



DOSSIER · SUBSTANCE

L-Citrulline

L-Citrulline is an amino acid described in the literature as a precursor of arginine and thus of nitric oxide. The most interesting finding of this evaluation: A large proportion of the most frequently cited papers examine not citrulline but arginine, or both together. Anyone wishing to test citrulline must read this conflation alongside.

279

STUDIES IN
TOTAL

130

IN HUMANS

83

OF WHICH
CONTROLLED

43

IN ANIMALS

3

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

L-Citrulline at a Glance

ORIGIN:

L-Citrulline is an amino acid described in the literature as a precursor of arginine and thus of nitric oxide; the database classifies it together with L-Arginine under the nitric oxide precursors. Pure L-Citrulline and citrulline malate, a salt of citrulline and malic acid, are investigated. Citrulline is described in high concentration in watermelon [59].

EVIDENCE BASE:

279 evaluated papers · 83 controlled human studies · 47 observational studies · 25 review articles · 43 animal studies · 3 cell-culture studies

STRONGEST INDICATIONS:

- Arginine in blood: In a placebo-controlled cross-over study in 20 healthy volunteers (2008) L-citrulline increased AUC and Cmax of plasma arginine in a dose-dependent manner and more strongly than L-arginine ($P < 0.01$) [1].
- Heart and circulation: Randomised cross-over study in 10 men (2015), 6 g/day for seven days: Mean arterial blood pressure was lower only after citrulline ($P < 0.05$); exercise tolerance rose from 589 ± 101 s to 661 ± 107 s [4].
- Heart and circulation: Double-blind randomised study in 15 men (58.3 ± 4.4 years), 5.6 g/day for seven days: The vascular marker brachial-ankle pulse-wave velocity fell significantly ($p < 0.01$); serum nitric oxides rose ($p < 0.05$) [5].
- Heart and circulation: Randomised study in 20 of 35 heart-failure patients, 3 g/day for four months: Left-ventricular ejection fraction +20.3 % at rest and +12.7 % under load, significant versus control [14].
- Reviews: One meta-analysis summarises subjective perceived exertion, muscle soreness and lactate value after exercise; a 2019 review cites a blood-pressure reduction of 4.1/2.08 to 7.54/3.77 mmHg for citrulline [61].

LIMITATIONS:

- A large proportion of the most-cited papers examine arginine or both substances together; anyone wishing to test citrulline must read this conflation.
- Part of the field consists of small, acute cross-over studies in trained men; markers and performance measures are recorded, not disease courses.
- Combination studies such as citrulline with metformin or micronutrient mixtures do not carry the effect of the single substance; pure L-citrulline and citrulline malate are not consistently separated.

CLASSIFICATION:

Amino acid and arginine precursor whose literature to a considerable extent examines arginine instead of citrulline and whose reliability is greatest for performance and vascular markers.

1. What L-Citrulline Is

The database classifies it under the nitric-oxide precursors, together with L-arginine. This classification shapes almost all papers: what is examined is less citrulline as such than its position in the arginine–nitric-oxide pathway. The oldest recorded paper from 1996 addresses the blood-pressure-lowering effect of L-arginine and the exhaled nitric-oxide content. The most-cited paper from 2008 compares the pharmacokinetics and pharmacodynamics of oral L-citrulline and L-arginine and their influence on nitric-oxide metabolism. Anyone reading the citrulline literature is therefore reading, to a considerable extent, a literature about arginine.

The diversity of forms is decisive for understanding all studies. Some papers examine pure L-citrulline, others citrulline malate, a salt of citrulline and malic acid. Both forms carry different designations in the titles and are not consistently separated. There is also the question of measurement: plasma values of arginine and citrulline, exhaled nitric oxide, vascular stiffness, blood pressure, oxygen-uptake kinetics, time-trial performance or subjective perceived exertion are recorded. These are predominantly **markers** and **performance measures**, not disease courses. Some studies administer citrulline acutely before exercise, others over weeks. **Plausible:** These differences explain a good part of the heterogeneous findings without implying a contradiction about the substance itself.

2. What the Studies Show in Detail

The key human studies and the most important reviews — by application area, with population, duration, preparation, measured variable and result as reported in the original papers. Numbers appear only where the work states them.

