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Dolna 17, Warsaw,
Poland 00-773
+48 226 0 227 03
editorial_office@rsglobal.pl

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CITRULLINE MALATE IN MEDICAL AND SPORT APPLICATIONS

Paweł Radkowski
Department of Anaesthesiology and Intensive Care, Regional Specialist Hospital in Olsztyn, Olsztyn, Poland
ORCID ID: 0000-0002-9437-9458

Urszula Justyna Wojciechowska *(Corresponding Author, Email: wojciechowskaula26@gmail.com)*
University Clinical Hospital in Bialystok, Białystok, Poland
ORCID ID: 0009-0006-8800-2386

Adam Rafałowicz
University Clinical Hospital in Bialystok, Białystok, Poland
ORCID ID: 0009-0005-2535-6884

Magdalena Rafałowicz
Medical University of Bialystok, Białystok, Poland
ORCID ID: 0009-0006-5270-305X

Paweł Jakub Wojciechowski
State Academy of Applied Sciences in Chełm, Chełm, Poland
ORCID ID: 0009-0000-7284-8148

Łukasz Grabarczyk
Alarm Clock Clinic, Coma Recovery and Neurorehabilitation Center, Warsaw, Poland
ORCID ID: 0000-0002-0022-2741

ABSTRACT

Background. Nitric oxide has emerged as a key physiological signalling molecule that has a significant impact on vessels, skeletal muscle function and exercise performance. With this in mind, increasing its production is of great interest to clinicians and athletes, making citrulline malate a potential medication and one of the most popular ergogenic supplements.
Aim. This article aims to review current knowledge on citrulline malate supplementation, with emphasis on its pharmacokinetics, proposed medical application and ergogenic benefits.
Material and Methods. Literature search in PubMed and Google Scholar for clinical trials, meta-analyses, and reviews on citrulline malate using keywords: citrulline malate, nitric oxide, muscle endurance, medical applications, supplementation".
Results. Citrulline malate exhibit its positive impact on many medical conditions. In pulmonary hypertension by improving exercise tolerance and modestly reducing arterial pressure. In metabolic conditions, leading to better glycaemic control, improved lipid profiles, and reduced inflammation in diabetes. Men with mild erectile dysfunction report subjective improvements when using citrulline malate alone or alongside other therapies. In atherosclerosis, it increases the elasticity of the arteries, which becomes weaker in advanced disease. Beyond medical applications, citrulline malate supplementation is primarily known for supporting short-term, high-intensity exercise by delaying fatigue, improving endurance, lowering perceived exertion during resistance training and reducing post-workout muscle soreness.
Conclusion: Citrulline malate could be used as medical application and can enhance exercise performance by delaying fatigue and reducing muscle soreness. Larger, rigorously controlled trials are required to establish optimal dosing, target activities and long-term safety.

KEYWORDS

Citrulline Malate, Nitric Oxide, Muscle Endurance, Medical Applications, Supplementation

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1. Introduction

Nitric oxide (NO) has emerged as a key physiological signalling molecule with considerable implications for skeletal muscle function and exercise performance, by augmenting NO synthesis through exogenous substances may improve skeletal muscle function and performance (Gough et al., 2021). NO influences exercise capacity via multiple mechanisms, including reduced fatigue during activity, enhanced nutrient and oxygen delivery to working musculature, and accelerated clearance of metabolic by-products generated during high-intensity exercise (Devrim-Lanpir et al., 2024; Stuehr, 2004). As a result, various dietary approaches aimed at "boosting" NO availability have gained prominence; common strategies to achieve this include the consumption of green leafy vegetables, beetroot juice, or specific amino acid precursors such as L-citrulline (Macuh & Knap, 2021). It is assumed that L-citrulline supplementation exerts favourable effects on both exercise performance and post-exercise recovery, likely through its role in the arginine–NO pathway (Gough et al., 2021). As surveys indicate, citrulline is listed among the most frequently used ergogenic pre-workout supplements by both recreational and professional athletes (El Khoury & Antoine-Jonville, 2012). Citrulline is administered in the form of citrulline malate (CM), wherein malic acid is chemically bound to L-citrulline in ratios ranging from 1:1 to 2:1, purportedly also enhancing workout results by increasing mitochondrial energy production (Murphy & O'Neill, 2018; Stuehr, 2004). In light of the great interest among consumers and scientific evidence supporting CM's potential to modulate NO production, enhance exercise capacity, and aid recovery, a thorough evaluation of its efficacy and underlying mechanisms is necessary (Trexler, Keith, et al., 2019; Trexler, Persky, et al., 2019).

