



DOSSIER · SUBSTANCE

Hesperidin

Hesperidin is one of the most extensively studied **flavanones** and is primarily found in citrus fruits. Research has concentrated on metabolism, the cardiovascular system, and inflammatory processes. The most compelling finding: controlled studies demonstrate consistent effects on **vascular markers** and **metabolic parameters**, while the translatability to clinical endpoints remains under investigation.

363

STUDIES IN
TOTAL

93

IN HUMANS

55

OF WHICH
CONTROLLED

14

IN ANIMALS

93

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

Hesperidin at a glance

ORIGIN:

Hesperidin is a glycosidic flavanone (hesperetin-7-O-rutinoside) found primarily in the peels and white membranes of citrus fruits such as oranges, grapefruits, and lemons. It is industrially extracted from citrus waste, for example, from peels generated during juice production. After oral intake, hesperidin is metabolised in the gut to hesperetin, which exerts systemic effects, although the bioavailability of the intact glycoside is low.

STUDY LANDSCAPE:

363 evaluated studies · 55 controlled human trials · 38 observational studies · 29 review articles · 14 animal studies · 80 cell culture studies

STRONGEST EVIDENCE:

- **Cardiovascular system** Controlled studies showed that hesperidin lowers diastolic and systolic blood pressure in hypertensive or overweight individuals. A 12-week study also demonstrated dose-dependent effects on vascular markers and gene expression (e.g., PTX3, NLRP3).
- **Inflammation** In type 2 diabetes and metabolic syndrome, controlled studies showed that hesperidin reduced inflammatory markers such as IL-6, hs-CRP, and TNF-α. Studies in patients with NAFLD showed effects on inflammatory parameters.
- **Oxidative stress** Controlled studies showed that hesperidin increased total antioxidant capacity (TAC) and reduced oxidative DNA damage (8-OHdG) and lipid peroxidation (MDA) in diabetic patients. Preclinical cell culture studies demonstrated inhibition of reactive oxygen species (ROS).
- **Metabolism** Controlled studies showed that hesperidin improved blood pressure, triglycerides, and fasting glucose in metabolic syndrome. Combined with flaxseed, additive effects on insulin resistance and anthropometric parameters were observed.
- **Venous disorders** In combination with diosmin, hesperidin reduced postoperative bleeding after haemorrhoidectomy and improved symptoms of chronic venous insufficiency (CVI), such as oedema and quality of life. The effects of hesperidin alone on venous disorders have not been investigated in controlled studies.

LIMITATIONS:

- Most studies investigate intermediate markers (e.g., biomarkers) rather than clinical endpoints such as morbidity or mortality. Long-term data on safety and efficacy are lacking.
- Dosage varies widely between studies, and acute effects (e.g., on endothelial function) are not always consistently detectable.
- It remains unclear whether observed effects are directly attributable to hesperidin or its metabolites, particularly in combination therapies (e.g., with diosmin).

ASSESSMENT:

Hesperidin, a flavanone found in citrus fruits, shows consistent effects on blood pressure, inflammatory markers, and oxidative stress in controlled studies, particularly in metabolic and cardiovascular diseases. The clinical relevance requires further investigation through long-term studies.

1. What Hesperidin Is and How It Works

Hesperidin is a **glycosidic flavanone** found primarily in the peel and white membranes of citrus fruits such as oranges, grapefruits, and lemons. Chemically, it is hesperetin-7-O-rutinoside, a compound consisting of the aglycone hesperetin and the disaccharide rutinose. Natural sources include fresh fruits and juices, though concentrations vary depending on variety, ripeness, and processing. Industrially, hesperidin is extracted from citrus waste, such as peels generated during juice production.

For understanding the study landscape, it is crucial that after oral intake, hesperidin is converted in the gut by microbial enzymes into **hesperetin**. This metabolite is absorbed and undergoes extensive **phase II metabolism** in the liver and gut, resulting in sulfated and glucuronidated forms. Bioavailability is low, but systemic effects can occur due to the conversion into active metabolites. Studies typically measure **plasma levels of metabolites** or their effects on biomarkers, not the intact glycoside.

2. What the Studies Show in Detail

The key human studies and most important reviews—by application area, including population, duration, preparation, measured parameters, and results, as reported in the original publications. Numbers are included only where the study provides them.

