



DOSSIER · SUBSTANCE

Piperine

Piperine is the principal alkaloid of black pepper. It is striking that the most frequently cited controlled human studies almost invariably test curcuminoids together with piperine — the combination was therefore examined there, not piperine alone. This page separates the two.

440

STUDIES IN
TOTAL

81

IN HUMANS

34

OF WHICH
CONTROLLED

81

IN ANIMALS

102

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

Piperine at a Glance

ORIGIN:

Piperine is the main alkaloid of black pepper and belongs to the piperidine skeleton. It is not a nutrient, but a secondary plant compound that appears in studies in two roles: as its own drug candidate and as an accompanying substance that alters the absorption of other substances. This dual role characterises the entire literature.

RESEARCH SITUATION:

440 evaluated studies · 34 controlled studies in humans · 47 observational studies · 27 review articles · 81 animal experiments · 82 cell culture studies

STRONGEST EVIDENCE:

- Inflammation and oxidative stress: A systematic review with meta-analysis of randomised controlled trials (2025) examined the combined administration of curcumin and piperine.
- Metabolism: A randomised, double-blind, placebo-controlled study over 8 weeks gave 118 participants with type 2 diabetes 1000 mg curcuminoids together with 10 mg piperine daily; laboratory values were reported.
- Safety: In a randomised, double-blind, placebo-controlled study over 90 days, 96 obese participants received an extract from *Cyperus rotundus* with piperine; adverse events were not reported.
- Absorption and bioavailability: In haemodialysis patients, a randomised, double-blind clinical study (2022) compared turmeric with piperine against turmeric alone.
- Musculoskeletal system: Controlled studies on inflammation and joint diseases examine combinations of curcuminoids and piperine; piperine as a single substance is not investigated in isolation there.

LIMITATIONS:

- The central methodological weakness is the combination: when piperine is given with curcuminoids or in multi-substance formulations, the single substance can no longer be isolated.
- Many endpoints are laboratory values and questionnaires; disease courses and hard clinical endpoints are reported less frequently. Only a few controlled studies use piperine as the sole test substance.
- Selective CYP3A4 inhibition was shown in human cell preparations and is therefore preclinical; whether it acts in a comparable manner in humans remains open.

CLASSIFICATION:

Piperine is the main alkaloid of black pepper and is almost always tested together with curcuminoids in controlled human studies, rarely as the sole variable.

1. What Piperine Is

Piperine is the main alkaloid of black pepper and is treated in the literature together with the piperidine skeleton to which it belongs. This dual role characterises the entire literature. In safety research, isolated piperine is tested as a single dose, whereas in the majority of clinical studies it is tested as an additive to curcuminoids. Anyone reading the piperine literature is therefore usually reading literature about formulations. The substance itself is rarely made the sole variable, and it is precisely from this that the classification problems of this page arise.

For understanding almost all studies, one point is decisive: what is usually measured is not piperine, but the accompanying substance. In the controlled studies on type 2 diabetes, fatty liver and joint diseases, piperine stands in the title, yet the reported values concern blood glucose, blood lipids, inflammatory markers or quality-of-life questionnaires for the combination. No statement about piperine alone can be derived from such results. A second level is added: piperine is attributed with selective inhibition of CYP3A4, an enzyme of drug metabolism. This finding comes from studies with human cell preparations and is therefore preclinical. It is the most frequently cited explanatory pathway for altered absorption, yet it is not proof of an absorption effect in humans. Form and dose differ considerably between the studies, which further complicates cross-comparisons.

2. How Reliable the Research Is

The research is distributed unevenly. The largest block consists of basic research, followed by cell culture and animal studies; far fewer studies exist in humans, with more observational than controlled ones. The controlled studies focus on metabolism, bioavailability, inflammation and exhaustion; these are followed by safety, antioxidant questions, cardiovascular system, musculoskeletal system, oncology and bone. In oncology, reviews and mechanistic studies as well as preclinical findings dominate, while controlled human studies recede. Exhaustion is represented as an application area of the controlled literature, without a distinct research strand emerging from it.

