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L-CITRULLINE AS A NATURAL ERGOGENIC SUPPLEMENT: A COMPREHENSIVE LITERATURE REVIEW OF ITS EFFECTS IN NITROGEN METABOLISM AND HUMAN PERFORMANCE

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ABSTRACT

Purpose: This study aims to provide a comprehensive examination of the role of L-citrulline in human physiology, with a particular focus on nitrogen metabolism and its potential applications in sports and exercise science. L-citrulline, a non-essential amino acid synthesized endogenously, participates in the urea cycle where it contributes to the detoxification of ammonia, a byproduct of protein catabolism. In addition, it plays an important role in the nitric oxide (NO) pathway, thereby influencing vascular tone and blood flow regulation. These biochemical functions have attracted considerable scientific attention, as they may translate into practical benefits for physical performance and recovery. Specifically, L-citrulline supplementation has been investigated for its ability to enhance exercise capacity, support training adaptation, reduce muscle soreness, and improve post-exercise recovery. Furthermore, there is growing interest in its potential to delay fatigue by improving oxygen delivery and nutrient utilization during strenuous activity. Beyond performance outcomes, the safety profile of L-citrulline has also been evaluated, with current evidence suggesting that it is well tolerated when consumed at doses commonly used in clinical and sports settings. Taken together, these factors highlight the multifaceted relevance of L-citrulline as both a physiological substrate and a promising ergogenic aid.

Methodology: A systematic review of scientific articles was conducted, focusing on studies related to the ergogenic effects of L-citrulline. The review mainly includes clinical trials, meta-analyses, and research on various populations.

Findings: Regular L-citrulline supplementation appears to enhance NO production, improve vasodilation, and facilitate ammonia clearance, which collectively support endurance and strength performance. The review suggests that L-citrulline also reduces muscle soreness, improving recovery, delaying fatigue, although effects vary by dose, training status, sex, and the long-term safety of regular use. Synergistic effects have been noted when L-citrulline is combined with other supplements like malate or BPGF.

Conclusions: Current evidence supports the potential of regular L-citrulline supplementation as a metabolic enhancer. However, further research is warranted to elucidate its precise role in broader aspects of metabolic health and to determine optimal dosing strategies. These remain important areas for future investigation.

KEYWORDS

L-Citrulline, Nitrogen Metabolism, Nitric Oxide, Exercise Performance, Human Performance, Endurance

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1. Introduction

Nitrogen metabolism is a fundamental biochemical process that maintains nitrogen homeostasis in the human body, supporting the synthesis and breakdown of amino acids, nucleotides, and other nitrogenous compounds. Efficient regulation of nitrogen is critical for maintaining cellular function, facilitating protein turnover, and preventing the accumulation of toxic metabolites such as ammonia. The urea cycle, also known as the ornithine cycle, plays a central role in this process by converting excess nitrogen into urea, which is excreted in urine. This tightly regulated pathway is especially active in the liver and involves several key intermediates, including L-citrulline.

Amino acids serve as both structural and functional components in human metabolism. Beyond their role in protein synthesis, amino acids act as signaling molecules, precursors to neurotransmitters, and regulators of immune and metabolic pathways. Within this context, L-citrulline has emerged as a compound of interest due to its unique metabolic functions. Unlike most amino acids, citrulline is not incorporated into proteins. Instead, it participates in the urea cycle and serves as a precursor to L-arginine, which is a substrate for nitric oxide synthase (NOS) - the enzyme responsible for nitric oxide (NO) production.

L-citrulline is produced endogenously in enterocytes from glutamine and can also be obtained through dietary sources such as watermelon. Unlike oral L-arginine, which undergoes extensive hepatic degradation, L-citrulline bypasses first-pass metabolism in the liver, making it a more efficient and bioavailable precursor for systemic arginine and subsequent nitric oxide production. Owing to this property, L-citrulline has garnered increasing attention within the domains of sports nutrition and clinical physiology.

Preliminary evidence suggests that it may enhance exercise performance, reduce muscle soreness, and improve recovery by supporting vasodilation, reducing ammonia buildup, and improving nutrient delivery to muscle tissue.