Distribution of **controlled human trials** by application area—the numbers are not additive, as one study may be assigned to multiple areas:

APPLICATION AREA	CONTROLLED STUDIES
Metabolism	23
Cardiovascular system	19
Inflammation	19
Safety and tolerability	14
Oxidative stress	13
Oncology	8

APPLICATION AREA	CONTROLLED STUDIES
Absorption and bioavailability	6
Fatigue and stress	4

Cardiovascular System

PROVEN In a randomised, controlled crossover study involving 24 healthy, overweight men (aged 50–65 years), daily intake of 500 ml orange juice or a control drink containing 292 mg hesperidin (CDH) over 4 weeks led to a significant reduction in diastolic blood pressure (DBP) compared to the placebo control drink (CDP) ($P = 0.02$). Postprandial microvascular endothelial function improved after acute intake of orange juice or CDH, while fasting values remained unchanged. The study demonstrates that hesperidin is causally involved in the vascular effects of orange juice ¹.

PROVEN A randomised, double-blind parallel-group study with 159 pre-hypertensive and stage 1 hypertensive participants investigated the effects of orange juice (OJ) with natural hesperidin content and hesperidin-enriched OJ (EOJ, 500 ml/day) over 12 weeks. A single dose of EOJ acutely reduced systolic blood pressure (SBP) and pulse pressure (PP), with the effect enhanced after chronic intake, additionally lowering DBP ($P < 0.05$). Effects were dose-dependent on hesperidin content. Homocysteine levels decreased, and four hypertension-relevant genes (PTX3, NLRP3, NPSR1, NAMPT) were differentially expressed in peripheral blood mononuclear cells ($P < 0.05$). The study confirms that hesperidin in OJ sustainably lowers SBP and PP and influences systemic and transcriptomic biomarkers ⁷.

PROVEN An acute, randomised crossover study involving 16 men (aged 51–69 years) with moderate cardiovascular risk compared the effects of orange juice (320 mg hesperidin), a hesperidin supplement (320 mg), and a control drink (matched for sugar and vitamin C). After 5 hours, no significant changes were observed in endothelial function (primary endpoint), blood pressure, arterial stiffness, or NADPH oxidase gene expression. However, plasma concentrations of 8 flavanone and 15 phenolic metabolites increased significantly following orange juice consumption ($P < 0.0001$). The study suggests that acute effects on cardiovascular biomarkers may only become detectable with longer-term intake or higher dosages ⁸.

PROVEN In a randomised study of 90 patients with chronic venous insufficiency (CVI) and severe venous hypertension, the effects of oxerutins (2 g/day) were compared with a combination of diosmin and hesperidin (D+H, 3×500 mg/day) over 8 weeks. Both groups showed improvements in vein-related quality of life (Ve-QOL), with the D+H group achieving comparable results in a second cohort of 122 patients. The study confirms the efficacy of the diosmin-hesperidin combination for CVI but does not isolate the specific contribution of hesperidin alone.

HYPOTHESIS Studies show consistent effects of hesperidin on blood pressure and microvascular function, particularly in hypertensive or overweight populations. Both acute and chronic effects appear dose-dependent, with potential synergistic effects when combined with other flavonoids (e.g., diosmin). It remains unclear whether observed changes in gene expression are directly attributable to hesperidin or represent secondary effects of blood pressure reduction. Further studies with longer intervention periods and larger sample sizes are needed to confirm long-term cardiovascular benefits.

Inflammatory Processes

PROVEN A randomised, double-blind study of 64 patients with type 2 diabetes showed that intake of 500 mg hesperidin/day over 6 weeks significantly reduced systolic blood pressure (SBP: 122.7 ± 8.5 vs. 119.0 ± 7.4 mmHg; $P = 0.005$), mean arterial pressure ($P = 0.009$), and inflammatory markers IL-6 ($P = 0.001$) and high-sensitivity C-reactive protein (hs-CRP; $P < 0.000$). Total antioxidant capacity (TAC) also increased ($P < 0.000$). Percentage changes in these parameters differed significantly from the placebo group ($P < 0.05$). The study demonstrates the antihypertensive and anti-inflammatory effects of hesperidin in metabolic diseases ².

The results suggest that hesperidin improves lipid profiles and modulates inflammatory processes via inhibition of NF- κ B ³.

PROVEN A randomised crossover study of 24 healthy overweight men investigated the effects of 500 ml orange juice or 500 ml control drink containing 292 mg hesperidin over 4 weeks on leukocyte gene expression.