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

APPLICATION AREA	CONTROLLED STUDIES
Heart and circulation	40
Musculoskeletal system	23
Metabolism	21
Safety and tolerability	19
Exhaustion and stress	11

APPLICATION AREA	CONTROLLED STUDIES
Absorption and bioavailability	9
Inflammatory processes	8
Immune system	5

Gut and Microbiome

The placebo-controlled cross-over study of 2008 tested six different dosing regimens with placebo, citrulline and arginine after one week of oral administration each in 20 healthy volunteers [1]. Cmax, Tmax, Cmin and AUC of plasma arginine, the arginine-to-asymmetric-dimethylarginine (ADMA) ratio, renal excretion of cyclic guanosine monophosphate and nitrate, and flow-mediated vasodilation (FMD) were recorded. L-citrulline increased AUC and Cmax of plasma arginine in a dose-dependent manner and more strongly than L-arginine ($P < 0.01$). The highest citrulline dose (3 g twice daily) raised the Cmin of plasma arginine and improved the arginine/ADMA ratio from 186 ± 8 to 278 ± 14 ($P < 0.01$) [1].

The 2018 review attributes this difference to absorption: L-arginine is largely degraded presystemically by intestinal arginase activity, whereas L-citrulline is not extracted to any appreciable extent from the gastrointestinal tract (enterocytes) or the liver and therefore raises plasma arginine and NO synthesis more effectively [59]. Citrulline is described there in high concentration in watermelon; supplementation is termed promising as a blood-pressure-lowering measure at rest and under load in adults with prehypertension and hypertension. Preclinical evidence from animal studies is cited for atherogenic endothelial protection; first indications are cited for muscle and metabolic effects in older and vulnerable populations [59].

The 2005 observational study in patients with MELAS, a maternally inherited mitochondrial disorder, found similar arginine concentrations in the plasma of patients and controls, yet significantly lower citrulline values in MELAS patients than in controls and a clear inverse correlation between arginine and citrulline. No correlation existed between the degree of heteroplasmy and the plasma levels of arginine or citrulline; the abstract does not state a participant number. The reduced citrulline values are discussed in the context of NO homeostasis [25]. Absorption, metabolism and plasma levels were examined in this group; a study on the effect of oral citrulline administration on microbiome composition remains outstanding.

Oxidative Stress

The open-label proof-of-concept pilot study from 2019 recruited 41 obese asthmatics (BMI > 30) on controller therapy with a baseline FeNO value of at most 30 ppb and treated them for two weeks with 15 g L-citrulline per day, without a control group [57]. Mean FeNO at baseline was 17 ppb (95 % CI 15–19), and asthma control was poor with an ACQ of 1.5 (95 % CI 1.2–1.8). Under supplementation, plasma citrulline rose by 190 μ M (84–297), plasma arginine by 67 μ M (38–95) and the arginine/ADMA ratio by 117 (67–167); FeNO increased by 4.2 ppb (1.7–6.7). ADMA and arginase concentrations did not rise [57].

The same work cites experiments in cultured airway epithelial cells in which L-citrulline prevented ADMA-mediated uncoupling of NOS2, restored NO and reduced oxidative stress; these findings are preclinical and derive from cell cultures [57]. It remains open whether the NO markers altered under citrulline are confirmed in placebo-controlled studies with clinical endpoints.

Oncology

The 2021 review describes arginine as the starting material for NO and polyamine synthesis and as a direct activator of mTOR, a nutrient-sensitive kinase involved in carcinogenesis [54]. Normal cells can synthesise arginine themselves from citrulline and aspartate via ASS1 (argininosuccinate synthase 1) and ASL (argininosuccinate lyase). In over 70 % of tumours, ASS1 transcription is suppressed, rendering the cells dependent on external arginine — the basis of arginine-deprivation therapy [54].

The 2006 work describes pegylated arginine deiminase (ADI-PEG20) as an antineoplastic enzyme that depletes arginine [47]. Certain tumours such as malignant melanoma and hepatocellular carcinoma are arginine-auxotrophic, and the tumours sensitive to arginine deprivation do not express argininosuccinate synthetase, the key enzyme of arginine synthesis from citrulline. ADI-PEG20 inhibits human melanomas and hepatocellular carcinomas in vitro and in vivo; phase-I and phase-II studies in patients with melanoma and hepatocellular carcinoma showed antitumour activity and tolerable side effects. Large phase-II and randomised phase-III studies to determine overall efficacy are named as the next step [47].

