



DOSSIER · SUBSTANCE

Olive Polyphenols (Hydroxytyrosol)

Olive polyphenols, particularly **hydroxytyrosol**, are among the most extensively studied secondary plant compounds. The database shows a strong focus on **metabolic and cardiovascular parameters**, while the applicability of laboratory findings to humans often remains uncertain. The most striking finding: even in frequently cited studies, **observational data** prevail over controlled efficacy evidence.

1,971

STUDIES IN
TOTAL

226

IN HUMANS

89

OF WHICH
CONTROLLED

324

IN ANIMALS

404

IN THE LAB

Figures from the IHR study database · Last updated 2026-10-15

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

Olive polyphenols (hydroxytyrosol) at a glance

ORIGIN:
Hydroxytyrosol is a phenolic alcohol from the group of olive polyphenols (secoiridoids) and occurs naturally in olive leaves, fruits, and extra virgin olive oil. It is formed through the hydrolysis of the glucoside oleuropein and exhibits high antioxidant capacity, comparable in vitro to vitamin E. Other structurally related compounds such as tyrosol, oleocanthal, and oleacein collectively contribute to its biological effects.

STUDY LANDSCAPE:
1,971 evaluated publications · 89 controlled human studies · 137 observational studies · 127 review articles · 324 animal studies · 327 cell culture studies

- STRONGEST EVIDENCE:**
- **Metabolism:** A randomised, double-blind study involving 40 patients with stage-1 hypertension demonstrated that an olive leaf extract (500 mg twice daily, standardised to oleuropein) lowered systolic blood pressure as effectively as captopril, with no significant differences between groups. Secondary endpoints such as diastolic blood pressure and lipid profile also improved. The study did not investigate the contribution of hydroxytyrosol alone.
 - **Inflammation** In a randomised, placebo-controlled crossover study with 46 overweight men, an olive leaf extract (51.1 mg oleuropein, 9.7 mg hydroxytyrosol) administered over 12 weeks led to a significant improvement in insulin sensitivity (15%) and β-cell reactivity (28%), while fasting interleukin-6 (IL-6) levels changed. The effects cannot be attributed to hydroxytyrosol alone.
 - **Cardiovascular** An acute crossover study with 18 healthy individuals showed that an olive leaf extract (51 mg oleuropein, 10 mg hydroxytyrosol) significantly reduced vascular stiffness and ex vivo production of IL-8 following LPS stimulation. The effects cannot be attributed to hydroxytyrosol alone.
 - **Absorption and bioavailability** A study with 20 participants found that the maximum plasma concentration of hydroxytyrosol was significantly higher (3.79 ng/ml) 30 minutes after consuming extra virgin olive oil compared to other matrices. Urinary excretion of hydroxytyrosol and its metabolites was also highest with extra virgin olive oil.
 - **Bone and joints** A 12-month study involving 64 postmenopausal women with osteopenia demonstrated that an olive polyphenol extract (250 mg/day) combined with calcium significantly increased the bone turnover marker osteocalcin, while bone density remained stable. The study did not investigate the effects of hydroxytyrosol alone.

- LIMITATIONS:**
- The applicability of laboratory findings (in vitro/animal models) to humans remains unclear, as antiproliferative, neuroprotective, or antiviral effects have only been demonstrated in preclinical studies. These effects have not been investigated in humans.
 - Methodological weaknesses such as small sample sizes, short intervention periods, and heterogeneous formulations (extracts vs. native oil) complicate the interpretation of dose-response relationships.
 - Long-term data on safety, efficacy, and interactions with medications (e.g., antihypertensives) are absent, and polyphenol profiles vary widely depending on cultivar, cultivation, and processing.

ASSESSMENT:
Hydroxytyrosol, an antioxidant phenolic alcohol derived from olive products, has been investigated for metabolic and cardiovascular effects in human studies. Its relevance to clinical endpoints and the role of individual **polyphenols** require further investigation to clarify potential effects.

1. What Olive Polyphenols Are

Hydroxytyrosol is a **phenolic alcohol** from the group of **olive polyphenols**, naturally occurring in **olive leaves, fruits, and extra virgin olive oil**. Chemically, it belongs to the **secoiridoids**, a subgroup of **phenolic acids**, and is formed through the hydrolysis of the bitter glucoside **oleuropein**. It is water-soluble and exhibits high **antioxidant capacity**, often compared in vitro to that of **vitamin E**. In addition to hydroxytyrosol, olive products contain other structurally related compounds such as **tyrosol, oleocanthal, and oleacein**, which are collectively responsible for the biological effects.

Critical to the **study landscape** is the **diversity of formulations**: research examines **extra virgin olive oil, extracts from leaves or pomace, isolated hydroxytyrosol, or enriched dietary supplements**. **Bioavailability** varies significantly depending on the matrix—fat-soluble forms (e.g., in oil) exhibit different absorption patterns compared to aqueous extracts. Furthermore, hydroxytyrosol is **rapidly metabolised** in the body, so **sulphate and glucuronide conjugates** are often measured in blood instead of the parent compound. Most studies therefore assess **metabolites** rather than the original substance, complicating the interpretation of **dose-response relationships**. Another key issue: the **polyphenol profiles** of olive products depend heavily on **cultivar, cultivation, processing, and storage**, making direct comparisons between studies often impossible.

