The Effects of Consuming Amino Acids L-Arginine, L-Citrulline (and Their Combination) as a Beverage or Powder, on Athletic and Physical Performance: A Systematic Review

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Abstract: Consumption of amino acids L-arginine (L-Arg) and L-citrulline (L-Cit) are purported to increase nitric oxide (NO) production and improve physical performance. Clinical trials have shown relatively more favorable outcomes than not after supplementing with L-Cit and combined L-Arg and L-Cit. However, in most studies, other active ingredients such as malate were included in the supplement. Therefore, the aim of this study was to determine the efficacy of consuming standalone L-Arg, L-Cit, and their combination (in the form of powder or beverage) on blood NO level and physical performance markers. A systematic review was undertaken following PRISMA 2020 guidelines (PROSPERO: CRD42021287530). Four electronic databases (PubMed, Ebscohost, Science Direct, and Google scholar) were used. An acute dose of 0.075 g/kg of L-Arg or 6 g L-Arg had no significant increase in NO biomarkers and physical performance markers ($p > 0.05$). Consumption of 2.4 to 6 g/day of L-Cit over 7 to 16 days significantly increased NO level and physical performance markers ($p < 0.05$). Combined L-Arg and L-Cit supplementation significantly increased circulating NO, improved performance, and reduced feelings of exertion ($p < 0.05$). Standalone L-Cit and combined L-Arg with L-Cit consumed over several days effectively increases circulating NO and improves physical performance and feelings of exertion in recreationally active and well-trained athletes.

Keywords: exercise performance; nitric oxide; vasodilation; L-arginine; L-citrulline

1. Introduction

The dietary supplements (DS) market is characterised by continuous growth in sales, which had an estimated global value of around USD 101.38 billion in 2018, and was estimated to reach approximately USD 220.3 billion by 2020 [1] and USD 272.4 billion by 2028 [2]. This is a poorly regulated industry [3], and around 50% of adults consume at least one DS daily [4]. During the COVID-19 pandemic, retailers experienced a rise in purchasing vitamin C, multivitamins, and zinc worldwide [5].

Supplements, and in particular functional beverages, that claim to enhance sports performance are relatively easily marketable to athletes, with usage prevalent across different levels of sport [6,7]. However, athletes are susceptible to the consumption of supplements and beverages that have a low level of scientific evidence relating to efficacy [8]. Tainted supplements with false claims may adversely impact health, performance, and undermine

anti-doping legislation [6,9]. Nevertheless, athletes search for convenient supplements that provide a competitive advantage over their counterparts [10].

Over the last few decades, there has been tremendous growth in the development and usage of supplements claimed to improve performance, accelerate recovery, and prevent illness and injuries [11]. Such supplementation products are available in various forms; bars, gels, pills, protein powders, and beverages. Functional sports and performance beverages in general, provide a convenient and efficient means to replenish the body's electrolytes, carbohydrates, and nutrients during physical activity [12]. Functional beverages are nonalcoholic drinks containing nontraditional ingredients such as minerals, vitamins, amino acids, dietary fibers, probiotics, and added raw fruits [13]. Sports and energy drinks have been particularly popular in the last two decades. However, relatively recent research interest in amino acids (AAs) proposed a need to investigate a convenient AA sports drink [14].

Supplements containing AAs, such as L-Arg that supposedly increase NO production, have gained attention among researchers for their potential ergogenic benefits [15].

NO can be produced from L-Arg, a semi-essential amino acid, via nitric oxide synthase (NOS) [16]. There are three types of NOS in the muscle; (1) neural (nNOS or NOS-1), (2) cytokine-inducible (iNOS or NOS-2), and (3) endothelial (eNOS or NOS-3) [17]. NO is a signalling molecule responsible for vasodilation, glucose uptake, mitochondrial respiration, calcium handling, and muscle contractility [18–20]. All of these are associated with improvements in exercise performance [20–23]. Therefore, maintaining physiologically adequate concentrations is paramount for skeletal muscle health. However, NO has a short life span. Therefore, nitrite and nitrate are typically used to quantify plasma NO concentrations [24]. Figure 1 represents NO synthesis via the L-Arg pathway.
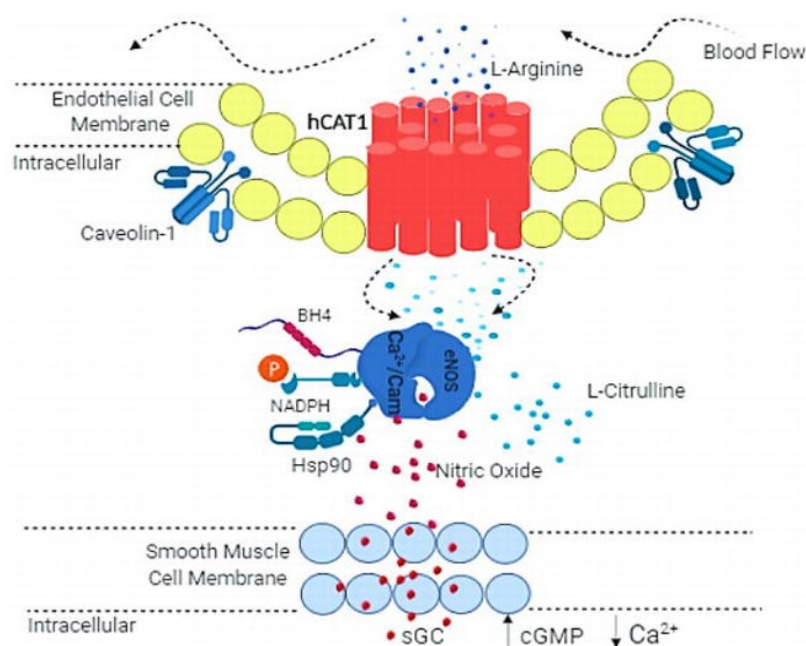
Figure 1. Nitric oxide synthesis from L-Arginine in endothelium. González & Rivas (2020) [25].