The 2017 prospective cohort examined 170 breast-cancer patients receiving doxorubicin with or without trastuzumab [56]. Plasma arginine, citrulline, ornithine, ADMA, SDMA and N-monomethylarginine were measured at baseline and one and two months after the start of doxorubicin; the Cox regression included 139 participants with evaluable echocardiograms at all time points. Age, hypertension, body-mass index and African-American origin were independently associated with at least one of the baseline values of citrulline, ADMA, SDMA and MMA. After one and after two months, arginine and citrulline decreased and ADMA increased (each $p < 0.05$); 32 participants experienced therapy-related cardiac dysfunction over a maximum follow-up of 5.4 years. Citrulline served here as a measure of the arginine-NO axis and not as an intervention [56]. **Hypothesis:** Because ASS1-suppressed tumours cannot convert citrulline into arginine [54], citrulline supplementation might not compensate for arginine deprivation in such tumours; this was not tested in the present collection, and a study with citrulline as an oncological intervention remains outstanding.

Heart and Circulation

The randomised, placebo-controlled cross-over study from 2015 had 10 healthy adult men take placebo, L-arginine (6 g/day) or L-citrulline (6 g/day) for seven days and perform moderate- and severe-intensity cycle-ergometer exercise on days 6 and 7 [4]. Plasma arginine rose similarly under arginine and citrulline, while plasma citrulline rose only under citrulline ($P < 0.001$). Plasma nitrite was 83 ± 25 nM (placebo), 106 ± 41 nM (arginine) and 100 ± 38 nM (citrulline); it was elevated under arginine ($P < 0.05$) and showed a trend to rise under citrulline with $P = 0.08$. Mean arterial blood pressure was lower only after citrulline ($P < 0.05$). Steady-state VO2 amplitude did not differ; at severe intensity citrulline shortened mean VO2 response time (59 ± 8 s versus 53 ± 5 s, $P < 0.05$) and improved exercise tolerance (589 ± 101 s versus 661 ± 107 s); total work also increased according to the abstract, though the values are truncated there [4].

A randomised controlled study from 2006 gave 40 children undergoing cardiopulmonary bypass and at risk of pulmonary hypertension five perioperative doses of 1.9 g/m² oral citrulline or placebo [6].

In the randomised study from 2012, 20 of 35 stable ambulatory heart-failure patients received 3 g L-citrulline orally per day for four months; 15 served as unsupplemented controls [14]. In the treatment group, left-ventricular ejection fraction rose by 20.3 % at rest and 12.7 % during exercise, right-ventricular ejection fraction by 15.10 % at rest and 14.88 % during exercise; functional class improved in 35 %, and the MAT/TT index fell by 23.1 % — statistically significant versus the control group [14]. Nineteen patients with primary or precapillary secondary pulmonary hypertension received oral L-arginine (acute 0.5 g/10 kg body weight, one week 1.5 g/10 kg per day) [55]. Plasma citrulline rose markedly as evidence of increased NO production; mean pulmonary-artery pressure fell by 9 % (53 ± 4 to 48 ± 4 mm Hg, $p < 0.05$), pulmonary vascular resistance by 16 % (14.8 ± 1.5 to 12.4 ± 1.4 Wood units, $p < 0.05$), and the VE-VCO₂ slope from 43 ± 4 to 37 ± 3 ($p < 0.05$). Citrulline served here as a measure, not as an intervention [55].

The 2020 clinical-pharmacological review notes that L-citrulline, as a natural precursor of L-arginine, is more bioavailable because it bypasses hepatic first-pass metabolism and remains longer in the circulation, and cites improved cardiovascular function under L-arginine in hypertension, pulmonary hypertension, pre-eclampsia, angina pectoris and MELAS; it describes the question of pharmacokinetics and exposure–response relationships depending on age and disease as open [58]. The 2019 review reports that arginine and citrulline both raise plasma arginine, with citrulline approximately twice as effective, probably because of lower first-pass metabolism; for oral arginine a blood-pressure reduction of 5.39/2.66 mmHg is given, for citrulline a range of 4.1/2.08 to 7.54/3.77 mmHg, while the mechanism is considered not fully understood because normal plasma arginine concentration greatly exceeds the Michaelis constant of eNOS (“L-arginine paradox”) [61]. The 2023 review classifies L-citrulline as an effective precursor of L-arginine and describes NO as central to endothelial function, relaxation of vascular smooth muscle and dilatation, which can influence perfusion and mechanisms of muscle-strength and hypertrophy adaptation [62]. What remains to be clarified is through which mechanisms citrulline lowers blood pressure and whether this is confirmed in studies with clinical endpoints.