2. What the Studies Show in Detail

Key human studies and major 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 studies** by application area — numbers are not additive, as a single study may be assigned to multiple areas:

APPLICATION AREA	CONTROLLED STUDIES
Metabolism	56
Cardiovascular	41

APPLICATION AREA	CONTROLLED STUDIES
Oxidative stress	34
Inflammation	33
Safety and tolerability	28
Fatigue and stress	25
Absorption and bioavailability	10
Immune system	8

Inflammatory Processes

In a randomised, double-blind, placebo-controlled crossover study involving 46 overweight men (mean age 46.4 ± 5.5 years, BMI 28.0 ± 2.0 kg/m²), a daily olive leaf extract containing 51.1 mg oleuropein and 9.7 mg hydroxytyrosol was administered over 12 weeks. The primary endpoint was insulin sensitivity (Matsuda method), with secondary endpoints including glucose and insulin profiles, cytokines, lipid profile, body composition, 24-hour blood pressure, and carotid intima-media thickness. Administration of the extract led to a significant 15% improvement in insulin sensitivity (p = 0.024) and a 28% increase in pancreatic β-cell reactivity (p = 0.013) compared to placebo. Additionally, fasting levels of the pro-inflammatory cytokine interleukin-6 (IL-6) rose significantly (p = 0.014), suggesting complex immunomodulatory effects. Limitations include the short 12-week intervention period, which precludes conclusions about long-term effects, and the lack of differentiation between the effects of oleuropein and hydroxytyrosol ¹.

An acute, randomised, double-blind, placebo-controlled crossover study with 18 healthy participants (9 men, 9 women) investigated the effect of an olive leaf extract (51 mg oleuropein, 10 mg hydroxytyrosol) on vascular function and inflammatory markers. Vascular stiffness (measured via digital volume pulse, DVP) and ex vivo production of the pro-inflammatory cytokine IL-8 following LPS stimulation decreased significantly (p < 0.05) compared to placebo. The effects correlated with the urinary excretion of hydroxytyrosol and oleuropein metabolites, which peaked at 8–24 hours. The small sample size and absence of a dose-response analysis limit generalisability ⁶.

In a randomised, controlled crossover study involving 10 healthy participants and 10 patients with chronic kidney disease (K-DOQI stages III–IV), the influence of white wine (4 ml/kg body weight, 0.48 g/kg alcohol) combined with extra virgin olive oil (2–3 glasses/day) on inflammatory markers was examined. After a two-week intervention, a reduction in systemic inflammatory markers was observed. The study suggests potential synergistic effects of polyphenols in the combination, but it does not isolate the contribution of hydroxytyrosol or other individual compounds. The short duration and small sample size limit the study's validity.

A randomised, controlled study involving 91 participants (33 men, 58 women) with obesity (BMI 30–40 kg/m²) and prediabetes investigated the effect of extra virgin olive oil (EVOO) with high oleocanthal and oleacein content compared to regular olive oil (OO) over one month. The primary endpoint was inflammatory status, with secondary endpoints including oxidative stress, body weight, glucose metabolism, and lipid profile. Following EVOO intake, interferon-γ levels decreased significantly (p = 0.041), while antioxidant capacity increased and lipid peroxides declined. The study showed effects of the **olive polyphenol mixture**, though data on long-term effects and the specific role of hydroxytyrosol are lacking ¹⁴.

HYPOTHESIS The studies suggest that **olive polyphenols** such as hydroxytyrosol and oleuropein exert anti-inflammatory effects through multiple mechanisms, including modulation of cytokines (IL-6, IL-8, IFN-γ) and improvement of endothelial function. However, effects vary depending on dose, preparation (extract vs. native oil), and population, complicating standardised assessment. It remains unclear whether the observed effects are primarily due to antioxidant or specific anti-inflammatory properties.

Large-scale, multicentre long-term studies with clearly defined dose-response relationships and differentiation of individual polyphenols remain to be conducted to validate the clinical relevance for chronic inflammatory conditions.

Absorption and Bioavailability

In a randomised study involving nine participants (5 men, 4 women; mean age 42.8 ± 7.4 years), the bioavailability and metabolism of oleuropein and hydroxytyrosol following intake of an olive leaf extract (OLE) were investigated. Participants received either capsules or liquid extract in two dosages (low: 51.1 mg oleuropein, 9.7 mg hydroxytyrosol; high: 76.6 mg oleuropein, 14.5 mg hydroxytyrosol). Primary metabolites in plasma and urine were conjugated forms of hydroxytyrosol (sulphated and glucuronidated). The maximum plasma concentration of oleuropein was significantly higher after liquid extract intake (2.74 vs. 0.47 ng/ml, p = 0.004), while the peak concentration of conjugated hydroxytyrosol was independent of preparation form (p = 0.94). Time to maximum concentration of hydroxytyrosol was shorter with liquid intake (64 vs. 93 minutes, p = 0.031). Sex-specific differences in bioavailability were observed but not quantified further ².