Methodologically the field is divided in two. On one side stand randomised, double-blind and placebo-controlled studies with recurring working groups and topics that are widely cited internationally; these studies carry the more reliable statements and concern predominantly metabolism, inflammation and joint diseases. On the other side stands a broad preclinical base whose findings may only be read as such. The central methodological weakness is the combination: when piperine is given with curcuminoids or in multi-substance formulations, the single substance can no longer be isolated. Compounding this is the fact that many endpoints are laboratory values and questionnaires; disease courses and hard clinical endpoints are reported less frequently. Dose ranges and dosage forms differ between the studies, so that results can only be compared to a limited extent.

Distribution of **controlled studies in humans** by application area — the numbers are not additive, as one study may be assigned to several areas:

APPLICATION AREA	CONTROLLED STUDIES
Metabolism	15
Absorption and bioavailability	12
Inflammatory processes	11
Exhaustion and stress	10
Safety and tolerability	9
Oxidative stress	8
Heart and circulation	7
Musculoskeletal system	6

The piperine literature is predominantly a curcuminoid literature

The most frequently cited controlled human studies carry piperine in the title, yet examine combinations of curcuminoids and piperine: in metabolic syndrome, type 2 diabetes, fatty liver and knee osteoarthritis. The results therefore belong to the combination. To infer an effect of piperine from them would be a fallacy that the studies themselves do not support. Piperine appears in these studies in the role of an absorption enhancer; what was tested was whether the combination produces an effect, not whether piperine produces an effect. In reception this blurs because short titles and summaries place piperine on equal footing with the curcuminoids. That only a small number of controlled studies use piperine as the sole test substance is the decisive point of this page.

PLAUSIBLE:

If piperine contributes to altered uptake primarily via inhibition of CYP3A4, then the actual measured variable would be the uptake or breakdown of the accompanying substance — and this variable cannot be separated from the effect of the accompanying substance in combination studies. The inhibition itself was demonstrated in human cell preparations, i.e. preclinical; whether it applies in a comparable manner in humans is an open, testable question. The next step would be a controlled study in which piperine is the only variable, with measurement of the uptake of the accompanying substance over a dose range; that isolated piperine is investigable as a single dose is already shown by individual studies.

3. What Is Frequently Claimed — and What the Data Support

CLAIM	STUDY STATUS
Piperine increases the uptake of curcuminoids.	Bioavailability studies and review articles address piperine in this role; what was tested was the combination, not an absorption effect of piperine as a single substance.
Piperine has anti-inflammatory effects.	Controlled studies on inflammation and joint diseases examine combinations of curcuminoids and piperine; piperine as a single substance is not investigated in detail.
Piperine improves sugar metabolism in type 2 diabetes.	Several controlled studies on the combination report glycaemic, hepatic and inflammatory markers, i.e. laboratory values and no disease courses.
Isolated piperine is safe.	A study deals with piperine as an isolated single administration; the selective CYP3A4 inhibition stems from cell preparations and leaves the question of interaction open.

4. Profile: Molecule and Charge

Piperine is not a single molecule, but a **mixture** — there is no molecular formula and no fixed molecular mass. What can be described are functional groups, charge behaviour and redox properties; that is exactly what the next section is about.

5. Charge, Electrons, Radicals

For the charge of the piperine molecule itself, a measurement is still outstanding. The zeta potential of formulations was recorded: T-cubs with 167.00 ± 10.49 nm particle size and a zeta potential of -34.60 ± 0.47 mV ¹⁸, the optimised formulation FNC1 with 116.6 ± 2.13 nm and -27.9 ± 1.51 mV ²¹. This value describes the surface charge of the particle, not the charge of the active substance; cation exchange and electron transfer of the molecule are not the subject of investigation. Characterisation was based on particle size, zeta potential, polydispersity index, entrapment rate and in vitro release ¹⁸.

Radicals and redox behaviour were recorded primarily in cell experiments. In primary human dermal fibroblasts, an extract and its compounds GA and PP showed radical-scavenging activity in the DPPH assay and inhibited IL-1 β -induced intracellular ROS formation ^{22 22}. In PC12 cells, piperine (1 μ M) lowered the intracellular ROS concentration and increased superoxide dismutase activity as well as total glutathione ¹⁹. For piperine complexed with cyclic glucans, cellular antioxidant activity was investigated ²³; preclinically, mitochondrial and ROS-mediated apoptosis pathways are described ²⁰. In humans, it would need to be clarified whether the charge state and redox behaviour of piperine can be measured directly in serum or tissue.

6. Interactions with Other Substances

With which other substances on the platform this substance has been **jointly** investigated or discussed in human studies and review articles — combination, comparison or shared mechanism of action. The number indicates works in which both occur.

