Optimizing Nitric Oxide Production for Exercise Performance & Vascular Function: A Narrative Review on the Combination of Glutathione and Citrulline

Short Review

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Abstract

Introduction: Citrulline has been thoroughly researched and well documented to increase plasma arginine levels, boosting nitric oxide (NO) synthesis via the nitric oxide synthase (NOS) pathway. While glutathione, a key antioxidant, protects NO from oxidative degradation and helps maintain vascular signaling integrity. When taken together, these nutrients may offer enhanced and/or sustained NO bioavailability, supporting vascular function, recovery, and exercise performance more effectively than citrulline alone.

Methods: A literature review was conducted to explore the relationships between glutathione, citrulline, NO, and vascular health. Three databases, PubMed, ScienceDirect, and Google Scholar and eight search terms were used to find relevant articles.

Results: Four double-blind placebo controlled human clinical trials found the combination of glutathione and l-citrulline to be more effective in enhancing and sustaining NO production levels and flow mediated dilation (vasodilation) better than citrulline alone ($p<0.03$).

Conclusions: Collectively, these studies support the functional synergy between citrulline and glutathione in promoting NO-related health and performance outcomes offering a promising nutritional strategy for athletes, aging individuals, and those seeking cardiovascular support.

Key Words: antioxidants, sports nutrition, nitric oxide, flow mediated dilation

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Introduction

Nitric oxide (NO) is a ubiquitous gaseous signaling molecule that contributes to a wide range of physiological processes.[1] Due to the fact that it is water-soluble and freely diffusible, NO crosses cell membranes easily. Nitric oxide's main role is vasodilation, contributing to blood vessel relaxation by increasing the diameter of the vessel, thus improving blood flow.[2] Extensive research has shown that NO is a key determinant of vascular health by exerting antiplatelet, antithrombotic, antioxidant, and anti-inflammatory effects.[2] This favorable impact on blood flow has led to research suggesting skeletal muscle performance, hypertrophy, and strength adaptations may be positively influenced

from increased vasodilation during exercise due to greater NO production.[3] According to a systemic review by Gamonales et al.[4] on nitrate intake and muscle recovery, it is suggested that NO production may not only be beneficial for performance measures (i.e., aerobic and anaerobic exercises), but it may also improve recovery indicators related to strength, inflammation, and muscle damage. Importantly, dietary nitrates (NO_3^-) are indirect precursors that are converted to nitrites (NO_2^-) and then to NO, while NO itself is the active signaling molecule responsible for immediate vasodilation. This clarification shows that nitrates support NO production rather than directly causing vasodilation. However, NO is a difficult molecule to stabilize in circulation due to an extremely short half-life (<2 seconds in plasma).[5] The presence of hemoglobin, oxygen, and superoxide trigger a rapid interaction, with NO being converted into nitrites and nitrates.[5] More specifically, when NO is present in red blood cells, hemoglobin reacts by forming methemoglobin and nitrate (NO_3^-). Furthermore, when oxygen reacts with NO, it leads to the production of nitrogen dioxide (NO_2), which can then also form nitrites and nitrates.[5] These metabolites serve as longer-lasting reservoirs of NO bioactivity but do not directly cause vasodilation. In contrast, NO itself produces the immediate physiological effects, such as quick vascular relaxation and increased blood flow. While both nitrites and nitrates contribute to sustained NO supply through their reservoir capabilities, NO possesses more immediate and direct physiological benefits, such as vasodilation, neurotransmission, exercise performance, and muscle recovery.