A randomised, controlled study involving 20 participants examined the pharmacokinetics and bioavailability of hydroxytyrosol (5 mg) in different food matrices (extra virgin olive oil, refined olive oil, flaxseed oil, grapeseed oil). The maximum plasma concentration of hydroxytyrosol was significantly higher 30 minutes after intake of extra virgin olive oil (3.79 ng/ml) compared to other matrices. Urinary excretion of hydroxytyrosol and its metabolites (hydroxytyrosol acetate, DOPAC, tyrosol, homovanillyl alcohol) was highest after intake of extra virgin olive oil (0.86 µg/mg creatinine) and enriched refined olive oil (0.63 µg/mg creatinine). The study shows that the bioavailability of hydroxytyrosol strongly depends on the food matrix, with native oils enhancing absorption. However, the short 12-hour observation period limits conclusions about long-term metabolism ⁸.

HYPOTHESIS The bioavailability of **hydroxytyrosol** is influenced not only by dose but also by preparation form (liquid vs. capsule) and food matrix (e.g., native vs. refined oil). Native oils appear to optimise absorption, potentially through synergistic effects with other oil components such as fatty acids. It remains unclear whether these differences have clinically relevant impacts on anti-inflammatory or antioxidant effects.

Systematic studies on the bioavailability of **olive polyphenols** in complex meals and long-term data on accumulation and metabolism in different populations (e.g., elderly patients, patients with malabsorption) are lacking.

Metabolism

In a double-blind, randomised, parallel-group study involving 40 patients with stage-1 hypertension, the effect of an olive leaf extract (500 mg twice daily, standardised to oleuropein) was compared to captopril (initial dose 12.5 mg twice daily, titrated to 25 mg) over 8 weeks. The primary endpoint was reduction in systolic blood pressure (SBP). Both groups showed a significant reduction in SBP (extract: -11.5 ± 8.5 mmHg; captopril: -13.7 ± 7.6 mmHg; $p < 0.01$ vs. baseline), with no significant differences between groups. Secondary endpoints such as diastolic blood pressure (DBP) and lipid profile (triglycerides, LDL cholesterol) also improved in both groups. The study showed an antihypertensive effect of the extract, though data on long-term effects and the specific role of individual components such as hydroxytyrosol within the complex are lacking ⁴.

A randomised, double-blind crossover study involving 33 participants with cardiovascular risk investigated the endogenous conversion of tyrosol to hydroxytyrosol and its effects on cardiovascular biomarkers. Participants received white wine (1–2 standard glasses/day), white wine plus tyrosol capsules (25 mg tyrosol per glass), or water across three intervention phases. The combination of white wine and tyrosol led to significantly higher urinary excretion of hydroxytyrosol ($p < 0.05$) and showed potential effects on endothelial function, HDL cholesterol, homocysteine, and inflammatory markers (IL-6, CD40L) in humans. The short duration and lack of a placebo control for tyrosol alone limit the study's validity ⁹.

In a randomised, double-blind study involving 16 healthy participants, the effect of yoghurt enriched with olive polyphenols (50 mg polyphenols/400 g yoghurt) was investigated over two weeks. Primary endpoints were body composition, blood parameters, and oxidative stress. Regardless of intervention, body weight, BMI, and hip circumference decreased significantly ($p < 0.05$). In the polyphenol arm, there was a trend towards reduced LDL cholesterol ($p = 0.06$) and thiobarbituric acid-reactive substances ($p < 0.05$). The study suggests metabolic effects of **olive polyphenols**, though data on the specific effects of individual polyphenols and long-term effects are lacking.

HYPOTHESIS **Olive polyphenols** such as oleuropein and hydroxytyrosol influence metabolism through multiple pathways, including improvement of endothelial function, reduction of blood pressure and lipids, and modulation of inflammatory markers. The endogenous conversion of tyrosol to hydroxytyrosol may represent an additional mechanism that enhances cardioprotective effects. It remains unclear whether these effects are dose-dependent and whether they are similarly pronounced in populations with metabolic syndrome or diabetes.

Long-term controlled studies with clearly defined metabolic endpoints (e.g., insulin resistance, HbA1c) and differentiation of the effects of individual **polyphenols** such as hydroxytyrosol in various patient groups are still pending.

Bone and Joints

In a double-blind, randomised, placebo-controlled study involving 64 postmenopausal women with osteopenia (lumbar spine T-score -1.5 to -2.5), the effect of an olive polyphenol extract (250 mg/day) combined with 1000 mg calcium was investigated over 12 months. The primary endpoint was changes in bone turnover markers, with secondary endpoints including bone mineral density (BMD) and lipid profile. Compared to placebo (calcium only), the osteoblastic marker protein osteocalcin increased significantly in serum ($p < 0.05$), while BMD remained stable. The lipid profile also improved (reduction in LDL cholesterol, $p < 0.05$). The study showed a positive effect on bone metabolism for the combination, though data on fracture rates and the specific effects of hydroxytyrosol or other individual polyphenols within the extract are lacking ⁵.

HYPOTHESIS The observed increase in osteocalcin suggests that **olive polyphenols** such as oleuropein and hydroxytyrosol promote osteoblast activity and may potentially counteract bone loss. However, it remains unclear whether these effects are sufficient to influence clinically relevant endpoints such as fractures or whether they are primarily due to antioxidant or hormonal mechanisms.

Long-term studies with hard endpoints (fracture rates) and larger sample sizes are lacking to assess the clinical relevance for osteoporosis prevention.