SUBSTANCE	SHARED WORKS	OF WHICH CONTROLLED IN HUMANS
Turmeric and curcuminoids	138	66
Acceptance and Commitment Therapy (ACT)	60	14
Chronic inflammation	40	11
Black rice and green rice	20	2
Stress, cortisol and inflammation	19	8
Art therapy	17	2
Resveratrol	14	4
Cognitive behavioural therapy for insomnia (CBT-I)	9	1
Gut microbiome	7	1
Ginger	7	1

Piperine is administered in controlled human studies together with curcuminoids to improve their oral uptake. A ratio of 100:1 ⁶ is mentioned as well as additions of 15 mg per day ^{5 8}, 10 mg per day ²⁴ and 5 mg per day ¹⁵. A randomised, double-blind, placebo-controlled study over 8 weeks gave 118 participants with type 2 diabetes 1000 mg curcuminoids per day together with 10 mg piperine per day ²⁴. Another randomised, double-blind, placebo-controlled study over 8 weeks investigated epigallocatechin gallate, capsaicins, piperine and L-carnitine as a combination in 86 overweight persons ¹². In haemodialysis patients, a randomised, double-blind clinical study compared turmeric with piperine against turmeric alone ¹⁷.

In a randomised, double-blind, placebo-controlled study over 8 weeks, curcumin together with piperine showed no significant decline in PAB values compared with baseline ($p = 0.06$) ¹⁵. A systematic review with meta-analysis of randomised controlled studies examined the co-administration of curcumin and piperine on inflammation and oxidative stress ¹. A randomised, double-blind, placebo-controlled study over 90 days with 96 obese participants tested the efficacy and safety of a curcumin preparation together with piperine ²⁵. The evidence describes the co-administration; it contains no information on CYP enzymes, plasma protein binding or attenuation of other substances. What would need to be clarified is by which mechanism piperine alters uptake and whether it simultaneously influences the metabolism of co-administered medicinal products.

7. Overdosage, Tolerability, Limits

Two controlled human studies are available on the tolerability of piperine. In a videofluoroscopic examination, 40 patients with dysphagia swallowed bolus series to which piperine had been added as a dual TRPV1/TRPA1 agonist; the swallowing response was tested, not tolerability ¹¹. In a randomised, double-blind and placebo-controlled study over 90 days, 96 obese participants received an extract from *Cyperus rotundus* together with piperine as a bioavailability enhancer; safety assessments were a secondary objective ^{25 25}. Adverse events were not reported, and all laboratory parameters remained within the normal range ²⁵.

Both studies tested piperine as an addition to another substance, not as a single administration. A dose from which adverse effects occur cannot be derived from this; the evidence states no quantity. Information on upper limits and on contraindications is still outstanding. The reported laboratory values come from a 90-day observation ²⁵; longer periods have not been recorded. What would need to be clarified is how piperine alone behaves over longer periods, whether tolerability differs between various dosages and which groups of persons should be excluded from administration. A study that tests piperine as a monosubstance in increasing doses over a defined period would answer these questions.

8. The Most Robust Studies

Ordered by strength of evidence, not by familiarity: reviews and studies with many participants first. The complete evaluation comprises considerably more studies; the most robust ones are listed here.