L-citrulline (CIT) is a non-essential amino acid endogenously produced within the body as a byproduct of the conversion of ornithine and carbamoyl phosphate through the urea cycle.[6] In the urea cycle, l-citrulline helps convert toxic ammonia, a waste product of protein metabolism, into urea, thereby preventing the buildup that may lead to certain metabolic conditions (i.e., hyperammonemia).[7] In plasma, l-citrulline is converted to arginine, the direct precursor required by the NOS pathway to generate NO.[6] Compared to arginine, citrulline is more efficiently absorbed in the gut and bypasses first-pass metabolism, making L-citrulline a more effective choice for supplementation than L-arginine.[8] This NOS-dependent pathway differs from the nitrate–nitrite–NO pathway by increasing NO production through amino acid metabolism instead of dietary nitrate reduction. Beyond its supportive role in detoxification, citrulline supplementation has been shown to be beneficial in sports performance by increasing NO production and promoting vasodilation. For instance, Theodorou et al.[9] conducted a randomized, double-blind, placebo-controlled crossover trial with 12 healthy males supplementing with a single dose of 6 grams of L-citrulline to assess its effect on NO bioavailability. Their findings demonstrated that one hour post-supplementation, the participants experienced a 19.2% increase in exhaled NO levels (a non-invasive biomarker of systemic or local NO production) compared to the placebo.[9] Citrulline may also reduce the perception of physical fatigue during intense exercise by assisting in the removal of ammonia. For example, Glenn et al.[10] conducted a double-blind, placebo-controlled trial with 15 healthy females examining the effects of 8 grams of citrulline malate (single dose) on resistance exercise performance. The participants who consumed the citrulline malate supplement completed more repetitions in both upper- (bench press, 34.1 ± 5.7 vs. 32.9 ± 6.0 repetitions, $p = 0.045$) and lower-body (Leg press, 66.7 ± 30.5 vs. 55.1 ± 20.6 repetitions, $p = 0.030$) exercises compared to those who received a placebo.[10] Additionally, they reported lower ratings of perceived exertion (RPE) during the exercises, with citrulline malate at 7.9 ± 0.3 and placebo at 8.6 ± 0.2 ($p = 0.20$). However, these effects in exercise are typically found in a single dose ranging from 6-12 grams, which have commonly been associated with gastrointestinal discomfort (i.e., stomach cramps, nausea, and bloating).[3]

Glutathione is a water-soluble tripeptide that comes in two forms: the reduced state (GSH) and the oxidized disulfide form (GSSG).[11] The tripeptide glutathione is made up of three amino acids: cystine, glutamic acid, and glycine.[12] The reduced form (GSH) plays critical roles within the body by defending cells from cellular oxidative stress, detoxifying harmful substances, and regenerating other antioxidants, such as vitamin E and C.[13] Glutathione is known as the "master antioxidant" offering powerful anti-aging benefits through free radical neutralization and mitochondrial preservation.[14] Extensive research has been conducted with glutathione in various areas due to its role in cellular health, affecting numerous biological processes.[15] While this tripeptide has produced relevant findings in the areas of immune health, detoxification/liver health, and cellular health, there appears to be limited information about its role in sports performance and NO production. Baldelli et al.[16] thoroughly described the relationship between glutathione and NO. The reactive oxygen/nitrogen species (ROS/RNS) signaling pathway and the production of S-nitrosylation derivative (P-SNO) link NO effects to the availability and redox status of GSH.[16] Additionally, when NO reacts with the thiol (-SH) group of glutathione, S-nitrosoglutathione (GSNO) is produced, which acts as a reservoir of NO and can release NO when needed. Unlike nitrites and nitrates, which are oxidized storage forms of NO activity, GSNO is a redox-sensitive reservoir that can release NO in a controlled way, connecting glutathione's antioxidant ability to the stabilization of NO. This suggests that when paired together, GSH may assist in stabilizing the NO molecule in plasma, contributing to further circulation of nutrients, oxygen, and glucose to working muscles far longer than if GSH was not present during times of NO release. In one study involving 17 patients with atherosclerosis, Prasad et al.[17]

investigated the effects of GSH administered intravenously on endothelial function and NO's activity in atherosclerosis. The results demonstrated that intravenous GSH treatment improved endothelium-dependent vasodilation mediated by acetylcholine without affecting endothelium-independent vasodilation.[17] Endothelium-independent vasodilation bypasses the endothelium and acts directly on smooth muscle while endothelium-dependent vasodilation requires a functional endothelium. This suggests that GSH enhances NO activity by improving endothelial function.