Heart and Circulation

In a randomised crossover study involving nine healthy men, the acute effect of extra virgin olive oil with varying oleocanthal and oleacein content on platelet function was investigated. Participants received 40 ml of olive oil weekly with either low (D2i 0.5: 1:2 oleacein/oleocanthal), high (D2i 2: 2:1 oleacein/oleocanthal), or predominantly tyrosol content. Maximum platelet aggregation (Pmax) following stimulation with 1 μ g/ml collagen decreased significantly after intake of oils with high oleocanthal content (D2i 0.5 and D2i 2), with the effect most strongly correlated with oleocanthal dose ($R = 0.56$, $p = 0.002$). Inhibition of eicosanoid production suggests a COX-independent mechanism. The study showed dose-dependent effects on platelet function, though data on long-term clinical outcomes and applicability to at-risk populations are lacking ⁷.

HYPOTHESIS The antithrombotic effects of oleocanthal may be due to direct inhibition of platelet activation, potentially via modulation of pathways such as TRPA1 (see study ²²). However, it remains unclear whether these effects are similarly pronounced in populations with cardiovascular risk factors (e.g., diabetes, hypertension) or whether they are influenced by other dietary components.

Controlled human studies with cardiovascular endpoints (e.g., myocardial infarction, stroke) and longer intervention durations are part of the research landscape, but represent a smaller subset of the available evidence on **olive polyphenols**.

Gut and Microbiome

In a randomised, controlled, blinded crossover study involving 12 healthy participants, the bioavailability and metabolism of hydroxytyrosol from two olive-based dietary supplements (30.58 mg and 61.48 mg hydroxytyrosol per dose, respectively) were investigated in comparison to hydroxytyrosol-enriched olive oil. Primary endpoints were plasma concentrations and urinary excretion of hydroxytyrosol and its metabolites (homovanillic acid, hydroxytyrosol-3-O-sulphate, DOPAC). Bioavailability increased in a dose-dependent manner, with the highest concentrations of metabolites measured after 1–2 hours in plasma and after 12 hours in urine. The study showed that hydroxytyrosol from dietary supplements is bioavailable; however, data on modulation of the gut microbiota and long-term effects are lacking ¹⁰.

HYPOTHESIS The bioavailability of hydroxytyrosol may be influenced by the gut microbiota, as part of its metabolism occurs in the gut. However, it remains unclear whether **polyphenols**, like hydroxytyrosol, directly alter the composition of the microbiota or primarily act via systemic effects (e.g., anti-inflammatory mechanisms).

Oxidative Stress

In a randomised, double-blind, placebo-controlled study involving 80 children with non-alcoholic fatty liver disease (NAFLD), the effects of a combination of hydroxytyrosol (HXT) and vitamin E were investigated over four months. Primary endpoints included oxidative stress parameters (e.g., advanced glycation end products, carbonylated proteins) and liver ultrasound. The combination treatment led to a significant improvement in oxidative stress markers and a reduction in steatosis, with the improvement in steatosis correlating with the reduction in oxidative stress parameters ($p < 0.05$). The study showed the antioxidant effects of the combination therapy; however, the specific contribution of hydroxytyrosol alone remains unclear, and data on its long-term effects are lacking¹³.

HYPOTHESIS

The antioxidant effects of hydroxytyrosol may be attributed to its direct radical-scavenging function as well as the induction of endogenous antioxidant enzymes (e.g., catalase, superoxide dismutase) (see study¹²). However, it remains unclear whether these effects are similarly pronounced in populations with chronic diseases (e.g., diabetes, cardiovascular diseases).

Controlled human studies on the dose-dependent effects of hydroxytyrosol on oxidative stress markers in different populations are limited, as are long-term investigations of its impact on clinical endpoints (e.g., progression of NAFLD).

Overall Picture

The available studies show that **hydroxytyrosol** from olive leaves and oils exhibits multiple health-promoting effects. Its anti-inflammatory, antioxidant, and cardioprotective properties are particularly investigated, mediated through the modulation of cytokines (IL-6, IL-8, IFN- γ), improvement of endothelial function, and reduction of oxidative stress. The bioavailability of hydroxytyrosol is dose- and matrix-dependent, with native oils and liquid extracts enhancing absorption. Additionally, preliminary data indicate positive effects on bone metabolism, glucose metabolism, and gut health.

Despite these promising results, the evidence remains limited in certain areas. In particular, there is a lack of long-term studies with clinically relevant endpoints (e.g., fracture rates, cardiovascular events, progression of NAFLD) and systematic dose-response analyses. Most studies have been conducted in healthy participants or small patient groups, leaving the applicability to high-risk populations (e.g., elderly patients, those with metabolic syndrome) uncertain. Furthermore, the preparations (extracts vs. native oils) and dosages used vary widely, complicating direct comparisons.

Methodology of the evidence base

The foundational controlled human studies comprise randomised controlled trials (RCTs) with crossover or parallel-group designs, alongside other controlled designs, with intervention durations ranging from single acute doses (e.g.,^{6, 7}) to up to 12 months (e.g.,^{1, 5}). Typical endpoints include biochemical markers (e.g., cytokines, lipid profiles, oxidative stress parameters), physiological parameters (e.g., blood pressure, vascular function), and, in a few cases, clinical surrogate parameters (e.g., bone density, liver steatosis). Systematic gaps include the lack of standardisation in dosages and preparations, the small sample sizes of many studies (often fewer than 50 participants), and the absence of long-term data. Additionally, hard clinical endpoints (e.g., mortality, fractures) have rarely been investigated. Observational studies and reviews complement the evidence but do not provide causal proof.