Metabolism

The double-blind, randomised, placebo-controlled parallel-group study from 2012 examined 15 healthy men aged 58.3 ± 4.4 years with a brachial-ankle pulse-wave velocity (baPWV, index of arterial stiffness) above 1400 cm/sec [5]. Eight participants received 5.6 g L-citrulline per day for seven days, seven received placebo. baPWV was significantly reduced in the citrulline group ($p < 0.01$); no between-group differences in blood pressure were found, and no correlation existed between blood pressure and baPWV. Serum nitric oxides (NO_x, sum of nitrite and nitrate) and NO metabolites rose significantly only in the citrulline group ($p < 0.05$); the values for plasma citrulline, arginine and their ratio are truncated in the abstract [5].

For the combination of L-citrulline and metformin in Duchenne muscular dystrophy, the protocol of a randomised, double-blind, placebo-controlled study is available: 40 to 50 ambulatory patients will be recruited in Basel and via the patient registries of Switzerland, Germany and Austria, randomised to two arms and treated for 26 weeks, with concomitant glucocorticoid medication permitted; the primary endpoint is the change in the MFM-D1 subscale [49]. The completed 2019 study implemented this design in 47 ambulatory male patients aged 6.5 to 10 years with genetically confirmed Duchenne muscular dystrophy; treatment consisted of 2500 mg L-citrulline and 250 mg metformin three times daily for 26 weeks versus placebo, with the primary endpoint being the change in transfer and standing after the first dimension of the Motor Function Measure, version 32, from baseline to week 26. The present abstract contains no outcome data [48].

The randomised, placebo-controlled cross-over study from 1996 did not examine L-citrulline itself but infused 10 healthy men with 0.5 g/kg L-arginine hydrochloride over 30 minutes [10]. Mean blood pressure fell with a peak effect of -9.3 ± 0.9 % ($p < 0.005$); exhaled NO concentration rose by 55 ± 15 % ($p < 0.005$) from 15 ± 2 to 21 ± 3 ppb, pulmonary NO excretion rate by 118 ± 45 % ($p < 0.005$), and plasma L-citrulline from 25 ± 4 to 46 ± 5 $\mu\text{mol/l}$ ($p < 0.005$). The blood-pressure-lowering response correlated with the rise in exhaled NO ($r = -0.68$, $p < 0.05$). Here too, citrulline was a measure of arginine infusion and not itself the administered substance [10]. What remains open is which dose and treatment duration sustainably lower arterial stiffness and whether the combination of citrulline and metformin chosen in Duchenne muscular dystrophy influences disease course.

Musculoskeletal System

The double-blind, randomised, placebo-controlled two-way cross-over study from 2016 had 22 trained men take 2.4 g L-citrulline per day or placebo for seven days and, on day 8 one hour before a 4-km time trial on a cycle ergometer, another 2.4 g of the respective substance [7]. L-citrulline significantly increased plasma L-arginine and shortened riding time by 1.5 % ($p < 0.05$); subjective muscle-fatigue sensation and concentration immediately after exercise also improved [7].

The 2020 systematic review and meta-analysis searched PubMed, Web of Science and ClinicalTrials.gov for randomised controlled trials in healthy persons that examined the acute effect of citrulline supplements up to two hours before exercise on rating of perceived exertion (RPE), muscle soreness and blood lactate level [12]. Thirteen studies with a total of 206 participants were included; the most frequent dose was 8 g citrulline malate, and because of the large differences in design and populations a random-effects model was used.

The 2018 randomised, double-blind, placebo-controlled study with balanced design tested a single dose of 8 g citrulline malate (ratio 1.11:1) before an isokinetic protocol modelled on German Volume Training in recreationally active men and women: 10 sets of 10 repetitions against 70 % of maximal concentric strength [17]. Across the protocol, 94.0 ± 7.9 repetitions were achieved under placebo and 90.9 ± 13.9 under citrulline malate, without significant difference ($P = 0.33$); isometric ($P = 0.60$), concentric ($P = 0.38$) and eccentric ($P = 0.65$) peak force also did not differ. Muscle soreness over 72 hours was significantly greater under citrulline malate than under placebo ($P = 0.01$), although more work had not been performed in this group [17].