L-citrulline supplementation, when taken individually, reliably increases NO production, enhances vasodilation, and improves exercise performance metrics like set volume, endurance, and perceived effort. [9,10,18-20] However, effective doses of 6–12 g may cause gastrointestinal discomfort. In contrast, glutathione is primarily recognized for its antioxidant and redox-regulating functions, with evidence showing it stabilizes NO activity through S-nitrosoglutathione formation and improves endothelial function. [11,13,14,17] Despite these established benefits, research directly linking glutathione to exercise performance remains limited. Most studies have examined these compounds separately, with few exploring their combined effects on NO bioavailability and exercise outcomes. Therefore, co-supplementing citrulline with glutathione might offer new insights into enhancing NO stability, efficacy, and tolerability.

While nitric oxide (NO), nitrites, and nitrates have been positively associated with enhanced exercise performance and muscle recovery, the short half-life of the NO molecule poses a challenge for sustaining its physiological benefits. Additionally, supplementation with effective doses of L-citrulline (typically 6–12 grams per day) may cause gastrointestinal side effects in some individuals. Emerging evidence suggests that stabilizing NO within the bloodstream could enhance its exercise-related effects. Taken together, NO itself is the immediate effector molecule, while nitrite and nitrate act as precursor reservoirs, and glutathione helps stabilize and facilitate redox-mediated release. This framework explains why combining glutathione with lower doses of citrulline may enhance NO bioavailability while minimizing side effects. As such, combining glutathione with a lower dose of citrulline shows promise, potentially supporting NO bioavailability while minimizing side effects. The purpose of this brief narrative literature review is to investigate studies with the combination of these two ingredients on vasodilation, NO production, and exercise performance parameters.

Methods

A narrative literature review was conducted to explore the relationships between glutathione, citrulline, NO, and vasodilation. Relevant peer-reviewed articles were identified through comprehensive searches in databases, such as PubMed, ScienceDirect, and Google Scholar, using keywords including "glutathione," "GSH," "citrulline," "nitric oxide," "vasodilation," "flow-mediated dilation," "cardiovascular health," and "vascular health." Inclusion criteria included healthy adult participants, oral supplementation with the combination of GSH + CIT, and follows the double-blind randomized placebo control design. Studies were selected based on their relevance to the biochemical pathways, physiological effects, and clinical implications of these compounds in vascular function and sports performance. Emphasis was placed on recent findings and mechanistic insights to synthesize current knowledge and highlight areas for future research around the combination of glutathione and citrulline. Papers were not included if they were outside the scope (e.g., animal or in vitro research), lacked sufficient methodological detail, or did not directly contribute to the narrative focus. It is important to note that this is a narrative review, and therefore, it does not follow the structured search, inclusion, and quality assessment methods used in a systematic review. While this approach allows for broader and more flexible synthesis of emerging evidence, it may also introduce selection bias and is less comprehensive compared to systematic methods.

Results

Four peer-reviewed original research studies were found exploring this combination in various populations including healthy men, resistance-trained males, and postmenopausal women (see Table 1). The duration of these studies ranges from seven days to eight weeks. The dose for citrulline varies by study, but the combination of l-citrulline (CIT) and reduced glutathione (GSH) remains the same at 200 mg of glutathione (Setria®) and 2 grams of l-citrulline. Participants from all four studies signed written informed consent and were cleared for participation by research/medical staff by passing a mandatory medical screening. Each study was reviewed and approved by Institutional Review Boards, and all experimental procedures conformed to the ethical consideration of the Declaration of Helsinki.

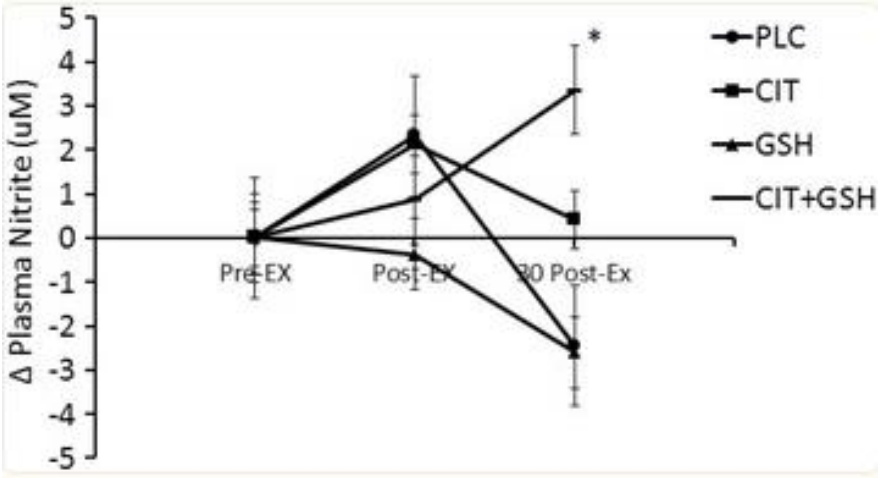
Table 1. Human clinical participant demographics