Hydroxytyrosol: From laboratory findings to clinical relevance

RESEARCH ON OLIVE POLYPHENOLS

is characterised by an **asymmetrical evidence base**: while **basic research** and **animal models** describe a wealth of **biochemical mechanisms**—such as **radical-scavenging properties**, **enzyme inhibition**, or **changes in gene expression**—there is a lack of **evidence for clinically meaningful effects in humans** for most applications. Even in frequently cited human studies, the majority involve **short-term interventions with surrogate markers**, the **relevance of which to disease progression** remains unclear. For example, the oft-cited **improvement in vascular function** (e.g., measured by **flow-mediated dilation**) provides no insight into **hard endpoints** such as myocardial infarction or mortality. The same applies to **metabolic markers** like **insulin resistance**—while some studies show **statistically significant effects**, it remains uncertain whether these are **clinically relevant in the long term**.

A central issue is the

LACK OF STANDARDISATION

in the preparations studied. Most trials use **extracts or enriched oils**, the **polyphenol composition** of which varies widely. Even **hydroxytyrosol** is administered in different **chemical forms** (free, conjugated, as an oleuropein precursor), making **direct comparisons** impossible. Furthermore, many studies **do not differentiate between hydroxytyrosol and other olive polyphenols**, such as **oleocanthal**, which is known for its **anti-inflammatory effects**. **Bioavailability** is another critical factor: while **in vitro** studies often use high concentrations, **oral administration** achieves only **low plasma levels**, which **fall below the effective doses observed in the laboratory**. Although the **most frequently cited reviews** highlight **potential synergistic effects** of polyphenol mixtures, **controlled studies with isolated hydroxytyrosol** are largely lacking. Without such data, it remains unclear whether **hydroxytyrosol itself** or **accompanying substances** are responsible for the observed effects.

3. How Robust the Research Is

The evaluated publications are unevenly distributed between **basic research** and **human studies**, with the latter predominantly **observational** in design. Controlled human studies focus mainly on **metabolic parameters**, **cardiovascular markers**, and **antioxidant/anti-inflammatory effects**. Far less frequently investigated are **gut health**, **immune modulation**, or **antiviral effects**. The most cited controlled studies primarily examine **insulin resistance**, **blood pressure**, **vascular function**, and **bone markers**, while **clinical endpoints** (e.g., disease progression) are rarely addressed. A notable **discrepancy exists between laboratory and human research**: while **antiproliferative**, **neuroprotective**, and **antimicrobial effects** are described in vitro and in animal models, these findings remain preclinical, and **controlled human studies** for these applications are almost entirely lacking.

The **methodological robustness** of human studies is **inconsistent**. Strengths of the field include **randomised, placebo-controlled designs** in the most cited studies and the **measurement of surrogate parameters** (e.g., LDL oxidation, inflammatory markers) using standardised methods. Weaknesses include **small sample sizes, short intervention periods, and heterogeneous formulations**. Many studies use **enriched extracts** whose **polyphenol profiles** are not always fully characterised. Additionally, **dose-finding studies** are often absent, leaving it unclear whether observed effects are **physiologically relevant**. While **review articles** highlight **potential mechanisms** (e.g., NF-κB inhibition, microbiome modulation), their **applicability to humans** remains speculative. Particularly critical: **long-term data** on safety and efficacy are lacking, and **interactions with medications** (e.g., antihypertensives) are scarcely investigated.

4. Common Claims and the Supporting Evidence

CLAIM	EVIDENCE BASE
Olive polyphenols have been studied for blood pressure reduction; controlled results are inconsistent	Controlled studies demonstrate short-term effects on surrogate parameters (e.g., systolic blood pressure), but no data on long-term outcomes or clinical
Hydroxytyrosol has been studied for neuroprotection; controlled results are inconsistent	Most of the data originate from cell culture and animal models . Controlled human studies on cognitive functions or neurodegenerative diseases are entire
Olive polyphenols have been studied for improving gut health; controlled results are inconsistent	Controlled studies exist, yet they examine heterogeneous endpoints (e.g., microbiome composition, inflammatory markers). Clinical relevance has not bee
Hydroxytyrosol has been studied for cancer prevention; controlled results are inconsistent	The evidence is limited to in vitro studies and animal models . Observational studies in humans show no robust associations , and controlled studies are lac

5. The Most Robust Studies

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

Controlled Human Studies

- ¹ Olive (*Olea europaea* L.) leaf polyphenols improve insulin sensitivity in middle-aged overweight men: a randomised, placebo-controlled, crossover trial (2013)
- ² Human absorption and metabolism of oleuropein and hydroxytyrosol ingested as olive (*Olea europaea* L.) leaf extract (2013)
- ³ Oleuropein, a bioactive compound from *Olea europaea* L., as a potential preventive and therapeutic agent in non-communicable diseases (2019)
- ⁴ Olive (*Olea europaea*) leaf extract effective in patients with stage-1 hypertension: comparison with Captopril (2011)
- ⁵ Twelve-month consumption of a polyphenol extract from olive (*Olea europaea*) in a double-blind, randomised trial increases serum total osteocalcin levels (2015)
- ⁶ Secoiridoids delivered as olive leaf extract induce acute improvements in human vascular function and reduction of an inflammatory cytokine: a randomised trial (2015)
- ⁷ Oleocanthal-rich extra virgin olive oil demonstrates acute anti-platelet effects in healthy men in a randomised trial (2017)
- ⁸ Pharmacokinetics and bioavailability of hydroxytyrosol are dependent on the food matrix in humans (2021)
- ⁹ Cardiovascular benefits of tyrosol and its endogenous conversion into hydroxytyrosol in humans: a randomised, controlled trial (2019)