Aim of the study

This article aims to review current knowledge on CM supplementation, with emphasis on its pharmacokinetics, proposed ergogenic benefits, and medical application.

2. Research materials and methods

A review of the literature available in the PubMed and Google Scholar databases was carried out, focusing on clinical trials, meta-analyses and systematic reviews related to citrulline malate consumption, its physiological mechanisms, impact on physical performance, and potential adverse effects and potential usage in medical conditions. To specifically evaluate the effect of citrulline malate on those topics, the search strategy included keywords such as "citrulline malate, nitric oxide, muscle endurance, medical applications, supplementation."

3. Research results

3.1. Citrulline malate

Citrulline malate is an organic salt synthesized industrially by combining L-citrulline with malic acid (malate), two compounds that naturally occur in the human body; however, it does not form endogenously but is manufactured in order to gain a dietary supplement in which citrulline and malate are combined in ratios ranging from 1:1 to 2:1 (Gough et al., 2021; Trexler, Persky, et al., 2019). L-citrulline is a non-proteinogenic amino acid produced endogenously that plays a crucial role in the hepatocellular urea cycle; it is formed by the condensation of ornithine with carbamoyl phosphate, therefore enabling the safe incorporation of ammonia into the pathway (Matsumoto et al., 2019). The second component, malate, is an important intermediate in the Krebs cycle (also known as the Citric Acid Cycle or TCA cycle), which plays a crucial role in aerobic respiration by producing NADH, a key substrate for energy production through oxidative phosphorylation (Murphy & O'Neill, 2018).

3.2. Mechanism of action

Although the precise mechanism of action of citrulline malate supplementation remains to be fully elucidated, after intestinal absorption citrulline is transported primarily to the kidneys and peripheral tissues where it is converted by the urea-cycle enzymes argininosuccinate synthase and argininosuccinate lyase into arginine, which then serves as the substrate for endothelial nitric oxide synthase to increase nitric oxide production (Gonzalez et al., 2023) [Figure 1, Figure 2].

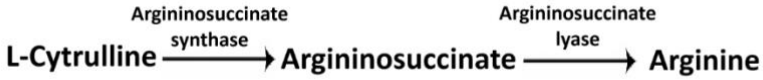

Fig. 1. *Arginine synthesis*

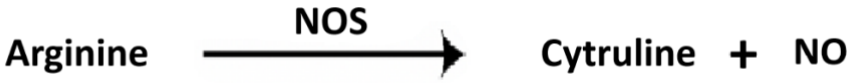

Fig. 2. *Nitric oxide synthesis*

L-citrulline is used as a supplement instead of L-arginine, mainly due to its superior pharmacokinetic properties: unlike L-arginine, citrulline avoids degradation by intestinal and hepatic arginase, and thus bypasses first-pass metabolism; once absorbed, it travels through the bloodstream to the kidneys, where it is efficiently converted to L-arginine (Gonzalez et al., 2023). Animal studies have further confirmed the advantages of citrulline supplementation, demonstrating that citrulline raises arginine levels in plasma and all muscle tissues much more effectively than direct arginine administration (Osowska, 2004). After NO synthesis in endothelium, it diffuses rapidly into the underlying smooth muscle cells, where it binds to the heme group of soluble guanylyl cyclase (sGC). This activation converts GTP to cyclic GMP (cGMP), a second messenger that activates protein kinase G (PKG). PKG then lowers intracellular Ca^{2+} levels and promotes dephosphorylation of myosin light chains, leading to smooth muscle relaxation and thus vasodilation (Nauli, 2022). Through these mechanisms, citrulline increases nitric oxide levels and is thought to exert ergogenic effects by improving blood flow and oxygen delivery during exercise via elevated NO concentrations (Devrim-Lanpir et al., 2024; Stuehr, 2004). It also delays fatigue and supports oxidative metabolism by promoting ammonia clearance via the urea cycle, which lowers blood lactate accumulation and facilitates greater pyruvate utilization for energy production (Devrim-Lanpir et al., 2024). Malate, the second supplement component, supports ATP production by replenishing TCA cycle intermediates and, upon dehydrogenation to oxaloacetate, generates NADH that feeds into oxidative phosphorylation for sustained aerobic ATP synthesis (Devrim-Lanpir et al., 2024) [Figure 3].