The consumption of 6 g/day L-Arg with trace amounts of vitamins and branched chained amino acids (BCAA) for three days increased plasma nitrate and nitrite [22]. Ingestion of a beverage rich in L-Arg and other AAs, including L-Cit, BCAA, and fructose, reduced the oxygen cost of moderate-intensity exercise and enhanced overall activity [22]; reduced exercise-induced plasma lactate and ammonia [26]; and enhanced exercise tolerance during severe intensity exercise [22]. An acute dose of 0.04 g/kg L-Arg ingested with BCAA reduced the average rate of perceived exertion (RPE) and improved sprint performance in well-trained handball players. However, 6 g/day L-Arg over three days

did not improve intermittent anaerobic exercise in well-trained athletes [27]. A study by Alvares et al. (2014) concluded that supplementing with 6 g L-Arg for four weeks did not change hormonal and metabolic parameters, beyond those achieved with only exercise [28]. Neither did acute 5 g L-Arg nor chronic 5 g L-Arg consumed two times a day for 13 days improved cycling performance in healthy young men [29]. Research suggests that supplementation with L-Arg alone does not improve aerobic athletic performance in well-trained or recreationally active participants; however, combined with other ingredients such as BCAA, L-Arg may improve performance [30].

L-Cit is a non-essential AA that increases L-Arg synthesis bypassing the hepatic metabolism and inhibiting the arginase effect [31–34]. Administration of combined L-Arg and L-Cit may increase circulating L-Arg concentration and rapidly enhance NO bioavailability more effectively than either individual L-Arg or L-Cit, probably due to the synergistic effect of the two AAs [31,35]. Combining the two AAs in supplements enhances performance by reducing energy expenditure, time exhaustion, and increases the power output [35,36]. A study by Chen et al. (2016) reported that combined L-Arg and L-Cit alleviated exercise-induced central fatigue among elite taekwondo athletes [37]. However, the L-Arg and L-Cit ingested in this study were included in a pill containing 0.17 g/kg BCAA.

Supplementing with L-Cit is more effective in increasing plasma L-Arg concentration than supplementing with L-Arg [31,38,39]. L-Cit supplementation prolonged the time to fatigue during high-intensity exercise by promoting ammonia removal and suppression of blood lactate accumulation through the urea cycle pathway [40]. L-Cit was suggested to enhance aerobic pathways by maintaining lower concentrations of plasma lactate [41]. However, a study by Jones (2016) reported that insufficient evidence was available to link increased exercise performance to the increased NO production in response to L-Cit supplementation [20]. Furthermore, several studies claiming that L-Cit supplementation improved exercise performance in recreationally active individuals and well-trained athletes did not use standalone L-Cit [42–45]; instead, they combined it with malate and other components [20]. Most of the available literature has combined L-Cit with malate because of its synergistic combination at the intramuscular level [45–47].

Malate is a tricarboxylic acid cycle intermediate that attenuates lactic acid production and increases energy production [44,48]. It remains challenging to associate the benefit of supplementing with citrulline malate (CM) solely with L-Cit. A study by Trexler et al. (2019) recommended that additional studies are needed to evaluate the efficacy of L-Cit independent of malate [49].

Several review studies conducted to assess the efficacy of L-Arg and L-Cit on NO biomarkers and sports performance included articles that added BCAA or malate for analysis [14,30,46,49–51]. Therefore, this review aimed to evaluate standalone L-Arg and L-Cit efficacy and their combinations on physical performance and physiological and perceptual responses to exercise.

2. Materials and Methods

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 guidelines as a methodological template [52]. It was prospectively registered in an international registry of systematic reviews (PROSPERO registration no. CRD42021287530).

2.1. Study Selection

Four electronic databases (PubMed, Ebscohost, Science Direct, and Google Scholar) were searched for relevant published literature from the database inception to August 2021. The following search terms were used: "Performance", "L-Citrulline", "L-Arginine", "L-Arginine and L-Citrulline", "L-Arginine OR L-Citrulline AND athletic performance", "L-Arginine AND athletic performance", "L-Arginine AND athletic performance AND supplementation", "L-Citrulline AND athletic performance", "L-Citrulline AND athletic

performance AND supplementation", "L-Arginine OR L-Citrulline AND (supplementation or supplements or supplement) AND (athletic performance or sports performance) AND Exercise". Inclusion and exclusion criteria were pre-determined before database searches. The lead author, together with a research assistant (SN and ZN) independently considered each article for its appropriateness for inclusion, which involved screening article titles and abstracts, and checking for duplications using Endnote X9.3.3. After reading titles and abstracts, articles that did not meet the inclusion criteria were excluded from the full text review. Where there was uncertainty regarding the inclusion of specific articles based on the search terms, there was discussion between the two researchers to rule on the article. Otherwise, a third researcher was involved if there were conflicts. Thereafter, full-text screening of articles based on the inclusion and exclusion criteria were conducted. Where there were unresolved conflicts between the two researchers, the third researcher was involved in resolving the dispute. The data extraction process of the included articles was completed using annotated bibliography.

2.2. Inclusion Criteria

Peer-reviewed journal articles published only in English were analyzed in this study. Studies conducted in vitro or in vivo were eligible for inclusion, while observational studies, reviews, abstracts, conference papers, study protocols, or studies that did not report relevant outcome measures were excluded.

Population. Studies that used healthy male and female participants of any age category that led a sedentary lifestyle, were recreationally active, or well-trained athletes, were included.

Intervention. Studies that used standalone L-Arg, L-Cit, or combined both L-Arg and L-Cit as a supplement acutely (single bolus) or chronically (over several days) were included. The supplement could be in any form but had to be orally administered.

Comparison. Studies that compared L-Arg and/or L-Cit against a placebo or a comparator were included.

Outcome measures. Studies were included if (1) blood markers such as serum or plasma L-Cit, L-Arg, and nitrate or nitrite, (2) physical performance, and (3) rate of perceptual responses to exercise were measured following supplementation with standalone L-Arg, L-Cit, or combined L-Arg with L-Cit.

Timeline. Studies published from 2010 to 2021 were included in this study.

Study design. Randomized, double-blind, placebo-controlled studies were considered for this review.