The article will provide a comprehensive analysis of the usefulness of L-citrulline as a supplement supporting human performance. Despite the increasing popularity of citrulline-based supplements, the precise mechanisms of its action, optimal dosage, and long-term effects remain incompletely understood. Therefore, a comprehensive review of the available literature is warranted to critically assess the role of L-citrulline in nitrogen metabolism and its practical applications in enhancing human physical performance.

2. Methodology

This review was conducted through a structured search and critical appraisal of the scientific literature related to L-citrulline nitrogen metabolism and physical performance enhancement. Electronic databases including PubMed, Scopus and Google Scholar, were systematically queried to identify relevant peer-reviewed publications. The selection criteria were mainly focused on clinical trials, systematic reviews, and meta-analyses that explored L-citrulline effects in Nitrogen Metabolism and physical performance, with particular emphasis on endurance, strength, recovery, and exercise efficiency. The initial search yielded a broad range of articles, which were subsequently filtered based on predefined inclusion criteria: original human studies, systematic reviews and meta-analyses, studies examining the impact of L-citrulline supplementation on physical performance metrics, publications in English, and exclusion criteria: animal studies, non-peer-reviewed articles, studies lacking a clear intervention with L-citrulline. Factors such as supplementation dosages, treatment durations, and demographic differences like sex and health status were also considered. Particular emphasis has been placed on evaluating both the efficacy and safety profile of L-citrulline supplementation across diverse physiological and clinical contexts.

3. The Mechanics of L-citrulline Action

Mechanisms of L-citrulline action in urea cycle

L-citrulline serves as a precursor to L-arginine, a critical amino acid in the urea cycle. In contrast to direct arginine supplementation, citrulline effectively bypasses hepatic first-pass metabolism, resulting in a more sustained and efficient elevation of systemic arginine concentrations. This enhanced bioavailability contributes to improved nitrogen disposal through increased ureagenesis. Consequently, L-citrulline supplementation has demonstrated efficacy in elevating plasma arginine levels, thereby supporting urea cycle function and offering therapeutic potential in the management of urea cycle disorders (1).

The synthesis of L-citrulline within the urea cycle occurs in the mitochondria of hepatocytes through the action of the enzyme ornithine transcarbamylase (OTC). This enzyme catalyzes the condensation of L-ornithine with carbamoyl phosphate, resulting in the formation of L-citrulline. Following its synthesis within the mitochondrial matrix, L-citrulline is transported into the cytoplasm of hepatocytes. However, the L-citrulline generated endogenously as part of the hepatic urea cycle serves a localized and tightly regulated function. It is not released into the systemic circulation. Instead, in the cytosolic compartment, L-citrulline is rapidly converted into argininosuccinate by the enzyme argininosuccinate synthase (ASS) through its condensation with aspartate. Argininosuccinate is then cleaved by argininosuccinate lyase (ASL), yielding L-arginine and fumarate. The resulting L-arginine is subsequently hydrolyzed by arginase to produce urea and regenerate L-ornithine, thereby completing the cyclical sequence of nitrogen elimination via the urea cycle (2,3,4).

L-citrulline is also synthesized in the small intestine from precursors like glutamine. Unlike the L-citrulline produced in the liver, the L-citrulline synthesized in the intestines is released into the portal circulation and transported to the kidneys. In the kidneys, L-citrulline undergoes a highly efficient conversion back into L-arginine, facilitated by the enzymes argininosuccinate synthase and argininosuccinate lyase. This property renders L-citrulline a more effective precursor for augmenting systemic L-arginine concentrations (3,5).

Nitric Oxide Production and Vasodilation Pathways

L-citrulline exerts significant effects on nitrogen metabolism through its function as a key precursor to L-arginine, the obligate substrate for the synthesis of nitric oxide (NO). Nitric oxide is a versatile signaling molecule with a wide range of physiological functions, most notably its potent vasodilatory effects, which play a critical role in regulating blood flow, oxygen delivery, and overall cardiovascular health. The complex interplay between L-citrulline and the L-arginine–nitric oxide (NO) pathway has attracted substantial scientific interest in recent years, particularly with regard to its implications for exercise performance, cardiovascular function, and broader physiological regulation (5,6,7). The synthesis of nitric oxide from L-arginine is catalyzed by a family of enzymes known as nitric oxide synthases (NOS). These enzymes, including endothelial NOS (eNOS), neuronal NOS (nNOS), and inducible NOS (iNOS), utilize L-arginine as a substrate, along with oxygen and several cofactors, to produce NO and L-citrulline as a byproduct. The nitric oxide (NO) synthesized by nitric oxide synthase (NOS) readily diffuses into adjacent cells, where it initiates a range of downstream signaling cascades. Within the vascular system, NO functions predominantly as a potent vasodilator. It achieves this by activating soluble guanylate cyclase in vascular smooth muscle cells, thereby increasing intracellular cyclic guanosine monophosphate (cGMP) levels. The elevation of cGMP promotes smooth muscle relaxation, resulting in vasodilation and enhanced blood flow (8,9).

