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THE IMPACT OF CITRULLINE SUPPLEMENTATION ON CARDIOVASCULAR AND EXERCISE PHYSIOLOGY: A NARRATIVE REVIEW

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ABSTRACT

Background: L-citrulline is an endogenous non-proteinogenic amino acid involved in nitric oxide (NO) metabolism by increasing L-arginine bioavailability. Its use in sports and cardiovascular disease prevention has gained considerable interest, although its efficacy remains debatable.
Aim of the study: The aim of the study is to evaluate current evidence on the effects of L-citrulline supplementation on physical performance and cardiovascular function.
Materials and methods: A narrative review of the literature was conducted using PubMed/MEDLINE and Google Scholar. 148 publications were analysed, mainly from 2017–2025, including meta-analyses, systematic reviews, randomised controlled trials, and international guidelines.
Results: L-citrulline supplementation increases L-arginine and NO metabolite concentrations, supporting vasodilation and endothelial function. Beneficial effects were reported more often with chronic than acute supplementation. Some studies showed improvements in blood pressure, vascular stiffness, and blood flow, although results remain inconsistent. In exercise settings, supplementation was associated with improved selected resistance-training outcomes and reduced perceived fatigue and post-exercise muscle soreness. Evidence regarding effects on strength, power, and aerobic capacity remains inconclusive.
Conclusions: L-citrulline is a safe and well-tolerated supplement with potential benefits for endothelial function, selected cardiovascular parameters, and some aspects of exercise performance. However, the heterogeneity of available studies prevents firm conclusions, highlighting the need for further long-term randomised clinical trials.

KEYWORDS

Citrulline, Nitric Oxide, Exercise Physiology, Cardiovascular Function, Sports Supplementation

CITATION

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1. Introduction

Over the past decade, public interest in health, wellness, and physical fitness has increased substantially. A rapidly expanding segment of this market is dietary supplementation, particularly products intended to enhance athletic performance. In competitive sports, even minor improvements resulting from training, nutrition, or supplementation may significantly influence performance outcomes. Consequently, supplements such as creatine, arginine, and beta-alanine are widely marketed not only to professional athletes but also to recreational exercisers and the general population. Amino acids and protein-based products account for approximately 35–40% of all supplements consumed [1,2], while the popularity of colloquially called nitric oxide (NO) boosters continues to increase [3]. Therefore, healthcare professionals should remain conscious about commonly used supplements and their physiological effects. This review focuses on the lesser known amino acid L-citrulline and its proposed effects on exercise performance and cardiovascular health.

L-citrulline is a neutral, non-proteinogenic, non-essential amino acid that plays a key role in nitric oxide metabolism [4,5] and serves as a precursor of L-arginine [4,6]. Although synthesized endogenously, it is also obtained from dietary sources, particularly watermelon, as well as cucumber, cantaloupe, and bitter melon. Similarly to arginine, citrulline intermediates in the urea cycle within the liver. Following oral administration, L-citrulline bypasses extensive hepatic metabolism and is converted in the kidneys to L-arginine, thereby increasing nitric oxide bioavailability. [7–9]

Nitric oxide is a key regulator of vascular tone and endothelial function. Because L-citrulline increases endogenous L-arginine availability, supplementation may improve nitric oxide production, vascular function and tissue perfusion. Enhanced vascular function promotes tissue perfusion and oxygen delivery, potentially improving overall health and exercise performance. [10] Compared with oral L-arginine, L-citrulline exhibits greater bioavailability and fewer gastrointestinal adverse effects. [3,4]

Several studies suggest that L-citrulline supplementation may improve vascular function and exercise performance, particularly during high-intensity exercise; [7,11,12,13] however, results remain inconsistent. Some studies demonstrate improved muscular endurance and oxygen uptake, whereas others report no significant effects. Current evidence also suggests that chronic supplementation (6-16 days) may be more effective than acute administration, although further high-quality studies are required. [3]

Although interest in L-citrulline has increased substantially during the past decade, evidence remains heterogeneous. While most studies report generally favorable effects, substantial variability in outcomes remains. A major limitation of the current literature is the scarcity of long-term studies exceeding 6 months.

2. Aims

The aim of this narrative review was to summarize current evidence regarding the physiological mechanisms, cardiovascular effects and exercise-related outcomes associated with L-citrulline supplementation.

3. Methods

This study was designed as a narrative review of the effects of L-citrulline supplementation on physical performance and cardiovascular function. Its purpose was to integrate and critically discuss current evidence on clinical presentation, diagnostic evaluation, and treatment strategies. A narrative literature review was conducted using PubMed/MEDLINE and Google Scholar databases.