Study	Sample Size (n)	Sex	Age Range / Mean Age	Population
McKinley et al., 2015	60	Male	18–30	Healthy, trained
Hwang et al., 2018	75	Male	18–30	Healthy, trained
Cabre et al., 2023	25	Male	22 ± 2.4	Healthy, trained
Figueroa et al., 2023	39	Female	51–74	Healthy, post-menopausal

Mean ±SD; n = number of participants

McKinley et al.[21] performed a double-blind, randomized, placebo-controlled trial with 60 healthy, resistance-trained males between the ages of 18 and 30. The participants were randomized into one of four groups (n = 15 per group): placebo (PLC), GSH (1 g/d), CIT (2 g/d), or citrulline + glutathione (200 mg GSH + 2 g CIT). At baseline, the participants were instructed to perform elbow flexor muscle strength tests to determine their one-repetition maximum (1-RM). On the testing day after seven days of supplementation (visit 3, day 7), participants completed 3 sets of 15 repetitions (70-75% of their 1RM) involving elbow flexion exercise on a weighted machine. Venous blood samples were taken immediately before supplementation, immediately after exercise, and again 30 minutes post-exercise. Plasma samples were analyzed for l-arginine, l-citrulline, nitrite, and NO levels, wherein the baseline concentrations of these biomarkers were not statistically significantly different between the groups ($p > 0.05$). On day 7 (visit 3), l-citrulline concentrations were significantly higher ($p < 0.05$) immediately post-exercise and 30 minutes post-exercise for both the CIT and CIT + GSH groups compared to the placebo and GSH alone. Nitrites and NO concentrations in the CIT +GSH group were significantly greater ($p < 0.05$) than placebo at 30 minutes post-exercise.[21] Figure 1 displayed these changes in nitrites following the supplementation protocol.

Figure 1. McKinley (2015) plasma nitrites study results.

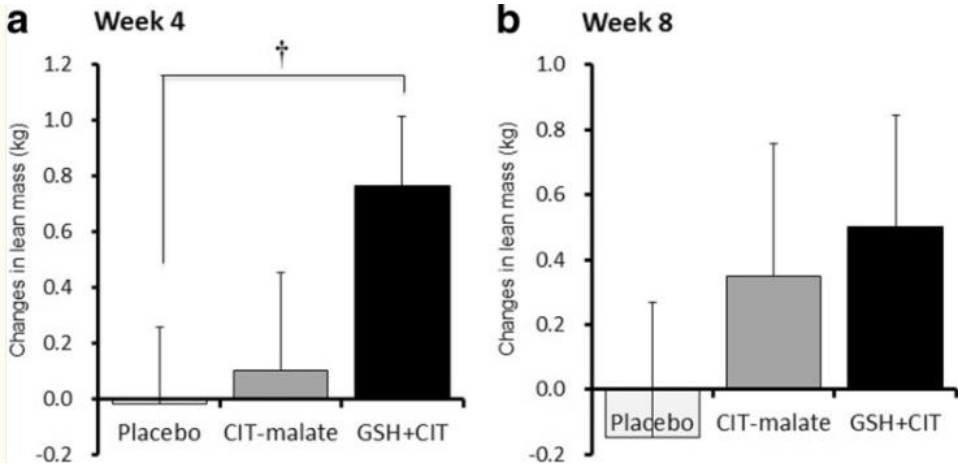


Plasma nitrite concentrations in humans following seven days of supplementation (pre-exercise, post-exercise & 30 min post-exercise). *Significantly different from Placebo ($p < 0.05$)