2.3. Exclusion Criteria

Studies that did not use the AAs mentioned above or co-ingested other compounds such as AAs or malate with L-Arg or L-Cit were excluded. Furthermore, studies that did not measure the supplement's effect on exercise performance were excluded from the study (Figure 2).
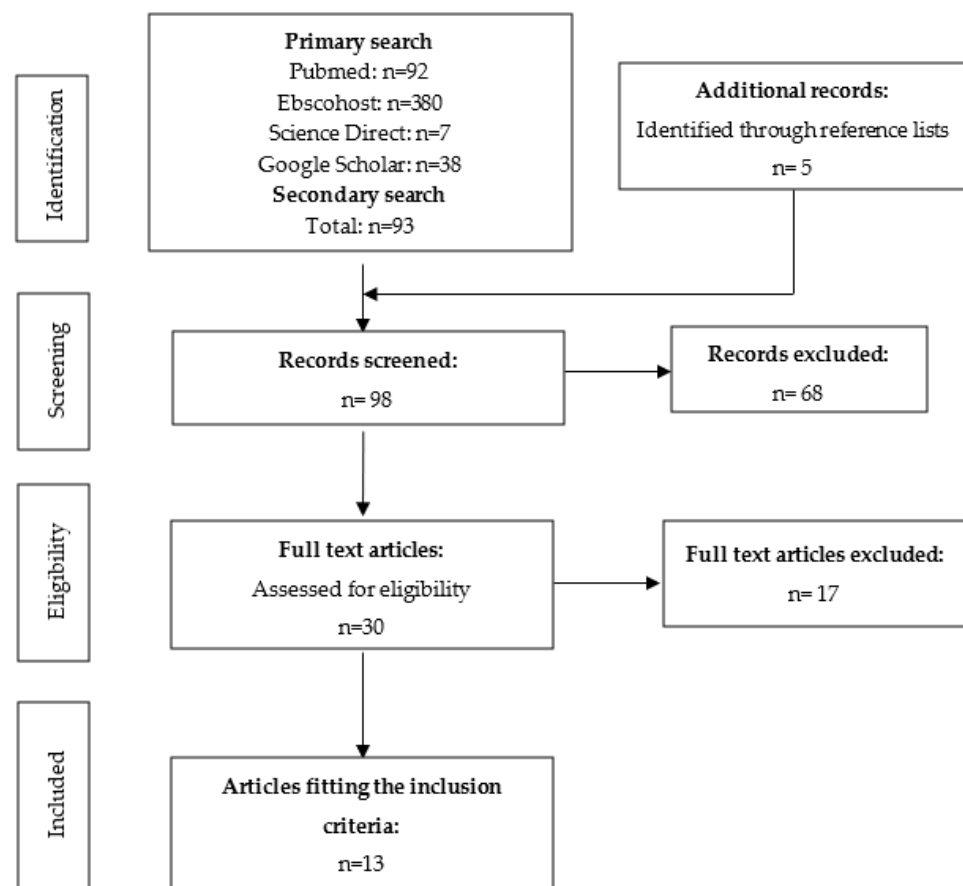
Figure 2. Schematic representation of the flow of information during the different phases of systematic review [52].

3. Results and Discussion

3.1. Study Characteristics

Thirteen articles met the inclusion criteria; six articles used L-Arg [53–58], six articles used L-Cit [59–64], and only one article combined L-Arg and L-Cit [35]. All L-Arg studies used an acute supplementation protocol. One L-Cit study used an acute protocol, while five studies used a chronic supplementation protocol. The combined L-Arg and L-Cit study used a chronic supplement protocol. L-Arg studies used dosages that ranged from 3 to 6 g or 0.075 g/kg of body weight. L-Cit doses ranged from 2.4 to 6 g/day, while the combined study used a dose of 1.2 g L-Arg and 1.2 g L-Cit.

Supplements were administered in capsules with water; powder dissolved in water and ingested as a beverage; and in a watermelon beverage. Ingestion timing ranged from 60 to 120 min before an exercise protocol. The washout period for crossover ranged from 2 days to 2 months. The number of participants in each study ranged from eight to thirty. Male participants dominated most studies [35,53–64], while only two studies included female participants [56,64]. All participants were healthy and physically active, from recreationally active [56,57,62,63] to trained athletes [35,53–55,58–61,64]. See Table 1 for a summary of study details.

Table 1. A summary of studies in the review.

L-Arginine Only

References	Exercise Protocol	Participants	Supplement: Duration of Supplementation	Supplement Timing; Wash out Period for Cross-Over	Main Findings
Forbes et al. [54]	VO$_2$max test on cycle ergometer—graded, incremental exercise to volitional exhaustion	15 males Trained cyclist Age (28 ± 5 years)	Acute (L-Arg 0.075 g/kg); 1 day	60 min before exercise protocol; 7 days washout period	↑ L-Arg, ↔ NOx, ↔ GH ↔ cardio-respiratory parameter measured
Forbes et al. [53]	Resistance exercise (3 sets of 8 exercises, 10 repetitions at ~75% 1 RM)	14 males Resistance trained Age (25 ± 4 years)	Acute (L-Arg 0.075 g/kg); 1 day	60 min before exercise protocol; 7 days washout period	↑ L-Arg, ↓ GH, ↔ RPE
Meirelles and Matsuura [55]	Maximal dynamic strength in the bench press and knee extension (one-repetition maximum (1 rM) test)	12 males Resistance trained Age (27 ± 3 years)	Acute (L-Arg 6 g); 1 day	60 min before exercise protocol; 7 days washout period	↔ NOx, ↔ in strength exercises
Streeter et al. [56]	Five sets of 10 maximal isokinetic extension repetitions of the elbow joint at 90° per second with 30 s of rest in between sets	15 males and 15 females Physically active Age (20.4 ± 1.8 years)	Acute (L-Arg 3 g); 1 day	60 min before exercise protocol; 2 days washout period	↓ in post-exercise elbow extension
Vanhatalo et al. [57]	Ramp incremental running tests on a motorized treadmill	18 males Recreationally active Age (22 ± 3 years)	Acute (L-Arg 6 g); 1 day	95 min before exercise protocol; 10 days washout period	↔ NOx and O$_2$ cost of exercise or exercise tolerance in healthy subjects
Yavuz et al. [58]	Maximal incremental exercise on cycle ergometer starting at—60–70 rpm (increase by 30 watts at every 3 min	9 males Trained wrestlers Age (24.7 ± 3.8 years)	Acute (L-Arg 1.5 g/10 kg); 1 day	60 min before exercise; 7 days washout period	↑ time to exhaustion ↔ Lactate

