The effects of citrulline supplementation on athlete´s performance: systematic review

Efectos de la suplementación con citrulina en el rendimientos de los atletas: revisión sistemática

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Abstract

Background: Citrulline is a non-essential amino acid that may enhance exercise performance and reduce soreness after exercise. This systematic review aims to determine the possible outcomes of L-citrulline of citrulline malate supplementation.
Methods: The effects of L-citrulline or Citrulline Malate on trained individuals or professional athletes were examined in a comprehensive literature search using PubMed from 2010 to 2023. A total of 10 studies that met the inclusion and exclusion criteria were selected. Randomized and double-blind study designs were used to include in this review.
Findings: L-citrulline or citrulline malate supplementation produced either positive or negative effects. By boosting repetitions, lowering RPE, or reducing muscular exhaustion, six out of ten trials found that taking L-citrulline or citrulline malate improved performance. However, four out of ten studies found that taking L-citrulline or citrulline malate only has a minor or nonexistent advantage.
Discussion: Nearly half of them reported no differences, while the other half reported successes. Numerous studies have shown that citrulline supplements minimize muscular soreness. Some research claims to have accomplished more repetitions, whilst other studies claim that there has been no difference in the number of repetitions attained.
Conclusion: Supplementing with L-citrulline or citrulline malate is still debatable. Regarding whether it truly works or not in certain sports, there were no definitive responses. Additional research is required on this subject as these data are insufficient to draw any meaningful conclusions.

Keywords

Citrulina-malate; L-citrulina; performance; supplementation.

Resumen

Introducción: La citrulina es un aminoácido no esencial que puede mejorar el rendimiento en el ejercicio y reducir el dolor muscular posterior al ejercicio. Esta revisión sistemática tiene como objetivo determinar los posibles resultados de la suplementación con L-citrulina o citrulina malato.
Metodología: Se examinaron los efectos de L-citrulina o citrulina malato en individuos entrenados o atletas profesionales mediante una búsqueda exhaustiva de literatura en PubMed desde 2010 hasta 2023. Se seleccionaron un total de 10 estudios que cumplían con los criterios de inclusión y exclusión. Los diseños de estudios aleatorios y doble ciego fueron utilizados para ser incluidos en esta revisión.
Resultados: La suplementación con L-citrulina o citrulina malato produjo efectos tanto positivos como negativos. Al aumentar las repeticiones, reducir el RPE (percepción del esfuerzo) o disminuir la fatiga muscular, seis de los diez ensayos encontraron que la ingesta de L-citrulina o citrulina malato mejoró el rendimiento. Sin embargo, cuatro de los diez estudios encontraron que la ingesta de L-citrulina o citrulina malato solo tuvo una ventaja menor o inexistente.
Discusión: Casi la mitad de los estudios no reportaron diferencias, mientras que la otra mitad reportó eficacia. Numerosos estudios han mostrado que los suplementos de citrulina reducen el dolor muscular. Algunas investigaciones afirman haber logrado más repeticiones, mientras que otros estudios indican que no hubo diferencia en el número de repeticiones alcanzadas.
Conclusión: La suplementación con L-citrulina o citrulina malato sigue siendo un tema debatido. En cuanto a si realmente funciona o no en ciertos deportes, no se encontraron respuestas definitivas. Se requiere más investigación sobre este tema, ya que estos datos son insuficientes para sacar conclusiones significativas.

Palabras clave

Citrulina malato; L-citrulina; rendimiento; suplementación.

Introduction

Impaired endothelial vasodilation mediated by nitric oxide is one of the first indicators of the onset of cardiovascular disease (Gamboa et al., 2016). Through the nitric oxide-L arginine pathway, the endothelium, the innermost layer of cells in the arterial wall, plays a significant role in controlling blood pressure and organ blood circulation (Vanhoutte et al., 2016; Wijnands et al., 2015; Zhao et al., 2015). Nitric oxide acts on a variety of physiological processes, including mitochondrial respiration, glucose uptake, calcium release from the sarcoplasmic reticulum, and muscle fatigue (Ramos et al., 2021). Vasodilation is the primary physiological effect of nitric oxide related to physical exercise, which increases the supply of oxygen and energy substrates to the active muscles (Joyner et al., 1997, Poderoso et al., 2019; Heunks et al., 2001; Smith et al., 2002). Nitric oxide-stimulating nutritional supplements (such as L-citrulline and L-arginine) have been recommended to improve performance during high-intensity exercises because of these numerous physiological effects (Bailey et al., 2015; Viribay et al., 2020). Dietary L-arginine supplementation may not be a useful method for producing nitric oxide. Since the enzyme arginase hydrolyzes L-arginine to urea and L-ornithine, considerable catabolism of L-arginine occurs (Wijnands et al., 2015; Zhao et al., 2015; Moinard et al., 2016).