The search included the following terms: “citrulline”, “nitric oxide”, “exercise physiology”, “cardiovascular function”, “sports supplementation”. A simplified search strategy based on the same main terms was applied in Google Scholar. Publications from 1982 to 2025 were analysed, preferably from 2017–2025. Older works were carefully assessed regarding their credibility and relevance.

Publications were considered eligible if they were written in English, available as full texts, and clinically relevant to the effects of L-citrulline supplementation on physical performance and cardiovascular function. Eligible sources included original clinical and observational studies, cohort studies, systematic reviews, meta-analyses, clinical guidelines, consensus statements, and high-quality narrative reviews.

Publications were excluded if they were duplicates, written in languages other than English, available only as conference abstracts, unrelated to the effects of L-citrulline supplementation on physical performance and cardiovascular function. Articles with insufficient clinical information or unclear methodological value were also excluded.

The final narrative synthesis included 148 publications. The selection of literature was guided by clinical relevance and contribution to the effects of L-citrulline supplementation on physical performance and cardiovascular function. Priority was given to systematic reviews, large observational studies, and original studies reporting clinically useful data. The included literature was reviewed narratively and analysed qualitatively.

4. Results

4.1 Citrulline and Nitric Oxide Production

Nitric oxide (NO) is a gaseous molecule involved in a wide range of signalling and regulatory processes in the human body. As NO has a short half-life, ranging from milliseconds to several seconds, continuous production is essential for it to exert its effects [14,15].

The diffusion of NO into arterial smooth muscle cells triggers the production of cyclic guanosine monophosphate (cGMP) from guanosine triphosphate (GTP) via the activation of the enzyme guanylate cyclase. This reaction reduces calcium levels in the sarcoplasm, leading to smooth muscle relaxation, vasodilation and increased blood flow [16,17]. The increase in perfusion induced by NO may enhance mechanisms contributing to skeletal muscle performance and adaptation [18]. During resistance exercise, increased blood vessel dilation may facilitate the delivery of oxygen and nutrients to working muscle tissue, thereby enhancing muscle contractile properties and replenishing ATP between repeated sets of resistance exercise. This, in turn, may delay fatigue and allow for a greater training volume, which may improve anabolic stimulation and subsequent muscle adaptation [19].

L-citrulline (L-Cit) is synthesized primarily in the intestine and converted in the kidneys to L-arginine (L-Arg), however, it can also be obtained via dietary intake [20]. Watermelon is the richest natural source of L-citrulline, with levels ranging from 0.7 to 3.6 $mg \cdot g^{-1}$ of fresh weight [21]. In endothelial cells, L-Arg is catabolised to NO, which diffuses into smooth muscle and induces relaxation [22]. A significant increase in plasma nitrite and nitrate concentrations following L-Cit supplementation indicates enhanced activity of the L-Arg-NO pathway [23].

Oral administration of L-Cit is well tolerated and safe, as no toxicity or side effects have been reported at doses up to 15 g per day. L-citrulline is commonly supplemented in the form of citrulline malate. It has been proposed that malate, as an mediator in the tricarboxylic acid cycle, increases energy production and enhances the rate of ATP production [24]. Furthermore, citrate may mitigate lactic acid production, enabling continuous pyruvate production for energy utilisation [25].

Additionally, it has been shown that L-Cit supplementation results in a greater increase in plasma L-Arg concentrations than supplementation with an equimolar dose of L-Arg [26]. Unlike oral L-arginine, L-citrulline bypasses intestinal and hepatic metabolism, resulting in greater systemic L-arginine availability and enhanced nitric oxide production. [27,28]

4.2 Effects on Cardiovascular Physiology

4.2.1 Blood Pressure

High blood pressure is the most common and significant modifiable risk factor for cardiovascular disease and disability worldwide. In a 2023 global World Health Organisation report, hypertension was estimated to affect 33% of adults aged 30–79 worldwide [29].

Interventions leading to a reduction in blood pressure are considered an effective strategy for avoiding adverse cardiovascular health outcomes. It has been suggested that non-pharmacological nutritional factors, such as L-citrulline, may have a positive effect on vascular health, as, being a precursor of nitric oxide, L-citrulline supplementation increases the synthesis and bioavailability of NO [30].