Hwang et al.[22] performed a randomized, double-blind, placebo-controlled trial involving 75 resistance-trained males ages 18 to 35. Each participant was enrolled into one of three groups (n = 25 per group): GSH + l-citrulline (200 mg GSH + 2 g CIT), l-citrulline-malate (2 g/d), or placebo for 8 weeks. Participants took their assigned supplement one hour prior to exercise. On non-exercise days, participants took their supplement with breakfast in the morning. Participants completed three testing sessions (baseline, 4 weeks, and 8 weeks) where body composition and muscle performance were assessed, and venous blood was obtained. Fat mass and lean mass were determined using a dual-energy X-ray absorptiometry (DEXA) scan, while muscle strength assessments were measured through 1-RM on the free-weight bench press and angled leg press exercises. Participants engaged in a supervised, periodized 4-day per week resistance-training program split into two upper- and two lower-extremity workouts per week for a total of 8 weeks. On testing days, a warm-up consisting of 10 repetitions at 50% of their total body weight was performed. The participant would then rest for one minute, followed by 3 to 5 repetitions at 75% of their body mass. The 1-RM was recorded as the maximum weight that the participant could lift for one repetition. After eight weeks of supplementation, there were no significant ($p > 0.05$) differences between the two groups in terms of body mass or

fat mass. However, lean mass in the GSH + CIT group experienced statistically significantly greater changes than the placebo group after four weeks of training ($p < 0.05$). After 8 weeks, although this change, approximately two-fold, was not statistically significant ($p > 0.05$), it was notable (**Figure 2**).

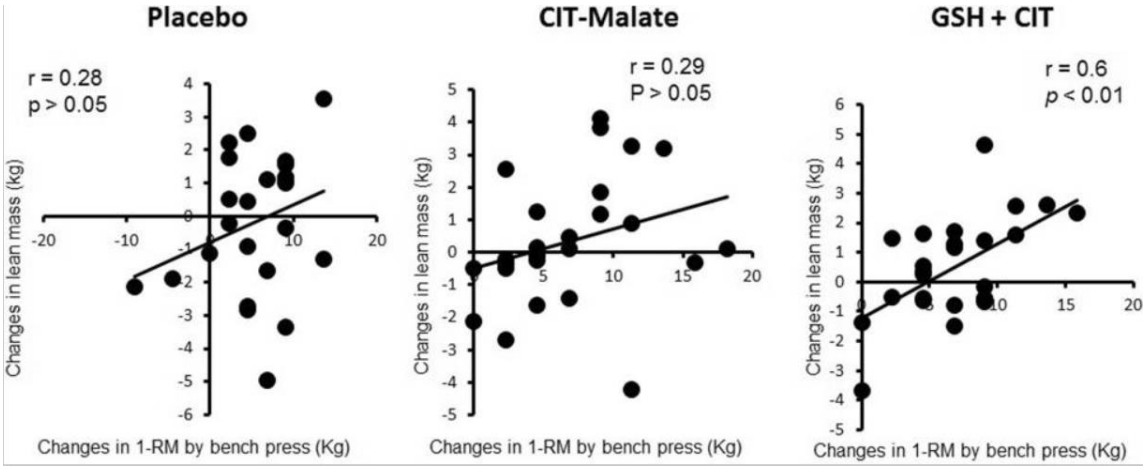
Figure 2. Hwang (2018) lean mass study results.



Changes in lean mass baseline vs 4 weeks (a) and 8 weeks (b) following resistance training and supplementation.
† Significantly different from Placebo ($p < 0.05$).

Muscle strength changes in all three groups were not significantly different for bench press ($p > 0.05$). Changes in 1-RM leg press performance over the eight weeks for all three groups were significantly different from baseline values ($p < 0.05$), but not between groups ($p > 0.05$). However, a statistically significant association between lean muscle mass and strength for 1-RM bench press was only observed in the GSH +CIT group ($p<0.01$) (**Figure 3**).

Figure 3. Hwang (2018) relationship changes lean mass & strength.