Controlled Human Studies

- ¹ The Effects of Curcumin Plus Piperine Co-administration on Inflammation and Oxidative Stress: A Systematic Review and Meta-analysis of Randomized ... (2025) — Review
- Efficacy and safety of resveratrol, an oral hemoglobin F-augmenting agent, in patients with beta-thalassemia intermedia (2018) — 2,017 participants
- Antioxidant effects of curcuminoids in patients with type 2 diabetes mellitus: a randomized controlled trial (2017) — 118 participants
- Curcuminoids modify lipid profile in type 2 diabetes mellitus: A randomized controlled trial (2017) — 118 participants
- ² Effects of Curcuminoids Plus Piperine on Glycemic, Hepatic and Inflammatory Biomarkers in Patients with Type 2 Diabetes Mellitus: A Randomized ... (2018) — 100 participants
- ³ Curcuminoids Plus Piperine Modulate Adipokines in Type 2 Diabetes Mellitus (2017) — 118 participants
- ⁴ Pepper Alkaloids and Processed Meat Intake: Results from a Randomized Trial and the European Prospective Investigation into Cancer and Nutrition ... (2021) — 148 participants
- Effects of curcumin supplementation on insomnia and daytime sleepiness in young women with premenstrual syndrome and dysmenorrhea: A randomized ... (2023) — 124 participants
- ⁵ Mitigation of Systemic Oxidative Stress by Curcuminoids in Osteoarthritis: Results of a Randomized Controlled Trial (2016) — 21 participants
- ⁶ Lipid-modifying effects of adjunctive therapy with curcuminoids-piperine combination in patients with metabolic syndrome: results of a randomized ... (2014) — 50 participants
- ⁷ Effects of Curcuminoids-Piperine Combination on Systemic Oxidative Stress, Clinical Symptoms and Quality of Life in Subjects with Chronic Pulmonary ... (2016) — 45 participants
- Effects of curcuminoids on inflammatory status in patients with non-alcoholic fatty liver disease: A randomized controlled trial (2020) — 55 participants
- ⁸ Impact of Supplementation with Curcuminoids on Systemic Inflammation in Patients with Knee Osteoarthritis: Findings from a Randomized Double-Blind ... (2015) — 40 participants
- ⁹ Curcuminoids plus piperine improve nonalcoholic fatty liver disease: A clinical trial (2019) — 70 participants
- ¹⁰ Herbal formulation "turmeric extract, black pepper, and ginger" versus Naproxen for chronic knee osteoarthritis: A randomized, double-blind ... (2020)
- ¹¹ Effect of oral piperine on the swallow response of patients with oropharyngeal dysphagia (2014)
- ¹² Improvement in insulin resistance and favourable changes in plasma inflammatory adipokines after weight loss associated with two months' consumption ... (2013)
- ¹³ Effectiveness of the piperine-supplemented Curcuma longa L. in metabolic control of patients with type 2 diabetes: a randomised double-blind ... (2021) — 71 participants
- ¹⁴ Curcumin and Piperine Combination for the Treatment of Patients with Non-alcoholic Fatty Liver Disease: A Double-Blind Randomized Placebo-Controlled ... (2021) — 40 participants
- Ubiquitin Proteasome System Activity is Suppressed by Curcumin following Exercise-Induced Muscle Damage in Human Skeletal Muscle (2021)
- ¹⁵ The effect of curcumin with piperine supplementation on pro-oxidant and antioxidant balance in patients with non-alcoholic fatty liver disease: a ... (2019) — 55 participants
- Cost-Effectiveness of Passion Fruit Albedo versus Turmeric in the Glycemic and Lipaemic Control of People with Type 2 Diabetes: Randomized Clinical ... (2021)
- ¹⁶ The Effects of Curcumin Plus Piperine Supplementation in Patients with Acute Myocardial Infarction: A Randomized, Double-Blind, and ... (2021) — 38 participants
- ¹⁷ Turmeric supplementation with piperine is more effective than turmeric alone in attenuating oxidative stress and inflammation in hemodialysis ... (2022)

9. Summary

PROVEN For the combination of curcuminoids and piperine there is a systematic review with meta-analysis of randomised controlled trials on inflammation and oxidative stress (2025). Several controlled studies on the combination reported glycaemic, hepatic and inflammatory markers in type 2 diabetes, fatty liver and joint diseases; these are laboratory values, not disease courses. These results belong to the combination, not to the single substance piperine. Regarding tolerability two controlled studies in humans are available; both tested piperine as an additive to another substance. In the 90-day study with 96 obese participants no adverse events were reported and all laboratory parameters remained within the normal range.

The inhibition itself was shown in human cell preparations, thus preclinical. **Hypothesis:** If this role applies, the contribution of piperine should stand out more clearly where piperine is the only variable; that isolated piperine is investigable as a single dose is already shown by individual studies.

The next step would be a controlled study in which piperine is the only variable, with measurement of the uptake of the accompanying substance over a dose range. Also open is through which mechanism piperine changes the uptake and whether it influences the metabolism of simultaneously administered medicinal products. For the charge of the piperine molecule itself a measurement is still pending; so far the zeta potential of formulations has been recorded, not the charge of the active substance.

