnosidase-treated orange juice in human subjects (2010)
- ⁴ Gastrointestinal absorption and metabolism of hesperetin-7-O-rutinoside and hesperetin-7-O-glucoside in healthy humans (2015)
- New Insights into the Metabolism of the Flavanones Eriocitrin and Hesperidin: A Comparative Human Pharmacokinetic Study (2021)
- ⁵ Urinary excretion of Citrus flavanones and their major catabolites after consumption of fresh oranges and pasteurized orange juice: A randomized cross (2016)
- ⁶ Flavanone-rich citrus beverages counteract the transient decline in postprandial endothelial function in humans: a randomised, controlled, double-mask (2016)
- ⁷ Stratification of Volunteers According to Flavanone Metabolite Excretion and Phase II Metabolism Profile after Single Doses of 'Pera' Orange and 'Moro' (2021)
- Sucrose reduction with maintained sweetness level lowers glycemic fluctuations and energy intake in healthy males (2025)
- ⁸ Hesperetin-7-O-glucuronide improves endothelial cell function through improving NO/ET-1 balance and reducing oxidative stress via miRNAs (2026)

Observational Human Studies

- Effects of citrus fruit juices and their bioactive components on inflammation and immunity: a narrative review (2021)
- The intestinal fate of citrus flavanones and their effects on gastrointestinal health (2019)
- Novel natural carrier-free self-assembled nanoparticles for treatment of ulcerative colitis by balancing immune microenvironment and intestinal barrier (2023)
- ⁹ Chemotherapeutic potential of hesperetin for cancer treatment, with mechanistic insights: a comprehensive review (2022)
- ¹⁰ Effects of several flavonoids on human gut microbiota and its metabolism by in vitro simulated fermentation (2023)
- ¹¹ Bioavailability of orally administered water-dispersible hesperetin and its effect on peripheral vasodilatation in human subjects: implication of endo (2012)
- ¹² Hesperidin and hesperetin against heavy metal toxicity: insight on the molecular mechanism of mitigation (2022)
- ¹³ Recent understanding of the mechanisms of the biological activities of hesperidin and hesperetin and their therapeutic effects on diseases (2024)
- ¹⁴ Hesperetin as an anti-SARS-CoV-2 agent can inhibit COVID-19-associated cancer progression by suppressing intracellular signaling pathways (2022)
- ¹⁵ Hesperetin ameliorates glioblastoma by inhibiting proliferation, inducing apoptosis, and suppressing metastasis (2022)
- Urinary biomarkers for orange juice consumption (2021)
- ¹⁶ Effects of hesperidin consumption on the cardiovascular system in pre- and stage 1 hypertensive subjects: targeted and non-targeted metabolomic approach (2021)
- ¹⁷ Inhibitory effects of citrus-derived flavonoids hesperidin and hesperetin on SARS-CoV-2 spike-mediated syncytia formation using in vitro cell model (2025)
- Plant-derived compounds normalize platelet bioenergetics and function in hyperglycemia (2024)

10. Summary

Evidence: In controlled human studies, hesperetin showed effects on bioavailability, endothelial function, and inflammatory markers as measured by surrogate parameters. Enzymatic modifications of the glycoside hesperidin markedly improved uptake, as demonstrated in healthy volunteers. Anti-inflammatory effects via inhibition of NADPH oxidase and promotion of NO release were also observed in surrogate parameters. Glycaemic regulation benefits from hesperetin were suggested by reduced glycaemic fluctuations in surrogate parameters.

Plausible and potential implications: Antioxidative effects through upregulation of enzymes such as haem oxygenase-1 (*HMOX1*) in preclinical models and modulation of the gut microbiota are plausible, potentially yielding antiviral or neuroprotective effects. **Hypothesis:** Observed inter-individual differences in metabolism may relate to genetic polymorphisms or gut microbiota composition. Hesperetin metabolites might also act synergistically with other agents (e.g., berberine), offering new therapeutic avenues in chronic inflammatory diseases.

What a study should clarify: Long-term trials with clinical endpoints are needed to assess cardiovascular and metabolic effects of hesperetin in at-risk populations (e.g., hypertension, diabetes). Systematic analyses of the role of gut microbiota and genetic polymorphisms in metabolism could explain inter-individual variability. Studies directly measuring neuroprotective or antiviral effects of hesperetin are also lacking. Standardised administration forms (e.g., isolated metabolites) would improve comparability of results.

11. Open Questions

- **Long-term effects:** Are there clinically relevant benefits from regular intake over months or years?
- **Metabolite activity:** What effects do circulating glucuronides and sulfates have compared with native hesperetin?

- **Dose-response relationship:** At what plasma concentration do physiologically relevant effects occur?

12. Further Paths

Themes, modes of action and chains in which this substance occurs — for anyone looking beyond the substance itself.

- Interaction network

Topics, mechanisms and chains in which this substance appears — for those who want to look beyond the substance.

Frequently Asked Questions

Why is hesperetin often confused with hesperidin?

Hesperetin is the **aglycone** of **hesperidin** and is formed only after enzymatic cleavage in the gut. While **hesperidin** itself has **poor bioavailability**, hesperetin is absorbed more efficiently. **Studies on hesperidin** therefore cannot be directly applied to hesperetin, as **uptake and metabolism** differ significantly. This confusion frequently leads to **incorrect assumptions about the efficacy** of citrus extracts.

Can hesperetin influence the effect of medications?

Plausible: Hesperetin is metabolised via **CYP enzymes** and could therefore **interact** with drugs that are also cleared through this pathway. **Controlled studies** addressing this question are still lacking. **Caution** is particularly warranted with **high-dose extracts**, as these may result in **plasma levels** substantially higher than those achieved through normal citrus consumption.

Why do cell studies often show stronger effects than human studies?

Cell cultures typically test **native forms** of hesperetin at **non-physiological, high concentrations**, whereas the human body circulates **metabolites** at lower levels. Moreover, in vitro systems lack **metabolic processes** such as glucuronidation, which can alter **potency and direction of effect**. **Preclinical findings** are therefore **not evidence of human efficacy**, but rather **indications of possible mechanisms**.

Sources

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