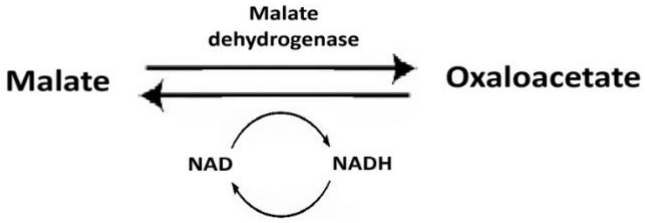

Fig. 3. *Malate T4 cycle*

3.3. Potential medical applications

3.3.1. Pulmonary hypertension

It has been suggested that CM may be used in the treatment of pulmonary hypertension, mainly due to its properties to increase NO synthesis, which results in vasodilation and affects the underlying mechanisms of this disease (Humbert et al., 2022; Sharif Kashani et al., 2014). A total of 25 patients with pulmonary hypertension received 1 g of L-citrulline malate three times daily for two weeks, resulting in an average increase of 44 m in the six-minute walk distance ($p = 0.005$) and a decrease in mean pulmonary arterial pressure from 83.3 mmHg to 79.1 mmHg ($p = 0.01$) (Sharif Kashani et al., 2014). The six-minute walk test (6MWT) and mean pulmonary arterial pressure (mPAP) are important indicators in pulmonary hypertension, and deviations from their normal values are associated with a poorer prognosis (Demir & Kucukoglu, 2015; Wang et al., 2023). Moreover, another clinical trial confirms L-citrulline's properties to decrease right ventricular afterload after two months of oral supplementation and improve ventricular contraction function (Orozco-Gutiérrez et al., 2010).

3.3.2. Diabetes

In diabetes, persistent hyperglycemia, oxidative stress (ROS), elevated endogenous NOS inhibitor, and the accumulation of advanced glycation end-products can impair NOS activity by disturbing the L-arginine–NO axis and exacerbating endothelial dysfunction and accelerating vascular damage (Hayashi et al., 2005). L-citrulline, through renal conversion to L-arginine, can restore NO synthesis even when NOS activity is partially compromised; in this way, CM can counteract endothelial defects and potentially lower cardiovascular risk and reduce the risk of vascular complications (Allerton et al., 2018).

In another study, it was noted that participants who took CM for eight weeks improved metabolic and inflammatory markers by reducing fasting glucose, HbA1c, insulin, HOMA-IR, triglycerides, TNF-α, and hs-CRP, along with increased HDL-C (Azizi et al., 2021).

3.3.3. Erection Dysfunction

L-citrulline, due to its properties of increasing NO concentration, can potentially be used as a treatment for erectile dysfunction (Gough et al., 2021). The use of L-citrulline in the treatment of erectile dysfunction remains controversial; some studies suggest that L-citrulline may serve as a standalone treatment with milder effects compared to standard therapies such as phosphodiesterase type 5 (PDE5) inhibitors, but with the advantage of lower treatment costs (Cormio et al., 2011). Other studies propose the use of L-citrulline as an adjunct therapy to PDE5 inhibitors to enhance efficacy (Shirai et al., 2018). In a clinical trial, during the first month, the participants (24 men with mild erectile dysfunction) received a placebo, followed by L-citrulline supplementation at a dose of 1.5 g/day during the second month. After one month of L-citrulline supplementation, 12 out of 24 men (50 %) achieved improvement and the average number of sexual intercourses per month also increased significantly ($p = 0.01$). No statistically significant improvements were observed during the placebo phase. Some studies suggest that L-citrulline may serve as a standalone treatment with milder effects compared to standard therapies such as PDE5 inhibitors, but with the advantage of lower treatment costs (Cormio et al., 2011). Other studies propose the use of L-citrulline as an adjunct therapy to PDE5 inhibitors to enhance efficacy (Shirai et al., 2018).

3.3.4. Atherosclerosis

It is believed that L-citrulline, due to its properties of increasing NO production, improving endothelial function, and reducing oxidative stress, could slow down the progression of atherosclerosis (Hayashi et al., 2005). In an animal model, L-citrulline supplementation in cholesterol-fed rabbits effectively slowed the development of diet-induced atherosclerosis (Hayashi et al., 2005). Furthermore, in a clinical study, the group receiving citrulline showed a significant increase in plasma citrulline concentration ($p < 0.05$) and increased levels of nitric oxide metabolites ($p < 0.05$); therefore, brachial-ankle pulse wave velocity (baPWV) was significantly reduced in the citrulline group ($p < 0.01$) (Hayashi et al., 2005). The BaPWV is a parameter that reflects arterial stiffness and increases in the final stage of atherosclerosis (Munakata, 2014). A decrease in baPWV, despite the lack of change in resting blood pressure, suggests improved vascular elasticity regardless of blood pressure at the beginning of the study (Papadia et al., 2018).