L-citrulline is a non-essential amino acid that the body produces endogenously via two major metabolic pathways. L-citrulline can be produced in the intestine from the amino acid glutamine. L-citrulline can also be generated by converting L-arginine to nitric oxide via nitric oxide synthase enzymes (van de Poll et al., 2004). The supposed advantage of L-citrulline supplementation is that it is efficiently recycled into L-arginine, the substrate for endothelial nitric oxide synthase. Orally taken L-citrulline, unlike pure L-arginine, is not systemically degraded by the liver. L-citrulline also blocks arginase, the principal catabolic enzyme of L-arginine, allowing L-citrulline to produce larger plasma levels of L-arginine over L-arginine alone.

Increased L-arginine and nitric oxide generation with L-citrulline supplementation may be especially useful to endurance athletes since increased blood flow enhances oxygen supply to contracting skeletal muscles. Ammonia clearance may be enhanced by L-citrulline, one of the amino acids involved in the urea genesis cycle. Because of the intracellular accumulation of ammonia that promotes glycolysis while blocking the aerobic use of pyruvate (Pérez-Guisado et al., 2010; Tarazona-Diaz et al., 2013). Lactate is produced because of this modified energy metabolism, which may lead to fatigue (Fitts, 1994; Allen et al., 2008). The rate of glycolysis increases within high-intensity workouts, and anaerobic glycolysis also causes blood lactate to accumulate (Allen et al., 2008). Since L-citrulline buffers ammonia through the urea cycle, it increases the aerobic use of pyruvate, which may reduce the production of lactate (Callis et al., 1991). It has been proposed that citrulline supplementation may enhance ammonia homeostasis, therefore enhancing muscular performance, given that urea is the major mechanism for eliminating ammonia, a stimulator of muscle tiredness (Breuillard et al., 2015). However, depending on the supplementation strategy utilized, testing this assumption has had inconsistent outcomes (Stanelle et al., 2020). Improved lactate and ammonia clearance during exercise has also been linked to increased plasma L-citrulline (Schaefer et al., 2002). L-citrulline supplements have been made in a variety of forms, including pure L-citrulline, watermelon juice, and citrulline malate, and their benefits have been examined in clinical and applied exercise contexts.

Citrulline malate is a combination of L-citrulline and malic acid and is a very popular form of supplement use among athletes. Watermelon (*citrullus vulgaris*) is the primary dietary source of citrulline, whereas malic acid is found in apples (m*alus pumila*) and grapes (vitis vinifera) (Curis et al., 2005). Citrulline malate was initially used as a pharmaceutical drug to treat asthenia patients to reduce recovery time after physical activity. Athletes' constant pursuit for competitive benefit has resulted in the foundation of citrulline malate as a potential ergogenic supplement. Citrulline malate has been shown to increase performance in both training modalities aerobic and anaerobic through several mechanisms, including increased ammonia and the metabolism of lactic acid, increased capacity of oxygen delivery through improved vasodilation, and increased production of adenosine triphosphate via increases in intermediates in Krebs-cycle (Curis et al., 2005; Bendahan et al., 2002).

Chronic citrulline malate supplementation has been demonstrated to increase skeletal muscle power output along with an increase in oxidative energy turnover and a decrease in pH-to-power ratio (Bendahan et al., 2002) and a reduced ATP cost for generating muscular force (Giannesini et al., 2011).

These findings imply that short-term supplementation with citrulline malate may enhance contractile function and/or skeletal muscle metabolism, which would be predicted to increase fatigue resistance. However, considering citrulline was given as citrulline malate in these tests and because malate is a crucial tricarboxylic acid cycle intermediary, it is possible that malate by itself could have an impact on muscle performance (Wagenmakers, 1998). Therefore, this systematic review aims to examine whether L-citrulline or citrulline malate significantly enhances performance in athletes.