As previously mentioned, orally supplemented L-citrulline is more bioavailable than L-arginine, making it a more efficient strategy for increasing plasma L-arginine levels and, consequently, enhancing nitric oxide production. This enhanced NO bioavailability, resulting from L-citrulline supplementation, has been shown to have several beneficial effects on vascular function. Studies have indicated that L-citrulline can improve endothelial function, which is the ability of the blood vessels to relax and contract properly, through the increased production of NO. This improvement in endothelial function is crucial for maintaining healthy blood pressure and preventing the development of cardiovascular diseases. Furthermore, the vasodilatory effects of NO, enhanced by L-citrulline supplementation, can lead to increased blood flow to various tissues and organs, improving oxygen and nutrient delivery. This is particularly relevant in the context of exercise, where increased blood flow to working muscles can enhance performance and reduce fatigue (5,6,9,10).

Numerous studies have examined the effects of L-citrulline supplementation on markers indicative of nitric oxide (NO) bioavailability, including plasma L-arginine and nitrate concentrations. These investigations consistently demonstrate that L-citrulline administration significantly elevates these biomarkers, suggesting an upregulation of endogenous NO production. In addition, the influence of L-citrulline on vascular function

has been evaluated through methodologies such as flow-mediated dilation (FMD), a non-invasive measure of endothelium-dependent vasodilation. Notably, several studies have reported significant improvements in FMD following prolonged L-citrulline supplementation, indicating enhanced endothelial function and vascular responsiveness (8,11,12,13). The L-arginine-NO pathway, fueled by L-citrulline supplementation, is implicated in a wide range of physiological processes beyond exercise and cardiovascular health. NO plays a role in immune function, neurotransmission, and various metabolic processes. The ability of L-citrulline to effectively enhance NO production underscores its potential therapeutic applications in conditions associated with impaired NO signaling, such as erectile dysfunction, pulmonary hypertension, and certain metabolic disorders (9,14,15).

4. Delaying Acidification and Reducing Ammonia Accumulation During Exercise

Intense physical exercise imposes substantial metabolic stress on the body, resulting in the accumulation of metabolites such as lactate, ammonia, and hydrogen ions, which collectively contribute to the onset of fatigue and impair athletic performance. Among these metabolites, ammonia and lactic acid are particularly noteworthy. Ammonia is generated as a byproduct of amino acid catabolism, and its concentration can rise markedly during prolonged or high-intensity physical activity. Elevated ammonia concentrations are believed to intensify fatigue by activating phosphofructokinase, a critical rate-limiting enzyme in the glycolytic pathway. This activation accelerates glucose catabolism and enhances lactate production. The subsequent accumulation of lactic acid contributes to a decline in intramuscular pH, resulting in localized acidosis that disrupts enzymatic function and impairs muscle contractility. This acidification disrupts both contractile function and enzymatic efficiency within muscle tissue, ultimately contributing to the onset of muscular fatigue and a subsequent reduction in overall exercise performance (5). L-citrulline's involvement in the urea cycle plays a crucial role in mitigating the buildup of ammonia during exercise. As a key intermediary in the urea cycle, L-citrulline serves a pivotal role in ammonia detoxification by enhancing its conversion into urea, a less toxic metabolite efficiently eliminated via renal excretion. Through its involvement in this metabolic pathway, L-citrulline supplementation has the potential to enhance the efficiency of ammonia clearance from the bloodstream. By promoting ammonia homeostasis—especially under conditions of elevated production such as intense physical exertion, L-citrulline may help mitigate fatigue and preserve exercise capacity (5,6,16).