PLAUSIBLE A 12-week randomised study of 100 patients with NAFLD compared the effects of 30 g flaxseed, 1 g hesperidin, or a combination of both. The hesperidin group exhibited significant reductions in inflammatory markers, while the combination therapy showed the strongest effects. The study suggests hesperidin may contribute to anti-inflammatory effects in NAFLD, though its standalone efficacy requires further investigation ⁵.

PROVEN A randomised, placebo-controlled study of 49 patients with metabolic syndrome (MetS) demonstrated that 500 mg hesperidin twice daily over 12 weeks significantly reduced fasting blood glucose ($P = 0.043$), triglycerides ($P = 0.049$), systolic blood pressure ($P = 0.048$), and TNF- α ($P = 0.009$). The results confirm the metabolic and anti-inflammatory effects of hesperidin in MetS ¹⁰.

HYPOTHESIS Studies in cell culture and animal models confirm that hesperidin modulates cytokines (IL-6, TNF- α), acute-phase proteins (hs-CRP), and transcription factors (NF- κ B). These preclinical findings suggest a systemic anti-inflammatory potential, particularly in metabolic diseases such as diabetes, NAFLD, and MetS. However, it remains unclear whether the observed effects are directly attributable to hesperidin or its metabolites, whether they translate into clinically relevant outcomes in humans, and what the underlying molecular mechanisms are. Further research should investigate these questions in clinical settings.

Oxidative Stress

PROVEN In a randomised, double-blind study of 64 patients with type 2 diabetes, intake of 500 mg hesperidin/day over 6 weeks led to a significant increase in total antioxidant capacity (TAC: 0.74 ± 0.16 vs. 0.82 ± 0.18 ; $P = 0.043$) and reductions in oxidative DNA damage (8-OHdG: 14.32 ± 6.4 vs. 11.00 ± 7.0 ng/ml; $P = 0.000$) and lipid peroxidation (MDA: 5.78 ± 1.76 vs. 4.60 ± 0.75 μ mol/l; $P = 0.000$). The study confirms the antioxidant effects of hesperidin in diabetes ⁶.

PROVEN A randomised, double-blind study of 68 healthy overweight participants investigated the effects of 450 mg hesperidin-2S/day over 6 weeks on endothelial function and oxidative markers. While no significant change in flow-mediated dilation (FMD) was observed, reductions in soluble adhesion molecules sVCAM-1, sICAM-1, and sP-selectin were noted. In a subgroup with baseline FMD $\geq 3\%$, hesperidin improved postprandial FMD following a

high-fat meal. The study suggests that hesperidin modulates oxidative processes, though longer intervention periods or higher dosages may be required for significant effects ⁹.

PLAUSIBLE An in vitro study using erythrocytes from healthy volunteers and sickle cell anaemia patients undergoing hydroxyurea therapy examined the antioxidant effects of flavonoids (quercetin, rutin, hesperidin, myricetin) against tert-butyl hydroperoxide-induced oxidative stress. Hesperidin significantly reduced reactive oxygen species (ROS) formation, though the strongest effects were observed for quercetin and rutin. The results provide a preclinical indication of hesperidin's antioxidant potential, but its effects in humans remain to be confirmed ²¹.

HYPOTHESIS Preclinical studies show that hesperidin reduces oxidative DNA damage and lipid peroxidation in cell culture and animal models, particularly in metabolic diseases such as diabetes. The antioxidant effects may stem from direct radical scavenging or modulation of antioxidant enzymes (e.g., SOD, CAT). However, it remains unclear whether these effects translate into clinically relevant outcomes in humans, whether they are dose-dependent, and how they manifest in healthy populations. Further studies should explore these questions in clinical trials.

Further Investigations

PROVEN A randomised, controlled study of 228 patients post-haemorrhoidectomy demonstrated that intake of Daflon 500 mg (450 mg diosmin + 50 mg hesperidin) over 1 week significantly reduced the rate of postoperative bleeding (0.9% vs. 6.1% in the control group; $P = 0.03$). The study confirms the efficacy of the *flavonoid combination* in reducing bleeding complications following surgical procedures, without isolating the effect of hesperidin alone.

A study on a *flavonoid mixture* (diosmin, troxerutin, hesperidin) in the treatment of acute haemorrhoids reported significant reductions in pain, bleeding, oedema, and thrombosis, as well as lower analgesic consumption compared to the placebo group. The study confirms the efficacy of the *flavonoid mixture* in symptomatic treatment, without attributing the effects specifically to hesperidin ¹⁴.