Method

Search Strategy

This systematic review follows the requirements of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement. A systematic literature search was performed using PubMed to identify articles published from 2010 to 2023 that evaluated the effects of L-citrulline or citrulline malate on trained people or professional athletes. The following terms were included in the search formula: L-citrulline OR citrulline malate AND trained OR performance OR athletes OR endurance OR weightlifting. To ensure that all relevant studies were included in the analysis, a manual search was done using reference lists of the identified relevant articles.

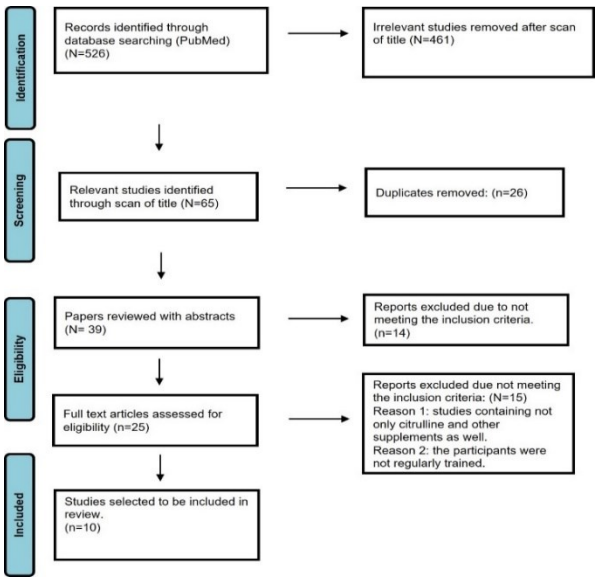
Study Selection Criteria

Inclusion and exclusion criteria were applied to the papers to ensure that relevant journal articles were selected for the review. Studies were considered for inclusion criteria if they met all of the following requirements: (a) studies that examined the effects of L-citrulline or citrulline malate, (b) studies that used actively trained participants, (c) using a randomized controlled trial design with one group receiving supplementation and one or more groups receiving a placebo or not receiving supplementation, (d) data of changes in RPE, blood lactate or muscle soreness as a result of exercise. Studies that did not meet the inclusion criteria were excluded, such as studies that were conducted on animals, children, and non-athletic individuals, or if the study's supplementation protocol included a combination with other substances and not just citrulline.

Data Extraction and Outcome Measures

For each paper, the study parameters, such as type and number of participants, types of exercise tests performed, supplementation regimens for L-citrulline or citrulline malate, and main (RPE and muscle soreness) or secondary (blood lactate level), were manually collected.

Figure 1. Prisma flow diagram illustrating the selection process.



Results

All the studies included were found through Pubmed. A total of 10 studies were extracted to be reviewed. Data and evidence from research were narratively synthesized, and data were presented using a PRISMA flow diagram, which visualized the number of studies detected, evaluated, chosen, and eliminated (Fig. 1)

Study Characteristics

A systematic literature search using database searching found 526 results. The title and abstract screening found 65 results for full-text consideration. Following full-text screening, 10 papers met the quality, inclusion, and exclusion criteria and were chosen for this systematic review. Table 1 provides a summary of participant and study characteristics. Only 1 study included master aged athletes (Glenn et al., 2016), 2 studies included only females (Glenn et al., 2017; Glenn et al., 2016) and 2 studies included both female and male athletes (Chappell et al., 2018; Esen et al., 2022). The rest included only male athletes (Stanelle et al., 2020; Suzuki et al., 2016; Cunnife et al., 2016; Pérez-Guisado et al., 2010; Wax et al., 2015; Wax et al., 2016).