Table 1. *Cont.*

L-Citrulline Only

References	Exercise Protocol	Participants	Supplementation; Duration of Supplementation	Supplement Timing; Washout Period for Cross-Over	Main Findings
Terasawa and Nakada [59]	Wingate test, using cycle ergometer, was adopted as the intermittent short-time high intensity exercise	9 males Track athletes Age (20.9 ± 1.6 years)	Chronic (L-Cit 3 g/day); 7 days	60 min before exercise protocol; 7 days washout period	L-Cit group; ↓ RPE, ↔ Lactate, ↑ NOx, ↑ mean power output, ↑ pedalling speed, ↑ VO$_2$
Stanelle [60]	Simulated 40-km TT on a cycle ergometer, and supramaximal sprint repeat task (six 1-min sprints at 120% of maximal power)	10 males Cyclists Age (24 ± 3 years)	Chronic (L-Cit 6 g/day); 7 days	120 min before exercise protocol; 7 days washout period	↔ TT time, ↑ average power output, ↑ HR and ↑ RPE
Suzuki et al. [61]	4-km cycling time trial on a cycle ergometer	22 males Mixed athletes age (29 ± 8.4 years)	Chronic (L-Cit 2.4 g/day); 8 days	60 min before exercise protocol; 3 weeks washout period	↑ NOx, L-Cit and L-arg, ↓ TT time, ↓ RPE
Bailey et al. [62]	Cycle ergometer; three "step" exercise tests: two moderate-intensity step tests followed by one severe-intensity exercise bout. Moderate-intensity step tests were completed to assess VO$_2$ economy in the absence of a VO$_2$ kinetics and cycling intensity step tests were completed to assess VO$_2$ presence of a VO$_2$ slow component	10 males Recreationally active Age (19 ± 1 year)	Chronic (L-Cit 6 g/day or L-Arg-6 g/day); 7 days	90 min before exercise protocol; 7–10 days washout period	↑ L-Arg for both L-Arg and L-Cit ↑ Nitrite for L-Arg. ↓ Mean arterial pressure, ↑ tolerance during severe exercise, ↓ lowered the VO$_2$ mean response time, ↑ total amount of work completed in the exercise performance test with L-Cit supple but not with L-Arg

Table 1. *Cont.*

L-Citrulline Only

References	Exercise Protocol	Participants	Supplementation; Duration of Supplementation	Supplement Timing; Washout Period for Cross-Over	Main Findings
Bailey et al. [63]	'Step' exercise tests including one moderate-intensity step test followed by one severe-intensity exercise bout	8 males Recreationally active Age (22 ± 2 years)	Chronic (300 mL/day of a watermelon juice concentrate, which provided ~3.4 g/day L-Cit)	75 min before exercise protocol; 7–10 days washout period	↑ L-Arg, ↑ L-Cit, ↑ nitrite, ↑ skeletal muscle oxygenation index during moderate-intensity exercise. ↑ resting blood pressure ↔ time-to-exhaustion during severe-intensity exercise
Cutrufello et al. [64]	Chest press; maximum number of repetitions at 80% 1 RM for 5 sets with a 30 s rest period between each set. Bruce protocol on treadmill.	11 males and 11 females Mixed athletes Age (20.6 ± 1.2)	Acute (L-Cit 6 g); 1 day	60 and 120 min before exercise protocol; 7 days washout period	↔ number of repetitions, time to exhaustion, VO$_2$max

L-Arginine and L-Citrulline

References	Exercise Protocol	Participants	Supplementation; Duration of Supplementation	Supplement Timing; Washout Period for Cross-Over	Main Findings
Suzuki et al. [35]	PWC75% HRmax, three stages of load (25, 75 and 125 W) for 3 min each (total, 9 min)	20 males Soccer athletes Age (19.0 ± 0.2 years)	Chronic (L-Arg 1.2 g and L-Cit 1.2 g) per day; 7 days	60 min before exercise protocol; 2 months washout period	↑ power output, ↑ L-Cit, ↑ L-Arg, ↑NOx, ↓ RPE

↑ = significantly greater ($p < 0.05$) than placebo; ↓ = significantly lower ($p < 0.05$) than placebo; ↔ = no significant difference ($p > 0.05$) compared to placebo. L-Cit = L-citrulline; L-Arg = L-arginine; RPE = rating of perceived exertion; NOx = plasma nitrate and nitrite; TT = time trial; HR = heart rate; GH = growth hormone.

3.2. Assessment Risk of Bias

　　The risk of bias was assessed using the Physiotherapy Evidence Database (PEDro) scale in Table 2. The PEDro scale evaluates the risk of bias and statistical reporting of randomized controlled trials. This scale used 11 criteria, including external validity (criterion 1), internal validity (criterion 2 to 9), and statistical reporting (criterion 10 to 11). However, criterion 1 was excluded from the total score calculation [65]. Overall, articles showed a low risk of bias as the assessment proved to be optimal, with only one article rated below 8.

Table 2. Results of risk of bias assessment.

Author	Cr1	Cr2	Cr3	Cr4	Cr5	Cr6	Cr7	Cr8	Cr9	Cr10	Cr11	Sum
Forbes et al. [54]	1	1	0	1	1	1	1	1	1	1	1	9
Forbes et al. [53]	1	1	1	1	1	1	1	0	0	1	1	8
Meirelles and Matsuura [55]	1	1	0	1	1	1	1	1	1	1	1	9
Streeter et al. [56]	1	1	1	1	1	1	0	1	1	1	1	9
Vanhatalo et al. [57]	1	1	1	1	1	1	1	1	1	1	1	10
Yavuz et al. [58]	1	1	1	1	1	0	0	1	0	1	1	7
Terasawa and Nakada [59]	1	0	0	1	1	1	1	1	1	1	1	8
Stanelle [60]	1	1	1	1	1	1	1	1	1	1	1	10
Suzuki et al. [61]	1	1	1	1	1	1	1	1	1	1	1	10
Bailey et al. [62]	1	1	1	1	1	1	1	1	1	1	1	10
Bailey et al. [63]	1	1	1	1	1	1	1	1	1	1	1	10
Cutrufello et al. [64]	1	1	1	1	1	1	1	1	1	1	1	10
Suzuki et al. [35]	1	1	1	1	1	1	1	0	0	1	1	8

Cr = criteria; Sum = summation.