A study on a *flavonoid combination* showed improvements in microcirculatory parameters (e.g., skin flow, capillary filtration) in both groups after 4 weeks. The study confirms the role of *flavonoid mixtures* in chronic venous insufficiency (CVI), without attributing the effects specifically to hesperidin.

HYPOTHESIS Studies show that hesperidin, *in combination with other flavonoids* (e.g., diosmin), may contribute to the treatment of haemorrhoids and CVI. The observed effects—such as improved vascular permeability, reduced oedema, and inhibition of inflammatory processes—are based on flavonoid mixtures, not hesperidin alone. It remains unclear whether hesperidin alone produces similar effects or whether the combination acts synergistically. Further studies should investigate optimal dosages and underlying mechanisms for hesperidin specifically.

Metabolism

The combination of hesperidin and flaxseed significantly reduced systolic blood pressure (-5.68 vs. -2.91 mmHg; $P = 0.041$) and triglycerides (-50.06 vs. 3.87 mg/dl; $P = 0.033$) compared to the control group. The study showed additive effects of the *combination* on these metabolic parameters, without isolating hesperidin's contribution ¹³.

HYPOTHESIS The study confirms that hesperidin improves metabolic parameters such as blood pressure and triglycerides in patients with metabolic syndrome. The effects may result from modulation of inflammatory processes, improved endothelial function, or influences on lipid metabolism. It remains unclear whether these effects are dose-dependent and whether they lead to long-term reductions in cardiovascular events.

Gut and Microbiome

PLAUSIBLE A double-blind crossover study of 12 healthy male participants compared the absorption of micronised (Daflon 500 mg, particle size 1.79 μm) and non-micronised ¹⁴C-diosmin (particle size 36.5 μm). Urinary excretion of radioactivity—a measure of absorption—was significantly higher for micronised diosmin ($57.9 \pm 20.2\%$ vs. $32.7 \pm 18.8\%$; $P = 0.0004$). The study demonstrates that micronisation improves the bioavailability of diosmin. Whether these findings extend to hesperidin or other flavonoids remains to be investigated.

Speculation: The study suggests that the particle size of flavonoids influences their absorption and bioavailability. Improved absorption could enhance the systemic effects of flavonoids, particularly in the treatment of venous diseases. It remains unclear whether similar effects occur with hesperidin. Further studies should investigate the role of the microbiome in hesperidin metabolism and its impact on efficacy.

Overall Picture

The available controlled human trials demonstrate the effects of flavonoid combinations—often including hesperidin—on cardiovascular, metabolic, and inflammatory parameters. Particularly well-documented in these studies are the observed blood pressure-lowering, antioxidant, and anti-inflammatory effects in combined formulations, reported across diverse populations (healthy overweight individuals, hypertensive patients, diabetics, and those with NAFLD). The effects appear dose-dependent and occur both acutely and after chronic intake. Studies suggest flavonoid combinations may act through multiple mechanisms, including the modulation of inflammatory markers (IL-6, TNF- α , hs-CRP), inhibition of transcription factors (NF- κ B), and improvement of endothelial function.

Despite these promising results, several questions remain unanswered: Most studies examined hesperidin in combination with other flavonoids (e.g., diosmin) or in the form of orange juice, making it difficult to isolate the specific effects of hesperidin alone. Additionally, long-term studies are lacking to confirm the clinical relevance of the observed effects (e.g., reduction in cardiovascular events). The optimal dosage and the role of the microbiome in hesperidin metabolism also require further clarification. Future research should focus on these aspects to fully unlock hesperidin's therapeutic potential.

Methodology of the evidence base

["Studies on hesperidin encompass a broad range of designs, including randomised controlled crossover and parallel-group trials, double-blind placebo-controlled studies, and observational studies. The duration of interventions varied from acute single doses (e.g., 5-hour follow-up) to chronic intake over up to 12 weeks. Typical endpoints included cardiovascular parameters (blood pressure, endothelial function, arterial stiffness), metabolic markers (glucose,

lipids, insulin resistance), inflammatory markers (IL-6, TNF- α , hs-CRP), and oxidative stress parameters (TAC, MDA, 8-OHdG). Systematic gaps exist in the investigation of long-term effects, clinical relevance (e.g., reduction in morbidity/mortality), and the specific effects of hesperidin alone (without combination with other flavonoids). Furthermore, studies detailing the underlying molecular mechanisms are lacking, particularly regarding the role of hesperidin metabolites and their interaction with the microbiome."]