Moreover, lactate synthesis is closely coupled with the rate of glycolysis, which can be upregulated in response to elevated ammonia concentrations. Through its role in the urea cycle, L-citrulline contributes to the buffering and clearance of excess ammonia, potentially attenuating this stimulatory effect on glycolytic flux. Consequently, L-citrulline supplementation may indirectly reduce lactic acid accumulation by facilitating lower systemic ammonia levels. This reduction is hypothesized to enhance the aerobic metabolism of pyruvate, a central intermediate in energy production, thereby diminishing the reliance on anaerobic glycolysis, the principal pathway responsible for lactic acid generation during high-intensity exercise (16). However, meta-analysis examining the effect of L-citrulline supplements on post-exercise blood lactate levels found no significant reduction. This suggests that while L-citrulline's role in ammonia metabolism is well-established, its impact on lactic acid production during exercise in humans may be more complex and require further investigation (16,17).

5. Review of Studies on the Impact of L-citrulline on Physical Performance

Effects of L-Citrulline Supplementation on Aerobic and Anaerobic Endurance Capacity

The potential of L-citrulline supplementation to enhance both aerobic and anaerobic endurance lies in L-citrulline's ability to increase nitric oxide production, which could improve blood flow and oxygen delivery to working muscles, thereby enhancing exercise performance. Additionally, its role in ammonia buffering could potentially delay fatigue during prolonged exercise. Regarding aerobic endurance, a recent meta-analysis (18) evaluating the effects of acute L-citrulline ingestion in healthy young adults reported no significant improvements in performance outcomes. Specifically, measures such as time-to-exhaustion (TTE) and time-to-completion (TTC) during continuous submaximal intensity exercise were not significantly altered by acute L-citrulline supplementation. These findings suggest that, in this demographic, acute administration of L-citrulline does not exert a meaningful ergogenic effect on aerobic exercise capacity. However, some individual studies (19) have reported potential improvements in VO₂ kinetics, which is the rate at which oxygen uptake increases at the start of exercise, with chronic L-citrulline supplementation over a period of at least seven days. Faster VO₂ kinetics may contribute to enhanced exercise efficiency and tolerance by facilitating a more rapid adjustment to the energetic demands of physical activity. However, the extent to which this translates into

measurable improvements in endurance performance appears to be variable. Importantly, current evidence does not consistently support a significant effect of L-citrulline supplementation on maximal oxygen uptake ($\text{VO}_{2\text{max}}$), a key indicator of cardiorespiratory fitness.

L-Citrulline in Muscle Recovery: Reducing Soreness, Improving Recovery Time and Alleviating Fatigue

Exercise-induced muscle damage, commonly observed following strenuous physical exertion can result in delayed-onset muscle soreness, fatigue, and a diminished capacity to perform in subsequent exercise sessions (20).

A meta-analysis (16) investigating the effects of citrulline supplementation on post-exercise ratings of perceived exertion (RPE) and muscle soreness found that citrulline significantly reduced muscle soreness at both 24 and 48 hours following exercise. This reduction in muscle soreness is potentially mediated by the increased production of nitric oxide, which can enhance blood flow to the muscles, facilitating the delivery of nutrients and the removal of waste products, thereby promoting muscle repair and recovery (6).

Some studies (21) have suggested that L-citrulline supplementation may support improved recovery status by attenuating cortisol elevation, and by enhancing the testosterone/cortisol ratio, a recognized marker of an anabolic environment favorable for recovery. Furthermore, L-citrulline's role in reducing ammonia buildup during exercise could also contribute to alleviating fatigue, as elevated ammonia levels are associated with both central and peripheral fatigue (5).

6. Variables Influencing the Effects of L-Citrulline Supplementation

Sex-Based Differences

Research suggests that there may be sex-based differences in the response to L-citrulline supplementation. For instance, one study (22) reported that supplementation with a combination of polyphenol extract and L-citrulline significantly reduced ambulatory systolic blood pressure in women with prehypertension, whereas no such effect was observed in men. This finding suggests that sex hormones may influence the hemodynamic response to L-citrulline, potentially by modulating nitric oxide pathways and vascular reactivity. However, other studies (23) investigating the effects of L-citrulline on exercise performance have not consistently reported significant sex-based differences.