- ¹⁰ Oral bioavailability and metabolism of hydroxytyrosol from food supplements (2023)
- **** Anti-inflammatory effect of white wine in CKD patients and healthy volunteers (2015)
- ¹¹ Effects of olive oil and its components on intestinal inflammation and inflammatory bowel disease (2022)
- ¹² Effects of postprandial hydroxytyrosol and derivatives on LDL oxidation, cardiometabolic state and gene expression: a nutrigenomic approach for cardiovascular prevention (2019)
- ¹³ The antioxidant effects of hydroxytyrosol and vitamin E on paediatric non-alcoholic fatty liver disease: a clinical trial—a new treatment? (2019)
- **** The effects of an olive fruit polyphenol-enriched yoghurt on body composition, blood redox status, physiological and metabolic parameters and yoghurt microbiology (2016)
- ¹⁴ Rich oleocanthal and oleacein extra virgin olive oil and inflammatory and antioxidant status in people with obesity and prediabetes: the APRIL study (2023)
- ¹⁵ Supplementation effect of a combination of olive (*Olea europaea* L.) leaf and fruit extracts in the clinical management of hypertension and metabolic syndrome: a randomised trial (2020)
- ¹⁶ The effect of olive leaf extract in decreasing the expression of two pro-inflammatory cytokines in patients receiving chemotherapy for cancer: a randomised trial (2013)
- ¹⁷ The effect of dietary intervention with high-oleocanthal and oleacein olive oil in patients with early-stage chronic lymphocytic leukaemia: a pilot randomised trial (2021)
- **** A randomised study of nutritional supplementation in patients with unilateral wet age-related macular degeneration (2021)
- ¹⁸ Systemic health effects of oleuropein and hydroxytyrosol supplementation: a systematic review of randomised controlled trials (2024)
- ¹⁹ Effect of a food supplement containing berberine, monacolin K, hydroxytyrosol and coenzyme Q₁₀ on lipid levels: a randomised, double-blind, placebo-controlled trial (2017)
- ²⁰ The effect of olive leaf extract on cardiovascular health markers: a randomised placebo-controlled clinical trial (2021)
- ²¹ Effect of a combination of citrus flavones and flavanones and olive polyphenols for the reduction of cardiovascular disease risk: an exploratory randomised trial (2020)

6. Summary

What is evidenced: **Polyphenols** such as hydroxytyrosol and oleuropein demonstrate effects on metabolic and cardiovascular parameters in controlled human studies. These include reductions in blood pressure, improvements in insulin sensitivity, modulation of inflammatory markers (IL-6, IL-8, IFN- γ), and enhancement of endothelial function. Bioavailability is highly dependent on the form of administration, with native olive oil favouring absorption. Additionally, there is evidence of positive effects on bone metabolism (e.g., increased osteocalcin). However, most studies assess surrogate parameters rather than clinical endpoints such as disease progression or fracture rates.

HYPOTHESIS The observed effects may stem from multiple mechanisms, including antioxidant properties, inhibition of NF- κ B, or modulation of the microbiome. However, it remains unclear whether the effects are primarily attributable to hydroxytyrosol or other polyphenols such as oleuropein, as studies often use mixtures. The endogenous conversion of tyrosol to hydroxytyrosol could amplify cardioprotective effects, but dose-finding studies are lacking to define physiologically relevant amounts. The discrepancy between laboratory and human research suggests that some in vitro effects (e.g., neuroprotective) may not be transferable to humans.

What a study would need to clarify: Large-scale, multicentre long-term studies with clearly defined dose-response relationships and differentiation of individual **polyphenols** are necessary to validate the clinical relevance for chronic inflammatory diseases, metabolic syndrome, or osteoporosis. Additionally, systematic investigations into bioavailability in complex meals and across different populations (e.g., elderly patients, those with malabsorption) should be conducted. Studies on interactions with medications and long-term safety, particularly for high-dose extracts, are also important. Finally, studies directly measuring clinical endpoints (e.g., cardiovascular events, fracture rates) are lacking to assess the transferability of surrogate parameters.

7. Broader Context

Evidence-based: Olive polyphenols, particularly hydroxytyrosol, demonstrate measurable effects on key metabolic and cardiovascular parameters in controlled human studies. Evidence includes improvements in vascular function (e.g., endothelium-dependent vasodilation), reductions in systolic blood pressure, and positive influences on insulin resistance and lipid profiles. These findings correlate with the substance's high antioxidant capacity, which in vivo is primarily mediated via metabolites such as sulphate and glucuronide conjugates. The data are largely derived from short-term interventional studies using standardised extracts or native olive oil, while long-term effects or clinical endpoints (e.g., cardiovascular events) remain scarcely documented. A critical consideration is transferability: bioavailability varies significantly depending on the form of administration (aqueous vs. fat-soluble), and the observed effects are often dose-dependent but not linear. Nonetheless, these findings position hydroxytyrosol as a relevant modulator in the oxidative stress regulation cascade—particularly in interplay with endogenous systems such as Nrf2 or glutathione, the activation of which has been demonstrated in vitro.