Hesperidin: Biomarker or clinical relevance?

EVIDENCE-BASED:

In controlled studies, hesperidin lowers **blood pressure**, **inflammatory markers** such as CRP, and **oxidative stress** in metabolic diseases. The effects are dose-dependent and primarily occur in individuals with **pre-existing dysregulations**, such as type 2 diabetes or hypertension. The most cited study (2011) demonstrated an improvement in **vascular function** following orange juice consumption, with hesperidin identified as the active component. **Plausible:** The mechanisms include **inhibition of inflammatory enzymes** (e.g., COX-2), **modulation of nitric oxide metabolism**, and **reduction of lipid peroxidation**. Cell culture and animal studies further suggest **inhibition of AGE formation** (Advanced Glycation Endproducts), which may be relevant for diabetic complications.

However, the

TRANSLATION INTO CLINICAL RELEVANCE

remains unresolved. While the observed changes in biomarkers correlate with a reduced risk of cardiovascular events, direct evidence for a **reduction in morbidity or mortality** is lacking. It is also unclear whether the effects are attributable to hesperidin alone or to **synergies with other citrus compounds** (e.g., naringenin, vitamin C). The evidence on **bioavailability** shows significant interindividual variability, complicating standardisation. The next step would be a **long-term study with clinical endpoints** to validate the significance of these biomarkers.

3. How Robust Is the Research?

Research on hesperidin spans **basic science**, **cell culture studies**, and **controlled human trials**, with the latter primarily addressing metabolism, the cardiovascular system, and inflammatory processes. The most cited studies, published between 2011 and 2021, investigate vascular protection, blood pressure reduction, and antioxidant effects. A notable focus lies on **intermediate markers**, such as inflammatory parameters, lipid peroxidation, or liver enzymes, while clinical endpoints like morbidity or mortality are less frequently examined.

Methodologically, controlled human studies are predominantly **randomised**, **double-blind**, and **placebo-controlled**, with participant numbers in the low to mid-hundreds. The strength of the evidence lies in the **consistent replication** of effects on biomarkers, particularly in type 2 diabetes or non-alcoholic fatty liver disease. Weaknesses include the **short duration of interventions** (typically 4–12 weeks) and **heterogeneous dosing**, which varies across the studied ranges. Additionally, long-term data on safety and efficacy, particularly with chronic intake, are lacking.

4. Common Claims — and What the Data Support

CLAIM	EVIDENCE
Hesperidin prevents cancer	Hypothesis: Cell culture and animal studies demonstrate antiproliferative effects, such as inhibition of tumour cell growth. Proven: In humans, only controlled stu
Hesperidin replaces blood pressure-lowering medication	Plausible: Controlled studies demonstrate a blood pressure-lowering effect on systolic and diastolic values , particularly in mild forms of hypertension. Establish
Hesperidin works the same for everyone	Studies demonstrate that only a subset of participants responds to the intervention, indicating responder–non-responder phenomena .
Hesperidin is safe at high doses	Supported: Short-term studies show no severe adverse effects, even at higher dosage ranges. Plausible: Long-term data are lacking, particularly regarding inter

5. Profile: Molecule and Charge

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

6. Charge, Electrons, Radicals

Electrochemical properties of hesperidin — measured in humans Hesperidin acts as a radical scavenger and reduces reactive oxygen species (ROS) in the human body. In controlled studies, the antioxidant effect following daily intake of orange juice correlated with measured hesperetin plasma levels and was associated with a decrease in ROS ²⁰. In patients with sickle cell anaemia, hesperidin significantly inhibited ROS production in erythrocytes, both in healthy individuals and those affected ²¹. In tissue samples, it reduced PM_{2.5}-induced ROS generation and oxidative cellular damage ²³. Its effects extend to the inhibition of inflammation-promoting transcription factors such as NF-κB, which are activated by ROS ²⁵. Biomarker modulation was also investigated: In models of degenerative disc disease, hesperidin lowered the expression of iNOS and COX2, reduced ROS and apoptosis, and decreased inflammatory markers ²². In cell cultures, it influenced the gene expression of P53, P21, Bcl-2, and Survivin, which are associated with oxidative stress ²⁸. Whether hesperidin directly transfers electrons or influences cation exchange processes has not been directly measured in humans. The observed effects suggest indirect redox modulation, such as radical neutralisation or enzyme activation ²⁷.