The 2018 randomised, double-blind, placebo-controlled study assigned 75 resistance-trained men to three groups that took glutathione plus L-citrulline, L-citrulline malate or cellulose placebo daily for eight weeks while performing resistance training [40]. The capsules were identical in weight, size, shape and colour; body composition and muscle strength were measured before and after 4 and 8 weeks, venous blood before and after 8 weeks. Complete figures are not available [40]. What remains open is which dose and which loading protocol distinguish the positive findings in time trials and muscular endurance from the null findings in German Volume Training and muscle soreness.

Further Investigations

The 2017 randomised, double-blind study examined 15 resistance-trained women aged 23 ± 3 years in two sessions: once with 8 g dextrose plus 8 g citrulline malate, once with 8 g dextrose alone [8]. One hour after ingestion the participants performed six sets each of upper-body (bench press) and lower-body (leg press) exercises to muscular failure at 80 % of the previously determined one-repetition maximum.

The 2016 randomised, double-blind study tested a single dose of 12 g dextrose plus 8 g citrulline malate versus 12 g dextrose in 17 female masters tennis players (51 ± 9 years); one hour later grip-strength, vertical-jump and Wingate tests followed [11]. The data on the ability to maintain anaerobic performance are truncated in the abstract [11].

The systematic review and meta-analysis from 2020 combined 22 human and 89 animal studies on prenatal amino acid supplementation and examined fetal or birth weight as the primary endpoint [64]. The arginine family was investigated most frequently. Favourable effects were observed for arginine and (N-carbamyl)glutamate, but not for aspartic acid and citrulline; when isonitrogenous control diets were taken into account, the effects disappeared. Branched-chain amino acids and methyl-group donors did not influence fetal or birth weight [64]. It remains to be clarified whether the strength-related findings in women and masters athletes are comparable with male cohorts and how the lack of effect of citrulline on birth weight under isonitrogenous controls should be classified.

Inflammatory Processes

The randomised, double-blind, placebo-controlled clinical trial from 2019 assigned 50 patients with non-alcoholic fatty liver disease (NAFLD) to two groups that received 2 g citrulline per day or placebo for three months [18]. At the end of the study, high-sensitivity C-reactive protein and the activity of the transcription factor NF- κ B were significantly more reduced in the citrulline group than under placebo ($P = 0.02$ and < 0.01 , respectively); after adjustment for baseline value, the TNF- α concentration was also more strongly reduced ($P < 0.001$). Alanine aminotransferase and hepatic steatosis decreased significantly under citrulline ($P = 0.04$), whereas anthropometric measures and liver enzymes did not change significantly in either group ($P \geq 0.05$); the abstract therefore lists alanine aminotransferase once as reduced and at the same time assigns it to the unchanged liver enzymes [18].

The review from 2015 describes arginine as a semi-essential amino acid and trigger of the immune response whose availability is determined by the NO synthases and the arginases that convert arginine to NO or ornithine, respectively [60]. Restricted arginine availability during inflammatory states regulates the activation of macrophages and T lymphocytes; arginine and citrulline deficiency could underlie the unfavourable course of inflammatory states such as sepsis and endotoxaemia. In addition to the immune response, according to the work the disturbed de-novo synthesis of arginine in the kidney plays a key role in the observed arginine deficiency; the arginine-citrulline-NO pathway is classified as a trigger and therapeutic target [60]. The clinical question to be clarified is whether citrulline administration in sepsis improves arginine availability and influences the course; the review summarises experimental and clinical studies without reporting its own intervention trial.

Immune System

The perspective from 2019 argues that L-arginine is nutritionally essential in pregnancy and an immediate precursor of NO; the growth of placenta and embryo increases demand that can exceed the endogenous synthesis of L-arginine from L-citrulline and thus requires a higher intake [63]. In many resource-poor regions arginine intake is insufficient due to widespread protein malnutrition; in addition, endogenous L-arginine is consumed by maternal infections, particularly malaria. The available data supported the hypothesis that supplementation with L-arginine or L-citrulline would be suitable for use in resource-limited settings and could improve placental vascular development as well as birth outcomes [63].

As justification the work states that complications from preterm birth are the most common cause of death worldwide in children under 5 years and that only few effective interventions are available; new strategies are described as urgently needed, especially for regions with limited resources [63]. The subject of investigation of the perspective is the L-arginine-NO biosynthetic pathway, the vascular development of the placenta and fetal growth; no own intervention study is reported. It still needs to be examined whether citrulline administration in pregnancy during maternal infections actually raises arginine availability and improves birth outcomes.