3.3. The Effects of L-Arg Supplementation Intervention on Physiological, Perceptual Responses and Physical Performance

3.3.1. Effects of L-Arginine on Nitric Oxide Production

　　Supplementation to increase L-Arg has drawn significant attention for its role in improving exercise performance through increasing NO synthesis [51]. Trained male cyclists ingested 0.075 g/kg L-Arg or a placebo 60 min before completing the submaximal cycling exercise protocol. Plasma metabolites were recorded in different time points including: 0 min (pre-supplementation), 60 min (start of exercise), 120 min (end of exercise/start of rest), and 180 min (end of rest period) [54]. Plasma L-Arg concentration increased from a resting concentration of 273 μM/L to about 679 μM/L at 60 min post-supplementation, and after that progressively decreased to eventually 377 μM/L at 180 min compared to 327 μM/L at 60 min and 265 μM/L at 180 min for the placebo. However, plasma L-Arg concentration was significantly increased for the supplement group compared to the placebo in all eight-time points from 60 min post-supplementation ($p < 0.05$). There were no significant differences in plasma nitrate/nitrite concentration in the supplement group compared to the placebo ($p > 0.05$). At time point 0, plasma nitrate/nitrite concentration was about 11.5 μM/L for the supplementation group and 15.1 μM/L for placebo; at time point 180, plasma nitrate/nitrite concentration was approximately 14.5 μM/L for supplementation group and 13.7 μM/L for placebo. Similarly, ingestion of 6 g/day L-Arg for three days significantly increased plasma L-Arg concentration from 60.1 ± 3.0 μM/L at baseline to 78.9 ± 6.5 μM/L 60 min post-supplementation ($p < 0.001$). Yet, there was no significant difference in plasma nitrate/nitrite concentrations for the supplement group (235.41 μM/L) compared to the placebo group (260.40 μM/L; $p > 0.05$) 60 min post-supplementation

among elite judo male athletes [27]. In a study with 6 g L-Arg acute supplementation, Meirelles and Matsuura (2016) reported no significant changes in plasma nitrate concentration from pre-supplementation values to 60 min post-supplementation and exercise; the supplement group's plasma nitrate concentration slightly increased from 10.95 ± 4.09 to 11.99 ± 2.5 mM compared to the placebo group, which slightly decreased from 13.01 ± 1.18 to 11.83 ± 2.81 mM ($p > 0.05$) among resistance trained physical education students [55].

Vanhatalo et al. (2013) reported no significant changes in plasma nitrite concentrations from the supplement group compared to the placebo at the same time points, 0 to 90 min [57]. Plasma nitrite concentration of the supplement group changed from 204 ± 79 to 241 ± 114 nM ($p > 0.05$) compared to the placebo group, which changed from 223 ± 107 to 222 ± 105 nM ($p > 0.05$). Similarly, ingestion of 6 g L-Arg had no significant differences in plasma NO markers at all-time points for the supplementation group compared to the placebo in healthy male participants (0 min: 17.6 ± 3.9 vs. 14.6 ± 2.3 μM/L; 60 min: 16.8 ± 4.9 vs. 13.7 ± 2.7; 120 min: 15.1 ± 2.8 vs. 13.5 ± 3.5 μM/L; all at $p > 0.05$) [66]. Blum et al. (2000) reported no significant changes in plasma NO synthesis following daily oral administration of 6 g L-Arg or the placebo for one month in healthy adult women (L-Arg: 42.1 ± 24.5 vs. Pla: 39.1 ± 61.1 μM/L; $p > 0.05$) [67]. Based on these studies, a dose of 6 g L-Arg was ineffective in increasing NO. Viribay et al. (2020) suggested that a higher dose might be more efficacious [51]. However, Tang et al. (2011) reported that even 10 g L-Arg supplementation did not significantly change plasma nitrate and nitrite concentration among recreationally active male participants [68]. In support of this, Forbes and Bell (2011) reported that low and high acute doses of L-Arg supplementation had similar effects on plasma L-Arg levels, with neither significantly increasing blood markers of NO synthesis among active young males [69]. Alvares et al. (2012) reported that acute ingestion of L-Arg is insufficient to change systemic NO synthesis [66].

Chronic supplementation with 6 g/day for four weeks among trained runners was not sufficient to significantly increase NO synthesis for the supplement group compared to the placebo group (week 0: 1.9 ± 0.4; week 4: 2.6 ± 0.8 μM/L vs. week 0: 1.8 ± 0.5; week 4: 2.2 ± 0.6 μM/L; $p > 0.05$) [28].

Increasing and maintaining NO synthesis plays a major role in vasodilatory capacity and increases oxygen uptake in skeletal muscle [70]. The possible reason for the limited impact of L-Arg supplementation on NO synthesis may be related to L-Arg metabolism. The level of circulating plasma L-Arg is fundamental to increasing NO synthesis, and depleted plasma L-Arg may fail to upkeep NO synthesis. Augmenting NO production via oral consumption of L-Arg may be compromised. An estimated 60% of L-Arg is metabolized in the gastrointestinal tract, while a further estimated 15% is metabolized by the liver [71]. Alvares et al. (2012) suggested that there should be no need to supplement with L-Arg in healthy participants since sheer vascular stress is considered the main stimulus of endothelial NO synthesis during exercise [66]. Instead, L-Arg supplementation may benefit participants with atherosclerosis risk factors where endothelial dysfunction may impact NO synthesis [66]. Similarly, Chin-Dusting et al. (1996) reported that supplementation with L-Arg may not consistently improve endothelial function and muscle blood flow during exercise among patients [72]. Instead, favorable outcomes such as improvement in cardiac performance were reported in patients with moderate congestive heart failure [73].

3.3.2. The Effects of L-Arginine on Physical Performance and Perceptual Responses to Exercise

A limited beneficial effect was reported for wrestling elite athletes after ingesting a single dose of 1.5 g/10 kg body weight L-Arg capsule or placebo [58]. Time to exhaustion during an incremental test on a cycle ergometer was longer for the supplement group (1386.8 ± 69.5 s) compared to the placebo (1313 ± 90.8 s) ($p < 0.05$). There were no significant differences between the supplement and the placebo group for oxygen consumption (L-Arg: 52.47 ± 4.01 mL/kg/min vs. Pla: 52.07 ± 5.21 mL/kg/min), and heart rate (L-Arg: 181.09 ± 13.57 bpm vs. Pla: 185.89 ± 7.38 bpm) ($p > 0.05$). Pahlavani et al.

(2017)reported that the ingestion of 2 g/kg body weight of L-Arg for 45 days significantly improved maximal oxygen consumption by 4.12 ± 6.07 mL/kg/min compared to the placebo (1.23 ± 3.36 mL/kg/min; $p < 0.05$) among male soccer players [74]. Interestingly, studies that reported significant improvements did not measure plasma concentrations of L-Arg, nitrate, or nitrite. Therefore, the mechanism that led to improvement in physical performance remains questionable in these studies.