Main Outcomes

The use of L-citrulline or citrulline malate supplementation had either beneficial or non-beneficial outcomes according to the studies. 6 out of 10 studies suggested that using L-citrulline or citrulline malate had a positive effect on performance by increasing the repetitions and decreasing the rating of perceived exertion (RPE) or muscle fatigue (Suzuki et al., 2016; Pérez-Guisado et al., 2010; Glenn et al., 2017; Wax et al., 2015; Wax et al., 2016; Glenn et al., 2016). However, 4 out of 10 studies showed that there is little or does not have any benefit of using L-citrulline or citrulline malate (Stanelle et al., 2020; Cunniffe et al., 2016; Chappel et al., 2018; Esen et al., 2022). Only 1 study also mentioned that citrulline malate led to gastrointestinal discomfort (Pérez-Guisado et al., 2010). Stanelle et al., (2020) concluded that citrulline supplementation did not prevent muscle fatigue during supramaximal sprint repeat tasks, however, it increased the average heart rate, average power and RPE. Suzuki et al. (2016) stated that L-citrulline usage increased plasma L-arginine levels and decreased 1.5% of completion time. Moreover, they also reported that L-citrulline decreased muscle soreness and increased concentration right after exercise. On the other hand, Cunniffe et al. (2016), supported that there were no changes in muscle fatigue and time to exhaustion. Chappel et al. (2018), also concluded no change in muscle fatigue due to citrulline supplementation and even they supported that it increased muscle soreness up to 72 hours. Moreover, they also found that there was no difference in the number of repetitions and blood lactate levels. However, Peréz-Guisado et al. (2010), stated there was a 40% decrease in muscle soreness in the first 24 hours and even in the 48 hours it increased up to 90% because of citrulline malate supplementation. Glenn et al. (2015) also found citrulline malate supplementation may increase resistance exercise capacity while decreasing RPE. Moreover, Wax et al. (2015), found in both of their studies; participants who got citrulline supplementation performed more repetitions. Glenn et al. (2016) in their another study, found that citrulline malate led to better average and maximal grip strength, time trials, peak power, and explosive power but no difference in peak or average vertical power across trials. Finally, Esen et al. (2022), also stated no notable change in plasma nitric oxide levels and in the 200 m and 100 m swimming time trials. The results are shown in more detail in Table 1.

Table 1. Study characteristics.

Study	Study Design	Subjects	Exercise Protocol	Supplement Protocol	Aim	Results
Stanelle et al. (2020)	Randomized, double-blind, placebo-controlled, Crossover study design	Male trained cyclists, N= 9, Age(y) =24±3 Height(cm)=181±7 Weight(kg) = 76 ±13	Simulated 40-kilometer time trial on a cycle ergometer. Supramaximal sprint repeat test consisting of six 1-minute sprints at 120% of maximum power.	6-g/day of L-citrulline 2 hours before exercise	The aim of this study is to determine whether prolonged supplementation with pure L-citrulline enhances cycling performance over a	Throughout the cycling time trial, L-citrulline caused a substantial rise in average heart rate, average rating of perceived exertion, and average power throughout the cycling time trial ($p<0.05$). However, L-citrulline supplementation had no effect on fatigue during the supramaximal sprint repeat task. As a

					maltodextrin placebo.	result, L-citrulline supplementation produce a little enhancement in endurance cycling performance in trained cyclists
Suzuki et al. (2016)	Randomized, double-blind placebo-controlled, 2-way crossover study design	Trained male N=22, Age (y) =29 ± 8.4 Body mass (kg)=74 ± 9.4 Height (cm)= 175 ± 4.1	4-km cycling time trial (TT) on a cycle ergometer.	2.4 g/day of L-citrulline	The aim of this study is to investigate the impact of oral L-citrulline supplementation on human cycling time trials.	When compared to placebo, L-Citrulline supplementation substantially boosted plasma L-arginine levels and decreased completion time by 1.5% (p 0.05). Furthermore, L-citrulline enhanced subjective symptoms of muscular tiredness and concentration directly after exercise.
Cunnife et al. (2016)	Randomized double-blind placebo-controlled crossover study design	Healthy well-trained men N=10, Age(y)=23.5±3.7, Height (m)= 1.81±0.1 Body mass (kg)=80.7±10.4	10 (x15 seconds) maximum cycle sprints (with 30-second rest intervals).	12 gr of Citrulline Malate 1 hour before completion of 2 exercise trials.	The goal of the study is to see how citrulline malate supplementation affected acid-base balance and high-intensity exercise performance.	Blood pH, PCO2, TCO2, HCO3, and base excess were all significantly lower soon after exercise. During testing, no significant variations in any acid-base balance marker were identified. Acute consumption of citrulline malate (12 g) did not reduce fatigue caused by repeated high-intensity cycling nor did it extend the time to exhaustion.
Pérez-Guisado et al. (2010)	Randomized, double-blind, 2-period crossover study design	Healthy well-trained men N=41, Age(y)= 29.80±7.64, Weight (kg)= 81.12 ±17.43	2 consecutive pectoral training session protocols (16 sets). Rest for 1 minute between sets and for 2 minutes between each exercise.	8 gr of Citrulline Malate 1 hour before exercise.	The goal of the study was to see how a single dosage of citrulline malate affected the outcome of flat barbell bench presses as an anaerobic workout and how it affected muscle soreness thereafter.	Citrulline malate supplementation resulted in a 40% reduction in muscle soreness 24 hours and 48 hours after the pectoral training, as well as a higher percentage response than 90%. The only negative effect noted by 14.63% of the subjects was gastrointestinal discomfort.
Glenn et al. (2015)	Randomized, double-blind, crossover study design	Resistance trained females N= 15, Age= 23±3 (y); Height(cm)= 162.6±19.2, Weight (kg)= 67.1±7	6 sets of upper-body (ex. bench press) and lower-body (ex. leg press) exercises until failure at 80% of one-repetition maximum previously attained.	8 gr of Citrulline Malate + Dextrose 1 hour before exercise.	The goal of this study was to determine how an 8 g acute dose of oral citrulline malate supplementation affected upper and lower-body submaximal resistance exercise capacity to exhaustion among trained female weightlifters.	In females, acute citrulline malate supplementation improved upper- and lower-body resistance exercise capacity while decreasing the rate of perceived exertion during upper-body training. These findings suggest that athletes engaged in sports requiring muscular endurance may benefit from acute supplementation with citrulline malate.
Wax et al. (2015)	Randomized, counterbalanced, and double-blind study design	Resistance trained males N= 12, Age (y)= 22.1±1.4 Height (m)= 179±0.10 Weight (kg)= 84.8±10.9	5 sets of leg press, hack squat, and leg extension machines to failure (60% 1 repetition maximum).	8 gr of Citrulline Malate 1 hour before exercise.	The purpose of this study was to determine the effects of citrulline malate supplementation on the performance of lower-body resistance exercise, heart rate, blood	When compared to the placebo group, those who consumed citrulline malate noticed less fatigue in the working muscles, leading them to do more repetitions. Furthermore, neither the citrulline malate nor the placebo supplementation increased heart rate, blood lactate, or