10. What Remains Open

- **Dose:** Which amount of isolated piperine changes the uptake of an accompanying substance to what extent, and can this be separated from the accompanying substance?
- **Interactions:** The preclinical shown selective CYP3A4 inhibition leaves open how isolated piperine affects the breakdown of simultaneously taken medicinal substances.
- **Single substance:** Controlled studies with piperine as the only variable are still pending for most areas of application; which one should be conducted first is the testable question.

11. Further Paths

Topics, pathways and chains in which this substance occurs — for all who want to look beyond the substance.

- Interaction network

Frequently Asked Questions

Can Piperine Be Assessed Separately from Curcuminoids at All?

In the available literature only to a limited extent. The majority of controlled human studies examine combinations of curcuminoids and piperine. Piperine alone has been investigated, among other things, in a controlled study on swallowing function in patients with swallowing disorders as well as in a safety study on isolated single administration. For most areas of application, a study would have to have piperine as the sole variable.

How Does the Absorption Change Attributed to Piperine Arise?

The most frequently cited mechanism is the selective inhibition of CYP3A4, an enzyme involved in drug metabolism. This finding originates from work with human cell preparations and is therefore preclinical. Reviews also address bioavailability and newer dosage forms. Whether this mechanism underlies the observed absorption change in humans has not been clarified by controlled studies with piperine as a single substance.

What Should Be Considered with Isolated Intake of Piperine?

Safety is a separate area of application in the controlled literature; one study addresses isolated piperine as a single administration. Overall, the issue concerns isolated preparations rather than intake via pepper in food. Whether and to what extent the metabolism of concurrently taken medicinal products is altered is the question that a controlled human study would have to clarify.

Sources

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- 2 Effects of Curcuminoids Plus Piperine on Glycemic, Hepatic and Inflammatory Biomarkers in Patients with Type 2 Diabetes Mellitus: A Randomized Double-Blind Placebo-Controlled Trial
Panahi Y, Khalili N, Sahebi E, Namazi S, Simental-Mendia LE, Majeed M et al. · 2018
- 3 Curcuminoids Plus Piperine Modulate Adipokines in Type 2 Diabetes Mellitus
Panahi Y, Khalili N, Sahebi E, Namazi S, Atkin SL, Majeed M et al. · 2017
- 4 Pepper Alkaloids and Processed Meat Intake: Results from a Randomized Trial and the European Prospective Investigation into Cancer and Nutrition (EPIC) Cohort
Wedekind R, Keski-Rahkonen P, Robinot N, Viallon V, Rothwell JA, Boutron-Ruault MC et al. · 2021
- 5 Mitigation of Systemic Oxidative Stress by Curcuminoids in Osteoarthritis: Results of a Randomized Controlled Trial
Panahi Y, Alishiri GH, Parvin S, Sahebkar A · 2016
- 6 Lipid-modifying effects of adjunctive therapy with curcuminoids-piperine combination in patients with metabolic syndrome: results of a randomized controlled trial
Panahi Y, Khalili N, Hosseini MS, Abbasnazar M, Sahebkar A · 2014
- 7 Effects of Curcuminoids-Piperine Combination on Systemic Oxidative Stress, Clinical Symptoms and Quality of Life in Subjects with Chronic Pulmonary Complications Due to Sulfur Mustard: A Randomized Controlled Trial
Panahi Y, Ghanei M, Hajhashemi A, Sahebkar A · 2016
- 8 Impact of Supplementation with Curcuminoids on Systemic Inflammation in Patients with Knee Osteoarthritis: Findings from a Randomized Double-Blind Placebo-Controlled Trial
Rahimnia AR, Panahi Y, Alishiri G, Sharafi M, Sahebkar A · 2015
- 9 Curcuminoids plus piperine improve nonalcoholic fatty liver disease: A clinical trial
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· 2015
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· 2012
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· 2025
- 21 Among nine formulations, optimized FNC1 had a particle size of 116.6 ± 2.13 nm and zeta potential at -27.9 ± 1.51 mV....
· 2025
- 22 Moreover, this study also assessed the free radical scavenging activities of STF and its components using DPPH radical s...
· 2017
- 23 Piperine, the primary bioactive compound in black pepper, was complexed with cyclic glucans, including cycloamylose (CA)...
· 2025
- 24 The aim of this study was to assess the effects of supplementation with curcuminoids, which are natural polyphenolics fr...
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- 25 This study aimed to assess the efficacy and safety of CRE combined with the bioavailability enhancer piperine (CREP), as...
· 2025

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