Contrary to the reported effect of L-Arg supplementation in improving favorable aerobic capacity outcomes among healthy participants when combined with other components such as aspartate, BCAA, or other amino acids [22,75,76], ingestion of 0.075 g/kg L-Arg 60 min before submaximal cycling exercise had no significant improvement in cardio-respiratory parameters measured at the start and finish of the 60 min cycling protocol among aerobi­cally trained cyclists compared to the placebo [54]. The volume of oxygen consumption had no significant changes in the supplement (start: 35.2 ± 6.5, end: 37.0 ± 6.1 mL/kg/min) or placebo groups, respectively (start: 34.9 ± 6.2, end: 36.5 ± 5.9 mL/kg/min); a non-significant result was also observed regarding heart rate in the supplementation group (start: 137 ± 12, end: 145 ± 14 bpm) and the placebo group (start: 137 ± 13, end: 144 ± 17 bpm) ($p > 0.05$). There were no significant differences between L-Arg and placebo conditions in the diastolic pressure at the start (79 ± 5 vs. 79 ± 8 mmHg) or finish (72 ± 11 vs. 72 ± 10 mmHg), and for systolic pressure at the start (125 ± 7 vs. 125 ± 7.5 mmHg) or finish (161 ± 13 vs. 159 ± 16 mmHg) (all at $p > 0.05$) of the cycling protocol. Another study reported no significant changes in steady-state pulmonary oxygen uptake during moderate-intensity exercise after 6 g L-Arg beverage consumption for the supplement group compared to the placebo group (2.422 ± 333 vs. 2.407 ± 318 m/kg/min; $p > 0.05$), and also no significant changes in the time to tolerate severe exercise (552 ± 150 vs. 551 ± 140 s; $p > 0.05$) [57]. Moreover, chronic L-Arg intake did not improve performance in trained endurance ath­letes [77]. Similarly, consumption of 5 g L-Arg or 5.5 g dextrin twice a day for a total of 13 days yielded no significant differences in mean power output, with a mean difference of 0.5 W during cycling performance ($p > 0.05$) [29]. The apparent ineffectiveness of oral L-Arg supplementation among healthy participants on enhancing physiological responses related to improvement in aerobic performance may be explained by the inability to increase NO synthesis via oral L-Arg supplementation, as discussed in the previous section.

Standalone L-Arg supplementation seems ineffective in improving strength among well-trained athletes or recreationally healthy participants [30]. For instance, growth hormone responses over time were blunted for the supplement group (288.4 ± 368.7 min/ng/mL) com­pared to a placebo (487.9 ± 487.0 min/ng/mL; $p < 0.05$), and there was no difference in RPE between the groups (14 ± 2 vs. 15 ± 2; $p > 0.05$) in resistance-trained athletes who consumed 0.075 g/kg of L-Arg or placebo 60 min prior to performing resistance exercise protocol [53]. Meirelles and Matsuura (2016) did not find significant differences in bench press and isokinetic knee extension performance after administration of 6 g L-Arg or placebo among resistance-trained physical education students [55]. Another study reported a substantial decline in post-exercise elbow extension ($p = 0.014$) and flexion peak torque ($p < 0.001$) after ingestion of 3 g L-Arg among physically active male and female participants [56]. The ineffectiveness of L-Arg may be related to its ability to blunt growth hormone response following exercise [78]. Resistance exercise alone is a potent stimulator of growth hormone release [79]. While L-Arg has been shown to increase growth hormone-releasing hormone, it does suppress endogenous growth hormone-inhibiting hormone and increases insulin-like growth factor 1 [80,81]. However, oral administration of L-Arg does not augment exercise-induced growth hormone increase [82]. Furthermore, growth hormone response to specific amino acid consumption is reportedly reduced in well-trained athletes [83]. A study by Alvares et al. (2014) suggested that only chronic L-Arg supplementation could stimulate growth hormone production in physically active participants [28]. Consistent with this suggestion, chronic L-Arg supplementation of about 1.5 to 2 g/day improved aerobic and anaerobic performance [51]. A study by Campell et al. (2006) reported that a chronic supplementation protocol might be effective for enhancing maximum bench press

in strength-trained male participants [84]. However, a number of studies that reported the effectiveness of chronic L-Arg consumption had other active ingredients in the supplement, such as aspartate, ornithine, and alpha-ketoglutarate [75,77,81,85]. A study Hurst and Sinclair (2014) claimed that all the current literature that reported significant improvement with L-Arg supplementation had combined it with other compounds [86]. Furthermore, other authors reported no benefit of acute or chronic supplementation protocol of L-Arg 6 g/day for muscle strength, endurance, or the maximum number of repetitions [87].

3.4. The Effects of L-Citrulline Supplementation on Physiological, Perceptual Responses and Physical Performance

Supplements containing citrulline are commonly found in three different forms: standalone L-Cit, citrulline malate, and watermelon juice [46]. Oral L-Cit supplementation increases plasma L-Arg concentrations, increasing NO synthesis [88]. L-Cit supplementation restores NO production when L-Arg availability is limited [89].