PLAUSIBLE The mechanistic plausibility of hydroxytyrosol's effects arises from its chemical structure and the actions observed in animal models and in vitro studies. As a secoiridoid with a phenolic hydroxyl group, it acts as a direct radical scavenger but also stabilises reactive oxygen species through chelation with transition metals. In the context of mitochondrial function, it exhibits a dual role: on the one hand, hydroxytyrosol protects against oxidative damage to mitochondrial DNA and membranes; on the other, it modulates the electron transport chain, which may lead to more efficient ATP synthesis. These effects are closely linked to the activation of the Nrf2 signalling pathway, which upregulates the expression of antioxidant enzymes such as SOD or glutathione peroxidase. Additionally, preclinical data suggest an interaction with the gut barrier: hydroxytyrosol promotes the proliferation of butyrate-producing bacteria (e.g., *Faecalibacterium prausnitzii*) and reduces pro-inflammatory cytokines in the gut milieu. Here, its profile overlaps with that of

zeolite, which also shares microbiome modulation as a common denominator—though studies investigating these substances in combination are lacking. The plausibility of these mechanisms is further supported by the structural similarity to other olive polyphenols such as oleocanthal, which additionally mediates anti-inflammatory effects via inhibition of COX enzymes.

HYPOTHESIS The available data suggest that hydroxytyrosol may exert its strongest systemic effects where oxidative stress regulation, mitochondrial function, and gut barrier integrity converge. A central, yet untested, hypothesis is that the substance—similar to butyrate—influences the gut-brain or gut-liver axis by modulating the production of short-chain fatty acids while simultaneously reducing intestinal permeability. This could explain why neuroprotective effects are observed in animal models, whereas human studies are lacking. Particularly worth investigating is whether hydroxytyrosol, in combination with other barrier-nourishing substances (e.g., L-glutamine) or microbiome-modulating agents (e.g., probiotics), demonstrates synergistic effects on inflammatory markers or metabolic parameters. Another unresolved question is whether the antiviral activity observed in vitro (e.g., against influenza viruses) stems from direct interaction with viral proteins or from strengthening mucosal immunity—and whether this is clinically relevant. Methodologically, controlled studies using standardised extracts and clearly defined biomarkers (e.g., zonulin for gut barrier integrity, mtDNA damage for mitochondrial function) would be required to validate the transferability of preclinical findings.

8. Open Questions

- **Dose-response relationship:** Unclear whether observed effects occur at **physiological concentrations** (e.g., through diet) or only with **high-dose extracts** within the studied dosage ranges.
- **Long-term safety:** No studies exceeding 12 months in duration exist, leaving **risks of prolonged use** unknown.
- **Interactions:** Potential interactions with **medications** (e.g., antihypertensives, anticoagulants) have **not been systematically investigated**.

9. Further Paths

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

- Gut barrier and binding: **polyphenols**, zeolite, butyrate, probiotics
- Oxidative stress, mitochondria, and energy

Frequently Asked Questions

Can hydroxytyrosol be recommended as a dietary supplement?

The **controlled studies** demonstrate **effects on surrogate parameters** (e.g., LDL oxidation, inflammatory markers), but **no efficacy on clinical endpoints**. **Bioavailability** is **matrix-dependent**—aqueous extracts are absorbed differently than fat-soluble forms. **Long-term data are lacking**, so **no recommendation for prolonged supplementation** can be derived. For **therapeutic purposes** (e.g., blood pressure reduction), there is **insufficient evidence**.

Do the effects of native olive oil and isolated hydroxytyrosol differ?

Native olive oil contains a **mixture of polyphenols** (hydroxytyrosol, oleocanthal, oleuropein), whereas **isolated preparations** often provide only a single component. **Synergistic effects** of the mixture are discussed but **not supported by controlled studies**. Additionally, **bioavailability** in oil is **higher** than in aqueous extracts, which **complicates dose comparisons**. Most human studies use **enriched extracts**, not native oil.

Is there evidence of antiviral effects of hydroxytyrosol?

Controlled studies on antiviral effects exist, but they examine **heterogeneous endpoints** (e.g., viral load, immune markers). The evidence base is **limited and methodologically weak**—most work derives from **cell culture or animal models**. **Clinical studies in humans** are lacking, so **no conclusions on efficacy** can be drawn. While **review articles** highlight **potential mechanisms** (e.g., inhibition of viral replication), **robust evidence** is still absent.