Plausible mechanisms and open questions In vitro, hesperidin exhibits high radical-scavenging activity, though lower than that of quercetin or rutin ²¹. Its efficacy against ROS overproduction has been demonstrated in human cells (e.g., fibroblasts in diabetic foot ulcers) ²⁶ and tissue samples, where it mitigated oxidative damage to organelles ²³. Reviews categorise its effects within a broad spectrum: neutralisation of ROS, enhancement of antioxidant enzyme activity, inhibition of pro-inflammatory cytokines, and regulation of lipid metabolism ²⁷. Unresolved is whether hesperidin itself acts as a redox partner or primarily modulates signalling pathways (e.g., AMPK/ACC ²⁴). Direct measurements of its electrochemical properties — such as charge distribution, cation exchange capacity, or electron transfer rates — are lacking in human studies. The next step would be to determine whether the observed antioxidant effects stem from a direct chemical reaction with ROS or from the induction of endogenous protective systems, such as the activation of SREBP-2/HMGCR ²⁴.

7. Interactions with Other Substances

Substances from this platform that have been **jointly** investigated or discussed in human studies and reviews — whether in combination, comparison, or via shared mechanisms. The number indicates studies in which both substances appear.

SUBSTANCE	JOINT STUDIES	OF WHICH CONTROLLED IN HUMANS
Chronic inflammation	64	19
Stress, cortisol and inflammation	35	3
Therapeutic fasting and intermittent fasting	11	10
Quercetin	10	2
Vitamin C	9	9
Gut microbiome	9	2
Turmeric and curcumin	7	2
Berberine	4	1
Pine bark extract	4	1
Resveratrol	4	0

Drug and nutrient interactions – absorption and bioavailability Hesperidin is not the subject of these studies in isolation, but interactions of hesperidin with other flavonoids and nutrients have been investigated. The bioavailability of hesperidin depends on its chemical form: an extract containing 2S-hesperidin showed a significantly higher relative urinary excretion (70 ± 14% of the ingested dose) than a mixture of 2S- and 2R-hesperidin (43 ± 8.0%) ¹⁸. This suggests better absorption of the 2S-diastereoisomer, possibly due to more efficient metabolism into hesperidin catabolites ¹⁸. In combination with diosmin —a structurally related flavonoid—hesperidin has been used in several studies, for example in diabetic neuropathy and metabolic syndrome. Co-administration led to a greater improvement in metabolic parameters (e.g., plasma glucose, HOMA-IR) than single administration ^{5 16}. The combination of diosmin and hesperidin also showed efficacy in reducing postoperative swelling after knee replacement ²⁹. Whether these effects result from pharmacokinetic interactions (e.g., enzyme induction) or additive mechanisms remains to be clarified. The combination with flaxseed was also studied: here, triglyceride levels, fasting glucose, and systolic blood pressure improved compared to placebo ¹³.

However, a controlled human study investigated a combination of hesperidin, luteolin, and naringenin, which had shown synergistic antioxidant properties in vitro ¹⁹. Whether this flavonoid mixture affects CYP enzymes in vivo—through inhibition or induction—was not examined. Since hesperidin has been used in many studies alongside oral antidiabetics (e.g., in type 2 diabetes) without reports of adverse interactions ^{16 16}, clinically relevant CYP modulation currently appears unlikely. The next step would be to determine whether hesperidin—like other flavonoids—affects the activity of phase II enzymes (e.g., UDP-glucuronosyltransferases) or transporters (e.g., P-glycoprotein). Such mechanisms could alter the pharmacokinetics of drugs, particularly with chronic use. It also remains to be investigated whether hesperidin inhibits the absorption of other substances (e.g., through chelation or competition for transporters).

8. Overdose, Tolerability, Limitations

Evidence: Good tolerability of hesperidin in controlled human studies In controlled human studies, the intake of hesperidin or hesperidin-containing flavonoid mixtures (e.g., Daflon 500 mg, S 5682 with 10% hesperidin, Cyclo 3 Fort) resulted in no or only minimal adverse effects. In a study with 100 patients, treatment with S 5682 showed **no significant side effects**³⁰. Daflon 500 mg also led to **no side effects**. With Cyclo 3 Fort (a combination of *Ruscus aculeatus*, hesperidin methyl chalcone, and ascorbic acid), **rare clinical side effects** were observed, leading to discontinuation in only 3 patients³². Another study with Cyclo 3 Fort reported **minimal adverse reactions**³¹. Even with longer-term use (e.g., 6 months), **few adverse events** were reported, while efficacy in haemorrhoidal bleeding remained statistically significant ($p = 0.003$)¹².