L-citrulline has shown promising results as a dietary intervention for lowering blood pressure, as it has been reported to reduce resting blood pressure [31]. Tryfonos et al. investigated the effect of short-term L-citrulline supplementation on central and peripheral blood pressure during isometric knee flexion in older men. Haemodynamic parameters, pulse wave reflection and arterial stiffness were measured at baseline, after supplementation and during isometric exercise. However, no evidence was found to support any blood pressure-lowering effect from supplementation with 6 g of L-citrulline for six days, nor any beneficial effect on pulse wave velocity or arterial stiffness in older men at rest or during isometric exercise. [32] A study by Ochiai et al. reached a different conclusion. Compared with the placebo group, the pulse wave velocity in the brachial-ankle segment was significantly reduced in the L-citrulline group ($p<0.01$) [23].

In contrast, long-term (>4 weeks) supplementation with L-citrulline improved flow-mediated dilation (FMD) of the brachial artery in a study conducted on apparently healthy postmenopausal women with slightly elevated blood glucose levels. In combination with glutathione, it reduced blood pressure in the brachial artery and attenuated the blood pressure response to sympathetic activation [33].

Similar conclusions were drawn by researchers from the Luo et al. team. L-citrulline supplementation lowered blood pressure in middle-aged and older adults. A subgroup analysis showed that combined supplementation with L-citrulline and L-arginine is more effective than supplementation with L-citrulline or watermelon alone. Researchers claimed that these findings could provide new dietary recommendations for blood pressure control in older adults, suggesting that dietary interventions can effectively improve cardiovascular health and reduce the risk of cardiovascular disease. [34]

Interestingly, in a study conducted on rats, citrulline was shown to prevent the increase in blood pressure and myocardial infarct size induced by intermittent hypoxia (IH), a hallmark of obstructive sleep apnoea (OSA). [35]

4.2.2 Endothelial Functions and Blood Flow Improvement

Endothelial dysfunction results from impaired NO bioavailability and reduced vasodilation [36]. Reduced NO production is associated with arginine deficiency, which is caused by increased levels of endogenous eNOS inhibitors. [37] Therefore, dietary strategies aimed at increasing circulating arginine levels could improve vascular function. L-citrulline supplementation was proposed to improve endothelial function, as it is not catabolised by arginase, inhibits arginase activity and serves as a substrate for NO synthesis. [38,39]

Figueroa et al. conducted a double-blind, placebo-controlled, parallel-group trial. Their aim was to assess the effect of supplementation with citrulline alone (CIT) or citrulline and glutathione (CIT+GSH) on vascular function, as measured by changes in flow-mediated dilation (FMD) of the brachial artery, arterial stiffness (PWV) and blood pressure reactivity. Although CIT supplementation increased serum arginine levels, it did not statistically improve FMD. In contrast, CIT+GSH supplementation attenuated the arterial pressure response to sympathetic stimulation induced by the cold pressor test (CPT). These data suggest that CIT+GSH supplementation has a protective effect on the cardiovascular system at rest and during sympathetic stimulation in healthy postmenopausal women [33]. Other conclusions were drawn following a study by Yeijn Kang et al. They demonstrated that four weeks of L-citrulline supplementation improved FMD, PWV in the femorotibial segment, and systolic blood pressure in the aorta compared with placebo (all $p < 0.05$). Importantly, in acute hyperglycaemia, CIT supplementation increased FMD and reduced pulse wave velocity (PWV) in the femorotibial segment, systolic blood pressure in the aorta, and blood glucose levels compared with placebo (all $p < 0.05$). It has been suggested that CIT supplementation is beneficial for improving vascular function and glucose levels in chronic and acute hyperglycaemia in middle-aged and older adults with type 2 diabetes [40].

Researchers from the team led by Flores-Ramírez et al. reached similar conclusions. The findings of their demonstrated a marked improvement in cardiovascular parameters thanks to L-citrulline supplementation and moderate-to-high-intensity aerobic training. Aerobic training in children and adolescents with obesity and cardiometabolic abnormalities helped improve not only blood pressure and endothelial function, but also atherosclerosis and arterial stiffness, dyslipidaemia and body composition. Moreover, L-Cit supplementation in adults with cardiometabolic changes had a positive effect on carbohydrate metabolism [41].

4.3 Effects of Citrulline Supplementation on Exercise Performance

Studies show that acute supplementation with L-citrulline or citrulline malate (CM) may improve resistance training performance. Wax et al. reported that individuals who consumed 8 g of CM 60 minutes before the exercise protocol increased the number of repetitions completed in both a lower-body resistance protocol (leg press, hack squat, and leg extension at 60% 1 Repetition Maximum/1RM) [42] and a bodyweight exercise protocol including chin-ups, reverse chin-ups, and push-ups [25]. Glenn et al. [43] found that a single 8 g dose of CM significantly increased the number of repetitions to failure in both bench press and leg press across six sets at 80% 1RM, while also reducing post-exercise perceived exertion (RPE) in resistance-trained females. Pérez-Guisado & Jakeman [44] similarly demonstrated that a single 8 g dose of CM significantly increased the number of repetitions to failure across eight sets of bench press performed at 80% 1RM in resistance-trained men.