					pressure, blood lactate.	blood pressure in this research.
Chappell et al. (2018)	Randomized double-blind placebo cross-over study design	Moderately trained females and males N=15, Sex= 11M, 4F Age (y) = 23.67±2.41 Height (m)= 1.72±0.10 Weight (kg)= 75.15± 13.67	3 sets of 3 isometric, concentric, and eccentric maximum voluntary contractions each, with a 3 minute rest between sets.	8 gr of Citrulline Malate 1 hour before exercise.	The purpose of this study was to test subjects' ability to resist fatigue while resistance exercise after an acute dosage of citrulline malate with the following key end measures: total number of repetitions, muscular soreness, and blood lactate.	The acute dose of citrulline malate was given one hour prior to resistance training and had no effect on the number of repetitions performed. Moreover, citrulline malate not only did not reduce the marker of muscular soreness, but it was also related with increased soreness 72 hours after exercise. Furthermore, citrulline malate supplementation had no influence on blood lactate levels after exercise.
Wax et al. (2016)	Randomized counterbalanced, double-blind study design	Resistance trained males N=14, Age (y) = 23.3 ± 1.5 Height (m) = 1.79±0.07 Weight (kg) = 87.8 ± 9.1	3 sets of chin-ups, reverse chin-ups, and push-ups until failure, with three minutes rest between sets	8 gr of Citrulline Malate 1 hour before exercise.	The purpose of this study was to examine the possible benefits of taking supplemental citrulline malate through repeated bouts of upper-body resistance training in a controlled laboratory environment.	The ones who received the citrulline-malate supplementation performed more repetition during the specified exercises; however, there weren't any significant differences between the treatments in the individual sets within each exercise. Consumption of citrulline-malate before to resistance exercise may aid in increasing resistance training volume.
Glenn et al. (2016)	PLA-controlled, randomized, double-blind, crossover study design	Masters-aged female tennis players N=17, Age (y) =51±9 Height(cm)=167.6±6.4 Weight (kg) = 66.6±9.5	Grip strength, vertical power, and Wingate anaerobic cycling assessments in respective order.	8 gr of Citrulline Malate + Dextrose 1 hour before exercise.	The goal of this study was to see how acute citrulline malate supplementation affected grip strength, vertical power, and anaerobic performance in female master-aged tennis players.	When consuming citrulline malate, athletes showed better maximal and average grip strength compared to placebo group. There were no changes in peak or average vertical power across trials. Peak power and explosive power were considerably higher when citrulline malate was consumed than the placebo group. For the ability to maintain power, time within trials had a significant effect, although there were no significant changes between trials in terms of supplement taken.
Esen et al. (2022)	Randomized, double-blind study design	Trained Swimmers and Triathletes N=15, Age (y)= 25±7 Height (cm)= 177±6.3 Weight (kg)= 78±12.3	Time trials of 200m and 100m freestyle swimming, with a 30-minute rest period in between.	8 gr of L-citrulline or 8 gr of L-arginine or 8 gr placebo consumed every morning (8-10am) over the first 7 days. On the last day of supplementation, 8 g of powder was consumed 1.5 hours before the 200 m.	The purpose of this study was to examine whether 8 days of L-Arginine or L-Citrulline supplementation will improve 200 m and 100 m freestyle swimming time trials.	There was no notable change in plasma nitric oxide levels across groups. There was no significant difference between groups in the 200 m and 100 m swimming time trials. There was a significant impact of time on blood lactate concentration, but no interaction effect between trial group and trial lactate group was found.