Overall Picture

Across all areas the finding contributes that oral citrulline administration reliably raises plasma arginine and does so more effectively than arginine itself, because citrulline escapes intestinal and hepatic first-pass elimination [1][59][61]. The measured effects build on this: lowered mean arterial pressure in healthy men [4], lower pulse-wave velocity in older men [5], increased FeNO and improved control values in obese asthmatics [57], higher plasma citrulline and arginine concentrations in children after cardiac surgery [6], shortened riding time in the 4 km time trial [7] and more repetitions in strength-endurance loads [8][11]. In several works of this material, however, citrulline is not the tested active substance but a measured variable of an arginine administration [10][55] or a predictor in observational cohorts [25][56].

Where citrulline itself was tested, the results are mixed: three months of 2 g/day lowered inflammatory markers in NAFLD [18], 5.6 g/day over seven days lowered arterial stiffness [5], 2.4 g/day shortened time-trial performance by 1.5 % [7], whereas a single dose of 8 g citrulline malate during German Volume Training produced no performance improvement and even increased muscle soreness [17], and citrulline in the meta-analysis on birth weights showed no effect without isonitrogenous controls [64]. For oncological arginine-deprivation therapy citrulline remains a substrate of endogenous arginine synthesis, which is absent in ASS1-suppressed tumours [47][54]. The next questions to be clarified are placebo-controlled studies with citrulline as the sole intervention and clinical endpoints.

Methodology of the study situation

The material comprises placebo-controlled cross-over and parallel-group studies, open before-and-after surveys, prospective cohorts as well as systematic reviews with meta-analysis. Treatment duration ranges from a single administration [8][11] over seven days [4][5][7] to four months [14] and 26 weeks [48]. Endpoints are predominantly plasma amino acids, NO metabolites, flow and pulse-wave measurements, FeNO, questionnaires and performance tests; hard

clinical endpoints such as mortality or event rates are reported only in the reviews [2][47][64]. Open questions for further research are studies in women outside strength-sport and pregnancy contexts as well as long-term data on clinical endpoints under citrulline.

The citrulline literature is to a large extent arginine literature

PROVEN:

The most frequently cited works in this field deal predominantly with arginine. The oldest recorded study from 1996 examines the blood-pressure-lowering effect of L-arginine. A frequently cited observational work from 2001 addresses oral L-arginine in pulmonary hypertension. The work from 2010 compares L-arginine or L-citrulline in heart failure with preserved ejection fraction. Two reviews from 2015 and 2019 list arginine and citrulline jointly in the title. Anyone searching for citrulline therefore regularly finds studies in which citrulline is only one of two tested substances. For statements about citrulline alone these works are only of limited use.

A second problem concerns combinations and neighbouring substances. The 2022 work on the reduction of cardiovascular risk examines micronutrients overall, not citrulline. The studies on Duchenne muscular dystrophy test citrulline together with metformin, so that the contribution of the individual substance cannot be read off. The oncological entries in the database concern predominantly arginine metabolism and an arginine-degrading enzyme, not citrulline administration. These works belong to the metabolic biology of arginine but do not carry any statement about a citrulline application. The assignment to the citrulline literature is misleading here.

3. How Reliable the Research Is

The research is distributed across several blocks. The largest share consists of controlled studies in humans, followed by observational studies in humans. In addition there are animal studies and reviews on mechanisms. Within the controlled human studies the field of **cardiovascular system** dominates, followed at a clear distance by **musculoskeletal system** and **metabolism**. Safety questions form a separate, independently investigated group. Smaller fields are exhaustion, bioavailability, inflammation, immune system, antioxidative questions and oncology. The distribution shows a field whose focus clearly lies in vascular and performance physiology and that has only begun to touch other applications.

Methodologically the controlled human research is predominantly characterised by small, acute crossover studies in trained men, as the works on time-trial performance and strength performance show. This is a clean but narrow design: it measures short-term performance and vascular parameters, not the course of diseases. Some of the works examine combinations, for example citrulline together with metformin or micronutrient mixtures, and therefore cannot support the effect of the individual substance. Several reviews summarise the area, including a meta-analysis on subjective perceived exertion, muscle soreness and lactate value after exertion. The reliability is therefore greatest for **performance and vascular markers** and lowest for clinical endpoints.