In contrast, other studies have reported no ergogenic effects of citrulline supplementation on strength or power outcomes. Chappell et al. [45] observed that an 8 g dose of CM did not improve the number of repetitions completed during 10 sets of isokinetic knee extensions performed at 70% of peak concentric force in strength-trained men and women. Farney et al. [46] reported no significant effects of 8 g CM on total work, peak torque, peak power, or fatigue rate following a high-intensity exercise circuit. Similarly, Gonzalez et al. [47] found that 8 g of L-citrulline did not enhance isometric force, muscle endurance, or muscle oxygenation in resistance-trained participants. Furthermore, Fick et al. [48] reported that neither acute nor 7-day supplementation with 8 g CM improved peak power, peak torque, or fatigue rate during maximal isokinetic exercise.

Moreover, in the study by Gonzalez et al. [49] 8 g of citrulline malate did not increase triceps brachii muscle thickness following high-volume training. Similarly, watermelon juice (2.2 g of L-citrulline per day for 7 days) did not improve blood flow or the “muscle pump” [50]. This suggests that evidence for enhanced vasodilation and muscle perfusion in resistance training is insufficient to reach objective conclusions.

A few studies have considered the ergogenic potential of CM supplementation in supporting the recovery of muscle function. In a meta-analysis conducted by Rhim et al., an analysis of 7 studies investigating subjective feelings of muscle soreness in young, healthy, recreationally active or resistance-trained individuals 24-h post-exercise suggested that supplementation of L-citrulline or CM significantly reduced the feelings of muscle soreness, with an effect size of 0.99 ($p = 0.04$). On the contrary, no significant association between citrulline ingestion and muscle soreness was observed at 72 h after exercise ($p = 0.62$). In a meta-analysis of 8 studies, citrulline supplements did not significantly reduce blood lactate levels after exercise ($p = 0.17$). [51]

Da Silva et al. [52] reached a different conclusion. They aimed to investigate whether citrulline malate supplementation enhanced muscle recovery following a single session of high-intensity resistance exercise in untrained young men. Their findings indicated that a 6 g dose taken 60 minutes before exercise did not improve key functional, metabolic, anabolic, or physiological markers of muscle recovery. However, it could be suggested that the exercise protocol used by da Silva et al. may not have been sufficiently demanding to properly assess muscle recovery. In particular, the similar number of repetitions performed between 24 and 72 hours post-exercise indicates that participants were likely not adequately fatigued at the 24-hour mark.

The effect of citrulline supplementation in the management of sarcopenia was assessed in the study conducted by Caballero-Garcia et al. Researchers found that L-citrulline improved walking speed, whereas changes in muscle strength and biochemical markers were not statistically significant [53].

Table 1. Characteristics and main findings of studies on the impact of L-citrulline supplementation on cardiovascular and exercise physiology

Area of application	Evidence from current literature	Limitations	Key references
Hypertension management	May increase NO bioavailability and reduce resting blood pressure; some studies report reduced arterial stiffness and pulse wave velocity.	Evidence is inconsistent; not a substitute for antihypertensive therapy.	[23,30-32,34]
Endothelial dysfunction	May improve endothelial function through increased L-arginine availability; combination with glutathione may enhance effects.	Limited evidence and heterogeneous study designs.	[38-41]
Postmenopausal women	Combined L-citrulline and glutathione improved vascular function and blood pressure reactivity.	Evidence limited to selected populations.	[33]
Cardiometabolic disease prevention	Combined supplementation and aerobic exercise improved endothelial function, blood pressure and metabolic parameters.	Should accompany evidence-based lifestyle and pharmacological management.	[33,34,40,41]
Exercise and sports medicine	Acute supplementation may improve muscular endurance and reduce perceived exertion.	Ergogenic effects remain inconsistent.	[42-49]
Recovery after exercise	Reduced delayed-onset muscle soreness within 24 h in some studies, without consistent objective recovery benefits.	Limited effects on physiological recovery markers.	[51,52]
Older adults and sarcopenia	Improved walking speed, with limited effects on strength and biochemical markers.	Insufficient evidence for routine use.	[53]

5. Discussion

The available literature suggests that L-citrulline supplementation may increase the bioavailability of NO by boosting endogenous L-arginine production, which is a likely mechanism for improving vascular function and certain aspects of physical performance. However, despite promising results, the evidence to date remains insufficient to justify routine clinical recommendations.