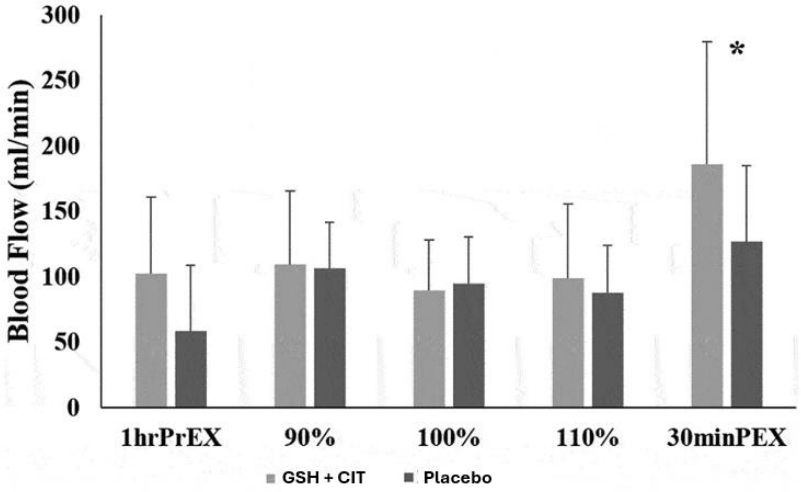


Relationship of changes in lean mass with 1-RM bench press in each group throughout the 8-week study period. A significant correlation was observed only in the GSH + CIT group ($p < 0.01$).

Cabre et al.[23] conducted a double-blind, randomized, placebo-controlled crossover trial with 25 healthy aerobically trained males ages 20 to 24. A washout period of 14 days was implemented based on a half-life of ≤8 hours for both nitrate and l-citrulline. Participants were randomly assigned to the l-citrulline + glutathione group (2000 mg CIT and 200 mg Setria® GSH) or placebo for eight days. Participants performed a maximal oxygen consumption treadmill test to determine peak velocity (PV) and returned after eight days of ingesting their assigned supplement. Treadmill runs to exhaustion (TTE) were performed at three different zones: 90%, 100%, and 110% peak velocity. The varying

intensities were randomly ordered for each participant but were maintained between both testing sessions per participant. Two recovery periods were provided between Trial 1 and Trial 2 and between Trial 2 and Trial 3. Ultrasound was used to measure blood flow and vessel diameter through the brachial artery at 1 hour prior to exercise (1hrPrEX), after each exercise bout, immediately post-exercise (immediate PEX), and 30 minutes post-exercise (30minPEX) at visits 2 and 4. There was no significant treatment effect on TTE at 90% ($p = 0.058$), 100% ($p = 0.405$) or 110% ($p = 0.159$).[23] There were no significant changes in vessel diameter after ingestion of either groups at all time points: 1hrPrEX ($p = 0.980$), 90% ($p = 0.501$), 100% ($p = 0.747$), 110% ($p = 0.374$), or at 30minPEX ($p = 0.124$). There was no significant treatment effect on blood flow at 1hrPrEX ($p = 0.711$), 90% ($p = 0.783$), 100% ($p = 0.631$), or 110% ($p = 0.433$). However, there was a significant treatment effect with GSH + CIT demonstrating significantly greater blood flow at 30minPEX exercise ($p = 0.004$) (Figure 4).[23]

Figure 4. Cabre (2023) blow flow study results.

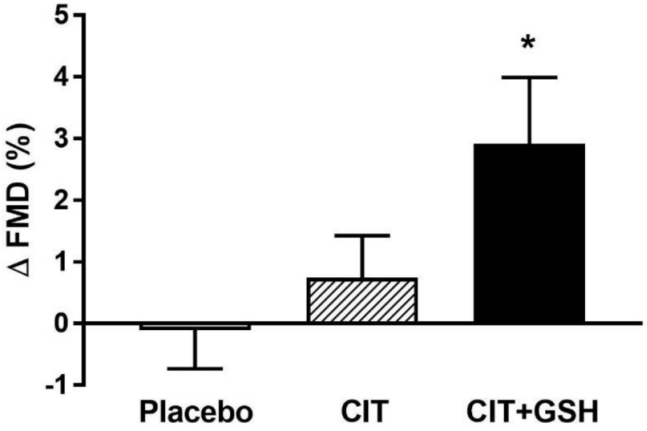


Mean ± SD for blood flow across time points. *Significance between time points ($p < 0.05$)