Discussion

In summary, six studies suggested that using L-citrulline or citrulline malate had a positive effect on performance, however, four studies showed that there is little or does not have any benefit.

Endurance Sports and Citrulline

According to the results of Stanelle et al., (2020) when compared to the placebo group, the time trial was shown to be around 5.2% lower following L-citrulline supplementation. Additionally, supplementing with L-citrulline led to a considerable improvement in average power production of about 5.4%. During the time trial, L-citrulline supplementation had no noticeable impact on average pedal force moment (PFM) or cadence. Average heart rate and average rated perceived exertion both increased significantly after using L-citrulline supplements throughout the time trial. Furthermore, Suzuki et al., (2016) stated that consuming L-citrulline for seven days and an hour prior to the time trial significantly raised plasma levels of L-citrulline and L-arginine and improved cycling time trial performance. L-citrulline also significantly reduced subjective feelings of muscular fatigue and increased concentration immediately following exercise. On the other hand, Cunnife et al., (2026) found that exercise heart rates were noticeably greater in the citrulline malate condition however there were no differences between participants who took a placebo and those who received citrulline malate for time to exhaustion. Moreover, Esen et al., (2022) also concluded that 8 days of either L-arginine or L-citrulline supplementation had no impact from placebo in terms of nitric oxide levels, 200- or 100-meter swimming time trials, or blood lactate levels in athletes.

Strength/Resistance Sports and Citrulline

According to Pérez-Guisado et al., (2010) there was a noticeable increase in repetitions between the placebo and citrulline malate treatments. Moreover, at 24 and 48 hours after exercise, the muscle soreness score was significantly reduced in the citrulline malate trial as compared to placebo, with an equivalent reduction in percentage of 40% at each time point. Furthermore, Glenn et al. (2015) also found that subjects who consumed citrulline malate as opposed to a placebo performed noticeably more repetitions of upper-body exercise, according to a repeated-measures analysis of variance. Similar noticeable increases in the total number of repetitions performed were seen for lower-body exercise after taking citrulline malate. Wax et al., (2015, 2016) in their studies also concluded that, when compared to the placebo group, participants in the citrulline malate group performed noticeably more repetitions during all exercises. Glenn et al., (2016) concluded that peak or average vertical power was not changed by citrulline malate. In terms of maximum and average grip strength as well as anaerobic cycling performance, citrulline malate may improve performance. On the other hand, Chappell et al., (2018) stated that, regarding the quantity of repetitions, there was no difference between the placebo and the citrulline malate treatment. In comparison to the placebo group, the citrulline malate group experienced considerably more overall muscular fatigue.

Muscle Fatigue

Some studies stated that they experienced less muscular soreness or fatigue when they supplemented L-citrulline or citrulline malate but on the other hand, some did not experience any differences, and one study even concluded that they encountered increased muscle soreness after 72 hours of exercise (Chappell et al., 2018). 2 of the studies consumed 8gr of citrulline malate 1 hour prior to exercise but they completely got different outcomes. Resistance trained males who consumed 8gr of citrulline malate 1hr prior to exercises experienced less fatigue but moderately trained females and males experienced increased muscle soreness after exercise even though they had the same supplement protocol (Wax et al., 2015; Chappell et al., 2018).

Conclusions

The effectiveness of supplementing with L-citrulline or Citrulline Malate remains a subject of ongoing debate. Definitive answers regarding its impact on specific sports are currently lacking. Further research is needed in this area, as current data is insufficient.

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