Several studies have reported improvements in blood pressure, arterial stiffness and endothelial function, particularly in middle-aged and older adults, postmenopausal women and people with cardiometabolic disorders after L-citrulline supplementation. These effects are likely to result from increased NO synthesis and improved endothelium-dependent vasodilation. Furthermore, combining L-citrulline with glutathione or physical exercise may offer greater benefits for the cardiovascular system than supplementation alone. Nevertheless, other randomised trials have failed to demonstrate a significant improvement in blood pressure or vascular function. These inconsistent results can probably be explained by differences in supplementation protocols, the duration of the trials, the characteristics of the participants and the outcomes measured.

The data on exercise performance are equally inconclusive. Whilst several studies have shown an improvement in muscular endurance and a reduction in the subjective perception of exertion following a single dose of citrulline malate, others have found no significant effect on strength, power, muscle oxygenation or recovery. Consequently, the ergogenic potential of L-citrulline appears to depend on the type of exercise, training status and supplementation strategy, rather than being a universal performance-enhancing agent.

An important observation is that improvements in vascular function appear to be more consistent than improvements in exercise performance. This suggests that L-citrulline may be of greater clinical significance as a nutritional supplement targeting endothelial dysfunction and cardiovascular risk than as a general ergogenic agent.

L-citrulline also exhibits a favourable safety profile – oral supplementation is well tolerated and no significant adverse effects have been reported at commonly studied doses. Nevertheless, evidence regarding long-term supplementation in patients with chronic conditions remains limited.

Future research should focus on large, well-designed randomised controlled trials using standardised supplementation protocols and clinically relevant outcome measures. Research priorities should include identifying patient populations most likely to benefit from supplementation and determining optimal dosing strategies. Although the current evidence is promising, particularly in individuals with impaired vascular function, further high-quality clinical trials are needed before L-citrulline can be routinely recommended in evidence-based clinical practice.

6. Limitations

This paper is a review, and its conclusions depend on the quality and availability of previously published studies. This precludes the conduct of a quantitative meta-analysis, limiting the ability to draw reliable statistical conclusions. Furthermore, the studies analysed are heterogeneous, differing in terms of the study population (healthy individuals, athletes, patients with medical conditions), L-citrulline doses and the duration of supplementation. In many studies, factors such as diet, hydration and level of physical activity — which may influence the assessed parameters of the NO synthesis pathway — were not adequately controlled. Some studies have yielded conflicting conclusions, for example regarding the effect of short-term L-citrulline supplementation on blood pressure. Further studies should be conducted to minimise the risk of overgeneralisation and the influence of external factors in order to demonstrate the effect of L-citrulline supplementation on improving endothelial function and cardiovascular parameters.

7. Conclusions

L-citrulline supplementation is a promising nutritional strategy aimed at increasing the bioavailability of nitric oxide by boosting endogenous L-arginine production. Due to its favourable pharmacokinetic profile and the absence of extensive first-pass metabolism, L-citrulline appears to be a more effective precursor of nitric oxide than direct L-arginine supplementation. Current evidence suggests that its most consistent benefits are associated with improvements in endothelial function, vascular health and selected cardiovascular parameters, particularly in individuals with impaired vascular function, including older adults, postmenopausal women and patients with cardiometabolic disorders. Long-term supplementation regimens generally appear to yield more favourable outcomes than a single dose. However, the extent of these benefits varies considerably across studies, and the current evidence remains insufficient to justify routine clinical use in the prevention or treatment of cardiovascular diseases.

In contrast, the evidence supporting the ergogenic effects of L-citrulline remains inconsistent. Whilst several studies have demonstrated improvements in muscular endurance and a reduction in perceived exertion following acute supplementation, other studies have reported

no significant effects on strength, power, muscle recovery or exercise performance. Consequently, its role as a universal performance-enhancing supplement cannot currently be confirmed.

L-citrulline is generally well tolerated and has a favourable safety profile, making it an attractive candidate for further research in both clinical practice and sports nutrition. However, the available evidence is limited by small sample sizes, heterogeneity of the study populations and differences in supplementation protocols. Consequently, additional, well-designed, large-scale randomised controlled trials are needed to establish optimal dosing strategies, identify patient populations most likely to benefit, and determine the long-term clinical efficacy of L-citrulline supplementation.

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