3.4.1. Effects of L-Citrulline on Nitric Oxide Synthesis

While clinical studies examining supplementation effects across several different chronic conditions, including obesity, heart failure, and arterial stiffness, reported consistent significant increases in plasma nitrate and nitrite following acute or chronic L-Cit supplementation [90–92], the effect is inconsistent among healthy participants [51]. The increase in blood nitrate and nitrite concentration after L-Cit supplementation seems to be dose- and duration-dependent [63,93]. Consumption of 3.4 g/day L-Cit from watermelon juice for 16 days increased plasma L-Arg (116 ± 9 μM) compared to placebo (67 ± 13 μM) ($p < 0.001$) and plasma nitrite (201 ± 106 nM) compared to placebo (106 ± 21 nM) ($p < 0.05$) among recreationally active participants [63]. Consistent with these findings, consumption of 3 g/day L-Cit for seven days increased plasma nitrate/nitrite concentration on day 7 (35.2 ± 14.2 μM), compared to day 0 (22.4 ± 9.1 μM; $p < 0.05$) among track athletes [59]. However, most studies have demonstrated no changes in NO biomarkers in response to supplementation. For instance, Bailey et al. (2015), compared the effects of L-Cit 6 g/day against L-Arg 6 g/day and a placebo on NO biomarkers among recreationally active male participants [62]. Participants ingested 6 g L-Cit and 4.3 g maltodextrins, 6 g L-Arg and 4.3 g maltodextrins, or a placebo in 10.7 g maltodextrin for seven days. Following L-Cit supplementation, plasma L-Cit concentration significantly increased (665 ± 205 μM) compared to L-Arg (26 ± 6 μM) and the placebo (23 ± 5 μM; $p < 0.001$). Plasma L-Arg concentration significantly increased similarly in both L-Arg (151 ± 14 μM) and L-Cit (135 ± 22 μM) compared to the placebo (57 ± 14 μM; $p < 0.001$). Plasma nitrite concentration following L-Cit supplementation showed improvement yet did not significantly increase (100 ± 38 nM) compared to L-Arg (106 ± 41 nM; $p = 0.08$), and significantly increased after L-Arg supplementation (106 ± 41) compared to the placebo (83 ± 25 nM; $p < 0.05$). Similarly, consumption of 2.4 g/day L-Cit for eight days significantly increased plasma L-Arg concentrations after cycling exercise protocol in the supplement group compared to the placebo group among trained male participants (192 ± 9 vs. 110 ± 4 nM/mL; $p < 0.001$) [61]. However, there was no difference in plasma nitrate and nitrite concentration in the supplement group compared to the placebo group ($p > 0.05$). Plasma NO was also not significantly different in the supplement group (58.4 ± 7.3 nmol/L^{-1}) compared to the placebo group (59.4 ± 13.6 nmol/L^{-1}) among swimmers, following eight days of supplementation with 8 g L-Arg or placebo ($p = 0.20$) [94]. A study by Hickner et al. (2006) reported a significant decrease in the plasma nitrate/nitrite concentration of the supplement group (21.18 ± 2.29) compared to the placebo group (24.58 ± 3.03 μM/L; $p < 0.05$) following ingestion of 3 or 9 g L-Cit and submaximal exercise protocol among recreationally active participants [95]. These findings contradict the reported efficacy of L-Cit to increase NO synthesis via increasing L-Arg bioavailability in healthy, active individuals.

3.4.2. Effects of L-Citrulline on Physical Performance and Perceptual Responses

An L-Cit dose of at least 3 to 4 g ingested 60 min before exercise is purported to be sufficient to alleviate fatigue [50]. In a systematic review and meta-analysis, Trexler et al. (2019) concluded that acute citrulline supplementation benefits high-intensity strength and power performance [49]. However, most analysed articles in these reviews examined the effects of co-ingested malate with L-Cit. Based on the predetermined inclusion criteria, one article focused on the effect of L-Cit supplementation on resistance exercise performance. A study by Cutrufello et al. (2015) reported that a single dose of 6 g L-Cit consumed with a sucrose mixture 60 and 120 min before athletes completed 1 RM and graded exercise on a treadmill was not enough to improve exercise performance [64]. In that study, there were no significant changes in the number of repetitions during the chest press test (32.2 ± 11.4) compared to the placebo sucrose mixture (32.2 ± 10.5; $p = 0.51$). A study by Figueroa et al. (2017) reported that acute L-Cit does not enhance high-intensity exercise performance [47].

Similarly, ingestion of 2 g/day L-Cit for eight weeks combined with a strength training programme did not significantly improve bench press performance among resistance-trained male participants [90]. Unlike when co-ingested with malate, standalone L-Cit may not effectively increase strength performance. Potentially, the performance improvement may be related to malate's ability to increase the rate of ATP production and reduce lactate production during high-intensity anaerobic exercise [44].

Consumption of 6 g L-Cit before completion of a graded exercise test on a treadmill did not significantly change the time to exhaustion in the supplement group compared to the placebo (568 ± 96 vs. 559 ± 101 s; $p = 0.41$) and maximal oxygen consumption (4.0 ± 0.9 L/min vs. 4.0 ± 0.8 L/min; $p = 0.52$) [64]. A single dose of 6 g L-Cit may not be enough to improve aerobic or anaerobic performance among healthy, trained athletes [46,64]. However, 8 g of L-Cit consumed over eight days was not enough to improve 100 m or 200 m swimming time trial among swimmers [94]. A lack of endothelial dysfunction might explain the ineffectiveness of acute L-Cit supplementation among healthy young participants, who may benefit less from augmented NO synthesis [47,95]. L-Cit may be more effective when taken over several days than as a single bolus supplementation [30]. However, consuming 3.4 g/day L-Cit from watermelon juice concentrate over 16 days seems to have increased systolic blood pressure after supplementation compared to the control group (130 ± 11 vs. 124 ± 8 mmHg; $p < 0.05$). There were no differences in time to exhaustion for the supplement group compared to the placebo group during the severe intensity exercise test (550 ± 143 vs. 539 ± 108 s; $p > 0.05$), despite increased plasma nitrite concentrations following supplementation [63]. In contrast, consumption of 6 g/day L-Cit for four weeks significantly attenuated systolic blood pressure in the supplementation group compared to placebo (133 ± 5 vs. 139 ± 4; $p < 0.05$) among healthy young men [91]. Furthermore, other studies have demonstrated decreased systolic blood pressure following L-Cit supplementation [92,96,97].

In one particular study, trained male cyclists consumed 6 g/day L-Cit or maltodextrin powder as a placebo for 7 days. On the final day, two hours after the last dose of the supplement, participants engaged in a cycling performance evaluation. In that study, time trial performance improved by 5.2% ($p = 0.08$), while average power output improved by 5.4% ($p < 0.05$) compared to the placebo [60]. Furthermore, the supplement group's average heart rate increased (159 ± 10 vs. 150 ± 13 bpm) and average RPE increased (16 ± 1 vs. 15 ± 1; $p < 0.05$) compared to the placebo. A similar dose of 6 g/day L-Cit lowered the mean arterial pressure in the supplementation group compared to the placebo (85 ± 2 vs. 87 ± 3 mmHg; $p < 0.05$) and reduced the volume of oxygen consumption mean response time (54 ± 5 vs. 60 ± 8 s; $p < 0.05$). At the same time, total work completed increased during the test for the supplementation group compared to the placebo (125 ± 19 vs. 123 ± 18 kJ; $p < 0.05$), and tolerance to severe intensity exercise significantly improved for the supplementation group compared to placebo (661 ± 107 vs. 589 ± 101 s; $p < 0.05$) among recreationally active participants [62]. Interestingly, in this study, plasma nitrate and nitrite only tended to be significant; suggesting that increased tolerance to severe intensity

exercise may result from a different mechanism. As an amino acid intermediate, L-Cit reportedly plays an essential role in the urea cycle in reducing ammonia toxicity in the muscles. Takeda et al. (2011) reported that L-Cit supplementation attenuated exercise-induced blood ammonia levels during high intensity exercise in rabbits and in mice, and suggested that human participants may gain similar effects [40].