Evidence: No immunomodulation or toxicity at standard doses The intake of hesperidin (e.g., via orange juice) in healthy, well-nourished participants **did not lead to immunomodulation**¹⁵. Safety studies focused on dosages in combination with other flavonoids (e.g., diosmin, troxerutin, rutin, quercetin), with no evidence of toxicity or overdose risks documented. The **upper limit for hesperidin alone** has not been systematically investigated in the available studies, as it is mostly used in combination products (e.g., 10% hesperidin in S 5682)³⁰. No contraindications were reported in the studies, though data on interactions with medications or specific patient groups (e.g., pregnant women, children) are lacking. The next step would be to assess whether hesperidin in monotherapy at higher doses (e.g., > 500 mg/day) demonstrates similar tolerability and whether long-term data on rare side effects are available.

9. The Most Robust Studies

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

Controlled Human Studies

- ¹ Hesperidin contributes to the vascular protective effects of orange juice: a randomized crossover study in healthy volunteers (2011)
- ² Blood pressure lowering and anti-inflammatory effects of hesperidin in type 2 diabetes; a randomized double-blind controlled clinical trial (2018)
- ³ Hesperidin improves hepatic steatosis, hepatic enzymes, and metabolic and inflammatory parameters in patients with nonalcoholic fatty liver disease: A (2019)
- ⁴ Hesperidin displays relevant role in the nutrigenomic effect of orange juice on blood leukocytes in human volunteers: a randomized controlled cross-over (2011)
- ⁵ The efficacy of flaxseed and hesperidin on non-alcoholic fatty liver disease: an open-labeled randomized controlled trial (2021)
- ⁶ Hesperidin Supplementation Alleviates Oxidative DNA Damage and Lipid Peroxidation in Type 2 Diabetes: A Randomized Double-Blind Placebo-Controlled Crossover Trial (2017)
- Marked antioxidant effect of orange juice intake and its phytonutrients in a preliminary randomised crossover trial in mild hypercholesterolaemia (2015)
- ⁷ Effects of hesperidin in orange juice on blood and pulse pressures in mildly hypertensive individuals: a randomised controlled trial (Citrus study) (2021)
- ⁸ Orange juice-derived flavanone and phenolic metabolites do not acutely affect cardiovascular risk biomarkers: a randomised, placebo-controlled, crossover trial (2015)
- ⁹ Randomised clinical trial on the efficacy of hesperidin 2S on validated cardiovascular biomarkers in healthy overweight individuals (2016)
- ¹⁰ The effect of hesperidin supplementation on metabolic profiles in patients with metabolic syndrome: a randomised, double-blind, placebo-controlled clinical trial (2020)
- ¹¹ Hesperidin supplementation modulates inflammatory responses following myocardial infarction (2015)
- Prospective randomised controlled trial of a micronised flavonoidic fraction to reduce bleeding after haemorrhoidectomy (1995)
- Venoruton vs Daflon: evaluation of effects on quality of life in chronic venous insufficiency (2006)
- ¹² Flavonoid mixture (diosmin, troxerutin, rutin, hesperidin, quercetin) in the treatment of grade I-III haemorrhoidal disease: a double-blind, multicentre trial (2018)
- ¹³ Flaxseed and/or hesperidin supplementation in metabolic syndrome: an open-label randomised controlled trial (2021)
- ¹⁴ Flavonoid mixture (diosmin, troxerutin, hesperidin) in the treatment of acute haemorrhoidal disease: a prospective, randomised, triple-blind, controlled trial (2015)
- ¹⁵ Orange juice and its major polyphenol hesperidin consumption do not induce immunomodulation in healthy well-nourished humans (2014)
- Veno-active drugs for chronic venous disease: a randomised, double-blind, placebo-controlled parallel-design trial (2014)
- ¹⁶ The effect of hesperidin and diosmin individually or in combination on metabolic profile and neuropathy among diabetic patients with metabolic syndrome (2023)
- ¹⁷ Hesperidin supplementation has no effect on blood glucose control: a systematic review and meta-analysis of randomised controlled clinical trials (2020)
- An open-label, randomised multicentre study comparing the efficacy and safety of Cyclo 3 Fort versus hydroxyethyl rutoside in chronic venous lymphatic insufficiency (2000)
- ¹⁸ Hesperidin bioavailability is increased by the presence of 2S-diastereoisomer and micronisation: a randomised, crossover, double-blind clinical trial (2022)
- ¹⁹ Controlling for sugar and ascorbic acid, a mixture of flavonoids matching navel oranges significantly increases human postprandial serum antioxidant capacity (2011)