Health-Based Differences

The health status of an individual can also impact the effects of L-citrulline supplementation. Studies (22) in individuals with prehypertension or hypertension have shown that L-citrulline supplementation may have blood pressure-lowering effects. However, these effects may not be as pronounced or even observed in normotensive individuals. Similarly, L-citrulline has demonstrated potential benefits in enhancing vascular function among individuals with specific cardiovascular conditions. The presence of such underlying health issues may modulate baseline nitric oxide levels and alter the responsiveness of the L-arginine–NO pathway to L-citrulline supplementation (24).

Training Status Differences

The training status of an individual, whether they are untrained, recreationally active, or highly trained athletes, can also affect the outcomes of L-citrulline supplementation. Some studies suggest that the ergogenic benefits of nitric oxide precursors, such as L-citrulline, may be more pronounced in untrained or moderately trained individuals compared to highly trained athletes. This discrepancy may be attributed to the fact that trained athletes often exhibit physiologically optimized nitric oxide production and vascular function as a result of chronic exercise adaptation. Nonetheless, other research has demonstrated performance-enhancing effects of L-citrulline supplementation even among well-trained individuals, indicating that the response to supplementation may vary depending on multiple factors, including training status, dosage, and exercise modality (8,19,25,26).

7. Optimal L-citrulline Supplementation Strategy for Exercise Performance:

Research has explored the effects of L-citrulline supplementation on various dimensions of endurance and resistance exercise performance. One study (27) investigated the impact of 6 grams of L-citrulline administered daily over seven days in healthy adults and reported improved tolerance to severe-intensity cycling exercise, along with enhanced oxygen uptake kinetics. These findings suggest that consistent, short-term L-citrulline supplementation may enhance physiological responses to strenuous aerobic activity. Conversely, a study involving soccer players (28) examined the combined effects of L-arginine (1.2 g) and L-citrulline (1.2 g) over six days and observed elevated post-exercise nitric oxide levels and an increased

perception of exertion. However, the specific contribution of L-citrulline within this combination remains unclear.

A meta-analysis (6) focusing on citrulline malate—a compound comprising L-citrulline and malic acid—found that single acute doses of 8 grams yielded inconsistent effects on endurance performance. Similarly, a study (26) examining elite soccer players reported no significant improvements in performance, fatigue, or recovery following a single dose of either 3 or 6 grams of citrulline malate, suggesting limited efficacy in acutely enhancing high-intensity, sport-specific performance in trained athletes.

Evidence indicates that chronic L-citrulline supplementation (ranging from 6 to 16 days at doses between 3.4 and 6 g/day) may be more effective in improving aerobic capacity compared to acute supplementation. Acute intake (1–3 hours prior to exercise) of 1–12 grams of L-citrulline has not been shown to significantly enhance aerobic performance or related physiological outcomes (19).

Moreover, a study examining the isolated effects of pure L-citrulline (23) found that a single 8-gram dose did not improve isometric force output or muscle endurance during a resistance exercise protocol in trained men and women, suggesting that L-citrulline alone may not yield substantial ergogenic effects in the context of resistance exercise.

Collectively, these findings suggest that for high-intensity and resistance training contexts, the efficacy of L-citrulline may depend more on supplementation duration than on acute dosing (19, 23, 26, 27). However, a meta-analysis (29) focusing on citrulline malate reported a small yet statistically significant improvement in muscle endurance with 6–8 gram doses during high-intensity strength training. The inclusion of malic acid may enhance mitochondrial ATP production and reduce fatigue, potentially accounting for the greater efficacy observed with citrulline malate formulations compared to L-citrulline alone.

8. Long-Term Effects of L-Citrulline Supplementation

Longer-term and postprandial effects on vascular function markers

Long-term supplementation with L-citrulline, administered for periods ranging from one week up to four months, has been consistently shown to produce a notable improvement in endothelial function. This beneficial effect was primarily reflected by a measurable increase in flow-mediated dilation (FMD), which rose by an average of 0.9 percentage points (95% CI: 0.7 to 1.1; $p < 0.001$). Importantly, the analysis did not reveal any evidence of heterogeneity across the included studies ($p = 0.85$), which strengthens the reliability and generalizability of these findings. In contrast, shorter supplementation protocols, lasting between 16 days and 6 weeks, demonstrated a different but also favorable cardiovascular outcome. Specifically, L-citrulline intake within this timeframe was associated with a statistically significant reduction in arterial stiffness, as reflected by a decrease in pulse wave velocity (PWV) by 0.9 m/s (95% CI: -1.5 to -0.1 ; $p < 0.001$). Taken together, these results suggest that L-citrulline supplementation exerts beneficial vascular effects both in the short and longer term, although the mechanisms and clinical implications may differ depending on the duration of administration (13).