Hypothesis: The narrow study population contributes to the fact that findings can be transferred to other groups only to a limited extent.

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

STATEMENT	STUDY SITUATION
Citrullin lowers blood pressure	Controlled studies and review articles are available, but several examine arginine or arginine and citrulline together. Der Blutdruck ist zudem ein Marker, kein Ve
Citrulline increases athletic performance	Several controlled crossover studies in trained men and women investigate time trial, strength and anaerobic performance, partly with citrulline malate. Eine Me
Citrulline acts in heart failure and vascular diseases	This is the largest field, but it includes arginine studies, a paper on vascular stiffness in middle-aged men and a randomised study in congenital heart surgery. T
Citrulline helps in Duchenne muscular dystrophy	There is a randomised study on the combination with metformin and a study protocol. The combination does not allow any conclusions to be drawn about citrul

5. Profile: Molecule and Charge

L-Citrulline are 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.

6. Charge, Electrons, Radicals

The evidence contains no information on charge, cation exchange, electron transfer, radicals or redox behaviour of L-Citrulline. No details on charge state or ion exchange are included therein.

In humans, the only observations regarding L-Citrulline are its classification as a non-essential amino acid and its synthesis via delta-1-pyrroline-5-carboxylate synthase in endothelial cells of the small intestine ²¹. The study does not investigate whether L-Citrulline is involved in this. What would need to be examined is whether the charge state, cation exchange or electron transfer of L-Citrulline can be measured under conditions corresponding to the radical and redox processes mentioned in ²² and ²³.

7. Interactions with Other Substances

Which other substances on the platform this substance is **jointly** investigated or discussed with in human studies and reviews — combination, comparison or shared mechanism of action. The number indicates studies in which both occur.

SUBSTANCE	SHARED STUDIES	OF WHICH CONTROLLED IN HUMANS
High-Intensity Interval Training (HIIT)	37	26
Art Therapy	35	18
Stress, Cortisol and Inflammation	23	6
Chronic Inflammation	23	9
Palmitoylethanolamide (PEA)	11	9
Beetroot and Nitrate	10	3
Gut Microbiome	7	2
Creatine	6	1
Glycine	5	0
Therapeutic Fasting and Intermittent Fasting	5	5

A controlled human study exists on the combination with medicinal products, in which L-Citrulline together with metformin was tested over 26 weeks; the combination is compared with placebo in Duchenne muscular dystrophy ⁽¹⁰⁾. The study examines whether the six-month administration of the combination is superior to placebo in the loss of motor function and muscle degeneration ⁽¹⁰⁾. The material contains no information on absorption, CYP enzymes or binding; no combination study with glucocorticoids exists for L-Citrulline.

Enhancements with other substances have been described: Oral L-arginine plus L-Citrulline raises plasma arginine and nitrite/nitrate (NOx) immediately and synergistically more strongly than citrulline or arginine alone ⁽¹⁸⁾; citrulline alone raises plasma arginine and NO production ⁽¹⁸⁾. Without additional protein, gynoid fat mass decreased more markedly and leg FFM and HSR increased more markedly than with protein (each $p = 0.02$) ⁽²⁴⁾. In hypertensive postmenopausal women, citrulline alone improved endothelial function of the leg; with SVLIRT it additionally improved leg muscle mass and curl strength ⁽²⁰⁾. Hypothesis: A higher protein intake could alter citrulline availability.

8. Overdose, Tolerability, Limits

Several controlled human studies report on the tolerability of L-Citrulline. One study in 75 resistance-trained men recorded safety via clinical-chemical markers ¹². A multiple-dosing study reports that no serious adverse events occurred and the administration was well tolerated ²⁵. In hospitalised patients, 40 of 42 (95 %) completed the seven-day supplementation without adverse events; blood pressure, complications and deaths were monitored ²⁶. A review notes that across all studies no adverse effects associated with citrulline supplementation were reported ²⁸.

One study provides the most concrete indication regarding the dose limit: Dose-limiting toxicities were not observed, yet the rise in guanidino compounds at 30 g and 40 g L-Citrulline must be examined in a future study with serial measurements to confirm the safety of these doses and to clarify whether the rise persists long-term ²⁷. One controlled study considers L-Citrulline safe and well tolerated ²⁹; a Phase-I dose-finding and safety study examined L-Citrulline in nitric-oxide deficiency in MELAS ²⁷. The next step would be to clarify which guanidino compounds rise and how contraindications can be recorded.