10. Summary

What is evidenced: Hesperidin demonstrates consistent effects on vascular and metabolic parameters in controlled human studies. In hypertensive or overweight individuals, it lowers blood pressure, inflammatory markers (IL-6, hs-CRP, TNF- α), and oxidative damage (8-OHdG, MDA). Studies also show improvements in chronic venous insufficiency (CVI) and postoperative complications, particularly in trials investigating hesperidin in combination with diosmin. The effects are dose-dependent and most pronounced in metabolic conditions such as diabetes or NAFLD. Methodologically, the findings are supported by randomised, placebo-controlled trials with participant numbers in the triple digits, measuring biomarkers such as gene expression, lipid peroxidation, or cytokines.

What is plausible and what this could imply: **Hypothesis:** The observed effects may stem from modulation of transcription factors (e.g., NF- κ B) or antioxidant enzymes (SOD, CAT). The combination with other flavonoids (e.g., diosmin) appears to produce synergistic effects, such as improved vascular permeability or anti-inflammatory activity. **Hypothesis:** Enhanced bioavailability through micronisation (as demonstrated for diosmin) could increase hesperidin's clinical efficacy. It remains unclear whether the effects are similarly pronounced in healthy populations or specific to at-risk groups. Additionally, long-term intake might reduce cardiovascular events, though this requires validation through long-term studies.

What a study would need to clarify: To confirm hesperidin's clinical relevance, studies with longer intervention periods (beyond 12 weeks) and larger sample sizes are necessary. It must be determined whether the observed effects are attributable to hesperidin itself or its metabolites and whether they are dose-dependent. Furthermore, research should explore whether combining hesperidin with other flavonoids or micronisation enhances its efficacy. Long-term data on safety and clinical endpoints (e.g., cardiovascular events) would be critical to defining hesperidin's therapeutic role in metabolic and vascular diseases.

11. Open Questions

- **Dosage:** What is the optimal amount for which indication? Studies employ varying dose ranges without establishing a clear dose-response relationship.
- **Synergies:** Does hesperidin act alone or only in combination with other citrus flavonoids? Controlled trials comparing isolated hesperidin with fruit extracts are lacking.
- **Long-term effects:** Are there risks or sustained benefits after years of intake? To date, studies have lasted a maximum of 12 weeks.

12. Further Paths

Topics, mechanisms of action, and pathways involving this substance—for those who wish to explore 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

Can hesperidin be used for non-alcoholic fatty liver disease (NAFLD)?

Proven: Controlled studies show an **improvement in liver enzymes** (ALT, AST), **liver fat content** (measured via ultrasound or MRI), and **metabolic parameters** (e.g., insulin resistance) in NAFLD patients. The most cited study (2019) also reports a **reduction in inflammatory markers** such as TNF- α .

Plausible: These effects may stem from **inhibition of lipogenesis** and **activation of AMPK**, a key regulator of energy metabolism. **Open:** Whether these changes lead to **regression of fibrosis** or a **reduction in liver cancer risk** has not been investigated.

How quickly does hesperidin take effect?

Proven: Acute effects on **vascular function** (e.g., flow-mediated dilation) are measurable **2–4 hours after ingestion**, as demonstrated in a crossover study with orange juice. **Plausible:** Chronic effects on **blood pressure** or **inflammatory markers** emerge after **4–12 weeks** of regular intake.

Hypothesis: The speed of onset may depend on **baseline conditions**—effects appear sooner in individuals with pre-existing dysregulation (e.g., diabetes) than in healthy subjects.

Are there interactions with medications?

Plausible: Hesperidin and its metabolite hesperetin inhibit **CYP3A4** and **OATP1A2** in vitro, enzymes responsible for the metabolism of many drugs.

Proven: A 2007 study shows that **grapefruit juice** (which contains hesperidin) increases the bioavailability of **antihistamines**. **Open:** Whether this interaction occurs with **isolated hesperidin** at relevant doses has not been systematically studied. Caution is advised with **immunosuppressants** or **chemotherapy drugs** until further data are available.

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