In another study, a dose of 3 g/day L-Cit for seven days reportedly decreased the RPE ($p = 0.015$), while mean power output ($p = 0.046$) and oxygen consumption ($p = 0.007$) increased after an intermittent short time duration high-intensity protocol for the L-Cit group compared to the placebo group among collegiate track athletes [59]. The effectiveness of L-Cit was also reported in response to a low dose of 2.4 g/day consumed for eight days by athletes; cycle ergometer time trial performance completion time was reduced by 1.5%, while mean power output was increased by 2% in the treatment group compared to the placebo group ($p < 0.05$) [61]. In that study, subjective feelings of fatigue and concentration also improved for the supplement group compared to the placebo. A study by Martínez-Sánchez et al. (2017) reported that L-Cit supplementation is vital to attenuate post-race muscle soreness and enhance aerobic pathways, resulting in lower plasma lactate concentrations during a half-marathon race [41]. The decreased plasma lactate was supported by reduced muscle glycogen utilisation during exercise, which suggested less reliance on anaerobic glycolysis for energy production [40]. L-Cit supplementation enhances oxidative production of ATP by inhibiting additional glycolysis by suppressing ammonia levels, thereby preventing activation of phosphofructokinase, which is a crucial marker for anaerobic glycolysis [41].

3.5. Effects of Combined L-Arginine and L-Citrulline Supplementation on Physiological, Perceptual Responses and Physical Performance

Few studies have assessed the efficacy of a combined L-Arg and L-Cit supplement on physiological responses and exercise performance [14]. Studies have combined L-Arg and L-Cit with BCAA at a ratio of 1:1 for L-Arg and L-Cit [37,98,99]. Based on the pre-determined inclusion criteria, only one study was included for analysis in the current review.

3.5.1. Effects of Combined L-Arginine and L-Citrulline on Nitric Oxide Synthesis

Male collegiate soccer players ingested 1.2 g L-Arg and 1.2 g L-Cit or placebo in granulated powder in a stick packet for seven days and then performed a cycling test [35]. In the supplement group, the plasma concentration of nitrite significantly increased post-exercise (45.2 ± 2.4 μM) compared to the placebo (37.8 ± 2.4 μM; $p < 0.05$). Supplementing with combined L-Arg and L-Cit reportedly demonstrates a synergistic effect [14,34]. L-Cit acts as a strong allosteric inhibitor, as it has an inhibiting effect on arginase, which metabolises L-Arg to urea and L-ornithine [31]. According to Khalaf et al. (2019), augmenting L-Arg as a substrate for NOS-3 maintains NO production, while L-Cit activates NOS-2 and indirectly activates NOS-1 in skeletal muscle leading to heightened NO synthesis [100]. However, a combination of 1 g L-Arg and 1 g L-Cit in a capsule for eight days was insufficient to increase plasma nitrate and nitrite concentration among healthy male participants, while plasma L-Arg concentrations reportedly increased [31]. This may be due to the ratio being 1:1 of L-Cit to L-Arg, instead of the recommended effective 2:1 ratio of L-Cit to L-Arg [14].

3.5.2. Effect of Combined L-Arginine and L-Citrulline on Physical Performance and Perceptual Responses

Ingestion of combined 1.2 g L-Arg and 1.2 g L-Cit or placebo in a granulated powder for seven days before completing a cycle ergometer test significantly increased power output (242 ± 24 vs. 231 ± 21 W; $p < 0.05$) and reduced subjective perception of ease of pedaling (5.8 ± 1.8 vs. 6.9 ± 19; $p < 0.05$) compared to the placebo among soccer players [35]. L-citrulline supplementation may also improve force production during anaerobic performance [101]. Similar effects on anaerobic performance are evident. Specifically, taekwondo athletes performed high-intensity intermittent exercise on a cycle ergometer to mimic taekwondo match physiological demands for 60 min following ingestion of amino acid

pills or placebo [37]. Their premotor reaction time was significantly faster (0.139 ± 0.016) in the supplement group compared to the placebo (0.162 ± 0.010 s; $p < 0.001$). In a similar supplementation protocol, the supplement group of the high school swimmers was faster in the first lap (30.47 ± 0.47 s) compared to the placebo group (31.34 ± 0.57 s; $p < 0.001$) during a high-intensity interval swimming protocol.

4. Limitations

It is essential to note the limitations associated with the studies included in this review. Not all studies measured plasma nitrate and nitrite concentrations, while one study indirectly measured NO bioavailability by using proximal cuff placement to assess flow-mediated vasodilation. Other studies did not specify if participants were restricted from using an antiseptic mouthwash during the study protocols. Antiseptic mouthwash may hinder the full effect of L-Arg by disrupting the enterosalivary cycle of nitrate [102].

5. Conclusions and Recommendations

Based on the included studies, an L-Arg supplementation dose of 0.075 g/kg or 6 g did not increase NO synthesis or improve physical performance and perceptual feelings of exertion among recreationally active and trained athletes.

Beverages or capsules containing 2.4 to 6 g/day L-Cit consumption over 7 to 16 days increased NO synthesis, improved physical performance markers, and reduced feelings of exertion. However, the consumption of beverages containing 6 g L-Cit did not improve physical performance markers.

The consumption of a beverage containing L-Arg and L-Cit over several days effectively increased NO synthesis, improved physical performance markers, and reduced perceptual feelings of exertion. However, this response to a combined L-Arg and L-Cit beverage requires verification.

Combined L-Arg and L-Cit trials are limited; as such, future research is recommended to study the efficacy of various doses of acute and chronic supplementation on physical performance, and physiological and perceptual responses. Secondly, it is recommended that future efficacy studies of L-Arg or L-Cit measure and report on changes in plasma nitrate or nitrite from supplementation to help justify its efficacy in improving physical performance.

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