Longer-term and postprandial effects on cardiometabolic risk markers

L-citrulline supplementation was also investigated in relation to metabolic outcomes, particularly glucose and lipid metabolism. The available evidence indicates that its administration was associated with a non-significant trend toward lower fasting glucose concentrations, with a weighted mean difference (WMD) of -0.9 mmol/L (95% CI: -1.9 to 0.8 ; $p = 0.06$). Although this reduction did not reach conventional statistical significance, the direction of the effect suggests a potential glucose-lowering tendency that may warrant further investigation in larger and longer clinical trials. In contrast, no meaningful alterations were observed in lipid parameters. Specifically, total cholesterol concentrations remained essentially unchanged during prolonged periods of L-citrulline intake, with a WMD of 0.0 mmol/L (95% CI: -0.4 to 0.4 ; $p = 0.98$), which indicates a neutral effect on this marker of cardiovascular risk.

In addition to fasting measures, the postprandial metabolic effects of L-citrulline were also assessed, although the evidence in this area remains very limited. To date, only a single clinical trial has examined the acute influence of supplementation on postprandial glucose, insulin, and total cholesterol levels. The findings of this study revealed no significant differences between the intervention and control groups, suggesting that short-term metabolic responses to L-citrulline are minimal or absent (13).

Longer-term and postprandial effects on circulating markers of L-arginine metabolism

Long-term supplementation with either L-citrulline or watermelon significantly increased plasma L-arginine concentrations (WMD: 40.7 μ mol/L; 95% CI: 19.1 to 62.3 ; $p < 0.001$ and WMD: 49.0 μ mol/L; 95% CI: 43.5 to 54.5 ; $p < 0.001$, respectively). Only watermelon intake was associated with a significant rise in L-

citrulline levels, whereas L-citrulline supplementation did not show a significant effect. Neither intervention influenced NO_x concentrations.

Postprandially, L-citrulline intake significantly increased plasma concentrations of L-citrulline, L-arginine, and L-ornithine (WMD: 1647.5 μ mol/L; 95% CI: 1362.7 to 1932.1; $p < 0.001$; WMD: 101.7 μ mol/L; 95% CI: 87.7 to 115.8; $p < 0.001$; and WMD: 55.8 μ mol/L; 95% CI: 35.2 to 76.3; $p < 0.001$, respectively) (13).

Side effects

In a double-blind, randomized, placebo-controlled crossover trial (30), twelve apparently healthy young men (mean age: 25.9 $\pm$ 4.0 years; body weight: 78.6 $\pm$ 10.0 kg; height: 181.0 $\pm$ 7.0 cm) were enrolled to assess the tolerability and safety of varying doses of L-citrulline nitrate. Participants received low (1.5 g/day), medium (3.0 g/day), and high (6.0 g/day) doses of L-citrulline over a 7-day period. All twelve subjects completed the protocol with full adherence. No major adverse effects were reported that impeded study participation. However, three participants (25%) in the high-dose condition experienced mild, transient dizziness upon standing (orthostatic dizziness) during the initial days of supplementation, with symptoms resolving after 2–3 days. Additionally, seven participants (58.3%) noted an unpleasantly sour taste associated with the high-dose citrulline nitrate. No side effects were reported during the low- and medium-dose phases or in the placebo condition. Overall, L-citrulline nitrate supplementation was deemed safe and well tolerated at doses up to 6 g/day for one week.

In a separate investigation (31), which evaluated the effects of a supplement containing BPFG (beetroot polyphenolic functional group) and L-citrulline in a cohort of trained cyclists, no harmful adverse events were reported. This study focused on the supplement's antioxidant capacity and its potential to improve athletic performance and endothelium-dependent vasodilation, further supporting the safety profile of L-citrulline-based interventions. No adverse effects were observed throughout the supplementation period.