3.4. Side effects

The number of studies examining the safety of CM supplementation is very limited. Amino acid intake is associated with gastrointestinal symptoms, such as diarrhoea and vomiting, particularly during arginine supplementation (Grimble, 2007). However, CM supplementation has not been shown to cause frequent gastrointestinal issues (Rogers et al., 2020). Additionally, liver, kidney, and haematological parameters did not undergo clinically significant changes, and participants in a study of 75 men taking 2 g of L-citrulline daily reported no adverse effects (Hwang et al., 2018).

3.5. The effects of citrulline malate on enhancing physical activity performance

Citrulline malate is a relatively new supplement, and as such there is currently a lack of studies conclusively demonstrating its positive effects on physical performance. It should also be noted that the results of individual studies vary considerably in terms of supplementation protocols, the types of exercise tested, and the populations examined.

3.5.1. Muscle endurance and strength

Performing resistance training sets to momentary muscular failure, which means maximum possible repetitions per set, is considered necessary for full motor-unit recruitment and is therefore viewed as optimal for eliciting strength gains and resistance-training–induced hypertrophy (Grgic et al., 2022). Across multiple studies included in a meta-analysis (n = 137), researchers examined the effect of ingesting 8 g of CM 60 minutes before exercise on muscle endurance in upper- and lower-limb strength movements, compared to placebo (Vårvik et al., 2021). Supplementation resulted in an average of three additional repetitions before failure (6.4 % increase), which is a small effect size (Hedges' g = 0.196; 95 % CI [0.029, 0.364]). In a subgroup analysis, lower-body exercises showed a near-significant improvement (p = 0.051; SMD = 0.266; 95 % CI [–0.0009, 0.534]), whereas upper-body movements did not show a statistically significant increase (p = 0.131; SMD = 0.166; 95 % CI [–0.050, 0.382]) (Vårvik et al., 2021). Although the overall effect is modest, these data suggest that CM supplementation may modestly boost training volume by delaying the onset of fatigue during high-intensity efforts (Vårvik et al., 2021). On the other hand, another meta-analysis indicates that citrulline malate supplementation did not result in a statistically significant increase in muscle strength in resistance-trained individuals, both overall and when separated into upper and lower limbs (Aguiar & Casonatto, 2022). Moreover, in a clinical trial it was shown that a single dose of 8 g of citrulline malate does not improve isokinetic leg extension in recreationally active men (Trexler, Keith, et al., 2019). There is currently no clear data indicating the positive effects of CM in physical exercise; longer studies with a larger group of subjects are needed.

3.5.2. Relieving fatigue and muscle soreness

A meta-analysis comparing the effects of supplementation and placebo during resistance exercise showed significant reductions in both fatigue and muscle soreness, suggesting significant improvements in physical performance outcomes (Rhim et al., 2020). L-citrulline or citrulline malate given before exercise significantly reduced ratings of perceived exertion (RPE), with effect sizes that were large (Hedges' g = 0.81, p = 0.03) (Rhim et al., 2020). RPE is a subjective measure of exercise intensity that correlates with cardiovascular load (increased heart rate, lung ventilation, and feeling of shortness of breath), metabolite accumulation (increased blood lactate reflecting anaerobic metabolism), and relative loading intensity (Morishita et al., 2018). In practice, rising RPE values signal that an individual is approaching their physiological limits and experiencing substantial musculoskeletal, cardiopulmonary, and metabolic stress during training (Morishita et al., 2018). In a similar analysis of seven studies looking at muscle soreness 24 hours after exercise, citrulline again helped: soreness ratings dropped by about one full standard unit (g = 0.99, p = 0.04) (Rhim et al., 2020). There was a lot of variation between studies here too (I^2 = 92.1 %, p < 0.001), but no single study skewed the overall result. Muscle soreness is a compensatory mechanism to physical training, but if an individual returns to sport prematurely, it can lead to increased risk of injury; therefore, citrulline malate can be used as an ergogenic aid (Cheung et al., 2003).

3.5.3. Sprint

A randomized, double-blind clinical trial investigated the effects of three days of citrulline malate supplementation (8 g/day) on performance in a 10-repeat, 40 m maximal shuttle-run test in male athletes. Compared with placebo, supplementation led to a significantly faster best sprint time and a markedly smaller decline in performance across successive sprints; however, no differences were observed in metabolic markers (Faria & Egan, 2024). These results suggest that short-term citrulline malate can enhance repeated, high-intensity efforts.