Sources

- 1 Olive (*Olea europaea* L.) leaf polyphenols improve insulin sensitivity in middle-aged overweight men: a randomized, placebo-controlled, crossover trial
de Bock M, Derraik JG, Brennan CM, Biggs JB, Morgan PE, Hodgkinson SC et al. · 2013
- 2 Human absorption and metabolism of oleuropein and hydroxytyrosol ingested as olive (*Olea europaea* L.) leaf extract
de Bock M, Thorstensen EB, Derraik JG, Henderson HV, Hofman PL, Cutfield WS · 2013
- 3 Oleuropein, a Bioactive Compound from *Olea europaea* L., as a Potential Preventive and Therapeutic Agent in Non-Communicable Diseases
Nediani C, Ruzzolini J, Romani A, Calorini L · 2019
- 4 Olive (*Olea europaea*) leaf extract effective in patients with stage-1 hypertension: comparison with Captopril
Susalit E, Agus N, Effendi I, Tjandrawinata RR, Nofiarny D, Perrinjaquet-Moccetti T et al. · 2011
- 5 Twelve-month consumption of a polyphenol extract from olive (*Olea europaea*) in a double blind, randomized trial increases serum total osteocalcin levels and improves serum lipid profiles in postmenopausal women with osteopenia
Filip R, Possemiers S, Heyerick A, Pinheiro I, Raszewski G, Davicco MJ et al. · 2015
- 6 Secoiridoids delivered as olive leaf extract induce acute improvements in human vascular function and reduction of an inflammatory cytokine: a randomized, double-blind, placebo-controlled, cross-over trial
Lockyer S, Corona G, Yaqoob P, Spencer JP, Rowland I · 2015
- 7 Oleocanthal-rich extra virgin olive oil demonstrates acute anti-platelet effects in healthy men in a randomized trial
Agrawal K, Melliou E, Li X, Pedersen TL, Wang SC, Magiatis P et al. · 2017
- 8 Pharmacokinetics and bioavailability of hydroxytyrosol are dependent on the food matrix in humans
Alemán-Jiménez C, Domínguez-Perles R, Medina S, Prgommet I, López-González I, Simonelli-Muñoz A et al. · 2021
- 9 Cardiovascular benefits of tyrosol and its endogenous conversion into hydroxytyrosol in humans. A randomized, controlled trial
Boronat A, Mateus J, Soldevila-Domenech N, Guerra M, Rodríguez-Morató J, Varon C et al. · 2019
- 10 Oral Bioavailability and Metabolism of Hydroxytyrosol from Food Supplements
Bender C, Strassmann S, Golz C · 2023
- 11 Effects of Olive Oil and Its Components on Intestinal Inflammation and Inflammatory Bowel Disease
Vrdoljak J, Kumric M, Vilovic M, Martinovic D, Tomic IJ, Krnic M et al. · 2022
- 12 Effects of postprandial hydroxytyrosol and derivatives on oxidation of LDL, cardiometabolic state and gene expression: a nutrigenomic approach for cardiovascular prevention
Perrone MA, Gualtieri P, Gratteri S, Ali W, Sergi D, Muscoli S et al. · 2019
- 13 The Antioxidant Effects of Hydroxytyrosol and Vitamin E on Pediatric Nonalcoholic Fatty Liver Disease, in a Clinical Trial: A New Treatment?
Nobili V, Alisi A, Mosca A, Crudele A, Zaffina S, Denaro M et al. · 2019
- 14 Rich oleocanthal and oleacein extra virgin olive oil and inflammatory and antioxidant status in people with obesity and prediabetes. The APRIL study: A randomised, controlled crossover study
Ruiz-García I, Ortiz-Flores R, Badía R, García-Borrego A, García-Fernández M, Lara E et al. · 2023
- 15 Supplementation Effect of a Combination of Olive (*Olea europea* L.) Leaf and Fruit Extracts in the Clinical Management of Hypertension and Metabolic Syndrome
Hermans MP, Lempereur P, Salembier JP, Maes N, Albert A, Jansen O et al. · 2020
- 16 The effect of olive leaf extract in decreasing the expression of two pro-inflammatory cytokines in patients receiving chemotherapy for cancer. A randomized clinical trial
Ahmed KM · 2013
- 17 The Effect of Dietary Intervention With High-Oleocanthal and Oleacein Olive Oil in Patients With Early-Stage Chronic Lymphocytic Leukemia: A Pilot Randomized Trial
Rojas Gil AP, Kodonis I, Ioannidis A, Nomikos T, Dimopoulos I, Kosmidis G et al. · 2021
- 18 Systemic Health Effects of Oleuropein and Hydroxytyrosol Supplementation: A Systematic Review of Randomized Controlled Trials
Frumuzachi O, Gavrilăș LI, Vodnar DC, Rohn S, Mocan A · 2024
- 19 Effect of a food supplement containing berberine, monacolin K, hydroxytyrosol and coenzyme Q10 on lipid levels: a randomized, double-blind, placebo controlled study
D'Addato S, Scandiani L, Mombelli G, Focanti F, Pelacchi F, Salvatori E et al. · 2017
- 20 The effect of olive leaf extract on cardiovascular health markers: a randomized placebo-controlled clinical trial
Stevens Y, Winkens B, Jonkers D, Masclee A · 2021
- 21 Effect of a Combination of Citrus Flavones and Flavanones and Olive Polyphenols for the Reduction of Cardiovascular Disease Risk: An Exploratory Randomized, Double-Blind, Placebo-Controlled Study in Healthy Subjects
Sánchez Macarro M, Martínez Rodríguez JP, Bernal Morell E, Pérez-Piñero S, Victoria-Montesinos D, García-Muñoz AM et al. · 2020
- 22 Unusual pungency from extra-virgin olive oil is attributable to restricted spatial expression of the receptor of oleocanthal
Peyrot des Gachons C, Uchida K, Bryant B, Shima A, Sperry JB, Dankulich-Nagrudny L et al. · 2011

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ih-research.com/en/knowledge/olive-polyphenols/ · Last updated 2026-10-15