9. L-citrulline with other Supplements and their Potential Synergistic Effects

Three months of combined supplementation with beetroot polyphenolic functional group (BPFG) and L-citrulline (marketed as N.O. Max) produced a significant synergistic effect on vascular and cardiorespiratory function in athletes. Compared to placebo, the combination markedly increased nitric oxide (NO) release ($p < 0.001$) and reactive hyperemia index (RHI) ($p < 0.001$), both at rest and post-exercise. These vascular improvements were accompanied by significant enhancements in cardiorespiratory fitness parameters, including increases in VO₂ max, ventilatory threshold 1 (VT1), ventilatory threshold 2 (VT2), peak power output, and a reduction in heart rate ($p < 0.01$), indicating improved cardiovascular efficiency and endurance capacity. Notably, no adverse effects were reported throughout the supplementation period.

When administered separately, BPFG (500 or 1000 mg/day) for three months also resulted in significantly elevated total NO levels and nitrite/nitrate ratios compared to placebo, effects that were associated with enhanced RHI as assessed by EndoPAT analysis. Similarly, L-citrulline supplementation (1000 or 2000 mg/day) over the same duration produced comparable increases in NO production and RHI both pre- and post-exercise. These findings support the efficacy of both compounds in improving endothelial function, while also highlighting the additive benefits of their combined administration (31).

Notably, combined supplementation with BPFG and L-citrulline at doses of 1000 and 2000 mg/day (Groups 6 to 9) elicited a highly significant increase in nitric oxide (NO) release and vasodilatation index compared to placebo ($p < 0.001$). Treadmill performance assessments demonstrated that this combination significantly enhanced exercise capacity, as evidenced by improvements in VO₂max, ventilatory thresholds (VT1 and VT2), peak power output, and heart rate parameters. In contrast, L-citrulline administered alone did not yield substantial performance benefits. These findings suggest that the synergistic interaction between BPFG and L-citrulline provides superior ergogenic and vascular effects relative to either supplement used independently (31).

Citrulline malate (CM), a widely used supplement in the athletic and fitness community, combines L-citrulline with malate, a tricarboxylic acid (TCA) cycle intermediate thought to enhance oxidative ATP production. This combination is proposed to exert synergistic effects on physical performance and recovery. Evidence indicates that pre-exercise CM supplementation significantly increases muscular endurance, as shown by a 6.4% increase in repetitions to failure during strength training. Subgroup analyses revealed a trend toward improved performance in lower body exercises ($p = 0.051$, SMD = 0.266; 95% CI: -0.0009 to 0.534), whereas no statistically significant benefits were observed for upper body exercises ($p = 0.131$, SMD = 0.166; 95% CI: -0.050 to 0.382). While the observed effect sizes are small, CM may still offer a practical benefit by enhancing training volume, particularly during high-intensity exercise. CM remains a common component in multi-ingredient pre-workout formulations and has demonstrated modest positive effects across various strength performance metrics, with an average effect size of 0.20 (29).

10. Conclusions

The body of research surrounding L-citrulline has expanded significantly in recent years, shedding light on its diverse roles in human physiology, metabolism, and exercise performance. As a key component of the urea cycle, L-citrulline plays a vital role in ammonia detoxification, and its efficient conversion to L-arginine underscores its importance in nitric oxide production and vasodilation. While acute L-citrulline supplementation may not consistently enhance aerobic endurance in young healthy adults, chronic use and specific forms like citrulline malate show promise in delaying fatigue and improving muscle endurance during anaerobic exercise. The evidence suggests that L-citrulline can be effective in reducing post-exercise muscle soreness and perceived exertion, potentially through enhanced blood flow and nutrient delivery to muscles.

However, the effects of L-citrulline supplementation are not uniform and can be influenced by a multitude of factors. Sex-based differences in vascular responses have been observed, and the health status of individuals, particularly those with pre-existing cardiovascular conditions, may also modulate the outcomes of supplementation. Furthermore, the training status of an individual appears to play a role in the ergogenic benefits of L-citrulline, with some evidence suggesting greater effects in untrained or moderately trained individuals. The dosage, duration, and form of L-citrulline supplementation, as well as its combination with other nutrients, are also critical variables that can impact its efficacy.

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All authors have read and agreed with the published version of the manuscript.

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