3.5.4. Post-Exercise Blood Lactate

Researchers in a randomized, placebo-controlled trial investigated whether supplementing with 3 g of citrulline/malate, taken over a four-week period, would alter blood lactate levels in active handball players during intense exercise (Kiyici et al., 2017). The study group's lactate levels, which were measured immediately after exercise, decreased significantly by 49.5 % ($p < 0.05$) and were lower compared to the control group ($p < 0.05$); however, the placebo group's lactate level change wasn't significant (Kiyici et al., 2017). Lactic acid is produced during anaerobic muscle metabolism by breaking down carbohydrates, which dissociates into lactate ions and free protons, thereby lowering pH and inducing acidosis (Theofilidis et al., 2018). Lowering pH is associated with disruption of muscle contraction, which is caused by impairing the release and reuptake of Ca^{2+} from the sarcoplasmic reticulum, decreasing myofibrillar sensitivity to Ca^{2+}, inhibiting ATPase activity and key glycolytic enzymes such as phosphofructokinase and phosphorylase (Theofilidis et al., 2018). All things considered, CM can be used as an ergogenic aid in short, intense workouts.

3.5.5. Effect on Hormone Concentrations

In a randomized placebo-controlled trial, both control and study groups, which received supplementation with citrulline malate, followed the same four-week training regimen, consisting of three 90-minute sessions per week. The study group exhibited a statistically significant rise in ACTH, cortisol, and total testosterone; in contrast, the control group showed a noticeable decrease in total testosterone following the training period and no significant changes were observed for the other hormones. When comparing as independent data after the intervention, those who had taken citrulline malate showed significantly higher levels of cortisol and total testosterone than the non-supplemented athletes. Observed differences may be caused by stronger activation of the hypothalamic–pituitary–adrenal axis, leading to elevated ACTH and cortisol associated with the stress response and increased circulating testosterone (Allen & Sharma, 2025; Tizar et al., 2024). Increased testosterone levels may enhance anabolic adaptations and support more efficient muscle mass gains (El Khoury & Antoine-Jonville, 2012).

4. Discussion

Reported benefits of CM supplementation presented in subjective perceptions of participants. A large decrease in rating of perceived exertion, and lesser muscle soreness 24 hours after the exercise were observed. These findings suggest that citrulline malate might delay fatigue and improve recovery, even if it does not improve strength or endurance. Such effects could potentially be caused by the citrulline malate effect on lowering the blood lactate and stabilizing pH. Beyond sports performance, CM has a potential use in various medical applications. Citrulline improved the six minute walk test distance in patients with pulmonary hypertension. It also reduced mean pressure in pulmonary artery, which is associated with a better prognosis. Citrulline supplementation presented a positive effect on glucose control, lipid profile and inflammatory markers in diabetic patients, which can lead to the decrease of cardiovascular risk. Small trials also report benefits for erectile dysfunction, half of participants experienced improved erection hardness. Early evidence suggests slowed atherosclerosis progression through enhanced endothelial function and reduced arterial stiffness. Overall, citrulline malate appears to be safe at the commonly used doses. It little to no gastrointestinal side effects and does not affect liver or kidney parameters. However, as there is a big heterogeneity in dosing regimens, duration of performed studies, and characteristics of studied groups, further large and standardized trials are needed to establish optimal dosing strategy and long-term safety of citrulline malate.

5. Conclusions

Citrulline malate appears to have a positive effect on nitric oxide synthesis and mitochondrial energy metabolism. It can also improve exercise outcome by decreasing fatigue perception and muscle soreness after the training. Studies indicate that it also has a potential clinical application in conditions such as pulmonary hypertension, diabetes, erectile dysfunction and atherosclerosis. Considering its wide range of uses and promising safety profile, it seems to be a usefull ergogenic aid. As there is a big variability in studies outcomes, large, randomised and placebo controlled studies need to be performed to show direct evidence for its ergogenic properties in different types of physical activity, best dosing protocols and safety of long term usage.

Disclosure

Author's contribution

Conceptualization: Adam Rafałowicz, Urszula Justyna Wojciechowska, Paweł Radkowski, Magdalena Rafałowicz, Łukasz Grabarczyk

Methodology: Adam Rafałowicz, Paweł Radkowski, Paweł Jakub Wojciechowski

Formal analysis: Urszula Justyna Wojciechowska, Magdalena Rafałowicz

Investigation: Adam Rafałowicz, Paweł Radkowski, Łukasz Grabarczyk, Paweł Jakub Wojciechowski

Writing – rough preparation: Adam Rafałowicz, Urszula Justyna Wojciechowska, Magdalena Rafałowicz

Writing – review and editing: Adam Rafałowicz, Urszula Justyna Wojciechowska, Paweł Radkowski, Magdalena Rafałowicz, Łukasz Grabarczyk

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