9. The Most Robust Studies

Ordered by strength of evidence, not by familiarity. The complete evaluation comprises considerably more studies; the most robust ones are listed here.

Controlled Human Studies

- ¹ Pharmacokinetic and pharmacodynamic properties of oral L-citrulline and L-arginine: impact on nitric oxide metabolism (2008)
- Micronutrient Supplementation to Reduce Cardiovascular Risk (2022)
- Pegylated arginine deiminase: a novel anticancer enzyme agent (2006)
- ² L-Citrulline supplementation improves O₂ uptake kinetics and high-intensity exercise performance in humans (2015)
- ³ Short-term effects of L-citrulline supplementation on arterial stiffness in middle-aged men (2012)
- ⁴ Nitric oxide precursors and congenital heart surgery: a randomized controlled trial of oral citrulline (2006)
- ⁵ Oral L-citrulline supplementation enhances cycling time trial performance in healthy trained men: Double-blind randomized placebo-controlled 2-way ... (2016)
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10. Summary

PLAUSIBLE The robustness of the field is greatest for performance and vascular markers, and least for clinical endpoints. A placebo-controlled cross-over study in 20 healthy subjects showed that L-citrulline increases plasma arginine in a dose-dependent manner and more strongly than L-arginine [1]; in a randomised cross-over study in ten men, mean arterial blood pressure was lower only after citrulline [4]; in 15 men over 58 years, brachial-ankle pulse wave velocity decreased under 5.6 g citrulline daily [5]. Safety questions were investigated as a separate group.

PLAUSIBLE The diversity of forms and the varying administration — acutely before exercise or over weeks — explain a good part of the inconsistent findings, without implying a contradiction regarding the substance itself. The higher arginine availability after citrulline is explained by the fact that it is not extracted to any appreciable extent from enterocytes or the liver and bypasses hepatic first-pass metabolism [58, 59].

What remains to be clarified is whether the NO-marker changes observed under citrulline are confirmed in placebo-controlled studies with clinical endpoints, and by which mechanisms citrulline lowers blood pressure. Also open is the pharmacokinetics and the exposure-response relationship depending on age and disease [58]. A study on the effect of oral citrulline administration on the composition of the microbiome is still outstanding. In Duchenne muscular dystrophy, citrulline is being tested in combination with metformin, so the effect of the single substance cannot be attributed there [49]. A study combining a pure citrulline arm, a clinical endpoint and separate reporting of citrulline and citrulline malate would clarify this question.

11. What Remains Open

- **Forms:** Whether pure L-citrulline and citrulline malate produce comparable effects at the same citrulline dose has not been clarified. A study directly comparing both forms would decide the question.
- **Separation:** It remains open how citrulline and arginine differ in plasma values and vascular markers at the same oral dose. The pharmacokinetic study from 2008 is the starting point here.
- **Endpoints:** Whether the observed marker changes translate into clinical courses is untested. Controlled studies with longitudinal endpoints instead of acute performance and vascular parameters would be needed.

12. Further Paths

Topics, modes of action and chains in which this substance occurs — for all those who wish to look beyond the substance.

- Interaction network

Frequently Asked Questions

Should I administer citrulline or arginine if I wish to influence the nitric oxide pathway?

The database does not cleanly separate the two. The pharmacokinetic study from 2008 compares oral L-citrulline and L-arginine and their influence on nitric oxide metabolism; it provides the best reference point for a direct comparison. Many further papers examine arginine alone or both together. No robust recommendation for one substance or the other can be derived from this literature.

What is the state of the evidence on athletic performance?

It is the second-largest area and consists predominantly of acute, placebo-controlled crossover studies in trained men and women, sometimes using citrulline malate. Time-trial performance, maximal strength, anaerobic performance and oxygen uptake kinetics are examined. A meta-analysis summarises perceived exertion, muscle soreness and lactate values. The endpoints are performance measures, not clinical outcomes.

What does the classification among nitric oxide precursors mean for the assessment?

It explains why citrulline is almost always studied in connection with arginine and nitric oxide. The majority of measurements concern plasma values, exhaled nitric oxide and vascular parameters. This yields a statement about the metabolic pathway, not about a disease-modifying effect. Examination of clinical endpoints is still pending.

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Research, put in context. Every statement leads to the original paper; the decision in the individual case rests with the treating professional.
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