Figueroa et al.[24] examined 39 healthy postmenopausal women (ages 51-74) in a double-blind, randomized, placebo-controlled trial evaluating flow-mediated dilation (FMD) through the brachial artery when supplementing with citrulline (6 grams) or citrulline + glutathione (2000 mg CIT and 200 mg Setria® GSH) for four weeks. All measurements were evaluated at baseline and after four weeks of supplementation: rachial artery FMD, aortic stiffness (pulse wave velocity, PWV), and brachial and aortic blood pressure (BP) reactivity to cold pressor test (CPT). Carotid-femoral PWV (cfPWV, aortic), carotid-radial PWV (crPWV, brachial), carotid-distal PWV (cdPWV, systemic), and femoral-ankle (dorsalis pedis artery) PWV (faPWV, leg) were determined by applanation tonometry. There were no significant time-by-group interactions for cfPWV, crPWV, cdPWV, or faPWV. However, CIT+GSH supplementation decreased crPWV (arm PWV) by 0.66 ± 0.93 m/s ($p = 0.05$). Endothelial function was assessed by brachial FMD. There was a time-by-group interaction for FMD. CIT+GSH increased the FMD by 2.9% ($p = 0.045$) compared with placebo, but not with CIT ($p = 0.18$). A low effect size was seen between CIT and placebo ($d = 0.32$) and, although insignificant ($p = 0.10$), there was a moderate effect size between CIT+GSH and CIT ($d = 0.67$). (**Figure 5**). To complement the significant increase in FMD, there was a large effect size between CIT+GSH and placebo ($d = 0.91$, $p = 0.03$).[24] Brachial SBP and diastolic BP (DBP) were measured using an automated oscillometric device. Radial artery pressure waves recorded using applanation tonometry were calibrated against brachial mean arterial pressure (MAP) and diastolic blood pressure (DBP). Evidence indicates that augmented systolic BP reactivity to a sympathetic stimulus (CPT) predicts future hypertension and heart failure. A minimum of two high-quality readings (operator index ≥ 80%) were obtained at rest and during the CPT. The average of the two scores were used for analysis. The CPT test involved having the participants introduce their right hand up to the wrist in cold water at 1–4 °C for 2 minutes. The increase in BP from rest to the second minute of the CPT (Δ) was used for the analysis since greater sympathetic activity occurs at this time point. There were significant time-by-group interactions for changes (Δ) in brachial SBP ($p = 0.02$), brachial MAP ($p = 0.04$), aortic SBP ($p = 0.03$), and aortic MAP ($p = 0.04$) responses to the CPT. CIT+GSH supplementation reduced ΔSBP compared to the placebo and CIT ($p < 0.05$ for both) and reduced ΔMAP compared to the placebo (p

< 0.05) but not to CIT (results not shown). No significant time-by-group interactions were observed for ΔDBP, Δ augmentation index normalized to a heart rate of 75, and Δ reflection time. Attenuation of aortic ΔMAP was significantly related to the improvement in FMD% ($p < 0.05$).[24]

Figure 5. Figueroa (2023) flow mediated dilation study results.



Changes in brachial artery flow-mediated dilation (ΔFMD%) from baseline to 4 weeks. *Significantly different vs placebo ($p< 0.05$).

Discussion

The enhancement of vasodilation and NO production remains a central focus in sports nutrition, as increased NO availability may improve physical performance and recovery.[3,19,25,26] Among the various NO-boosting strategies, the combination of l-citrulline and glutathione (GSH) has emerged as a novel and potentially synergistic approach, which may help to optimize the ergogenic and recovery benefits potentially synergistic approach.[21-24]

L-citrulline, a non-essential amino acid and precursor to L-arginine, bypasses hepatic metabolism and enhances systemic arginine levels more effectively than direct arginine supplementation. This promotes sustained NO synthesis via endothelial NO synthase (eNOS), particularly during exercise when demand for blood flow and oxygen delivery increases. Some studies suggest that citrulline supplementation can improve endothelial function, decrease perceived exertion, and delay fatigue; however, results are inconsistent, with many trials showing modest or nonsignificant effects.[18,20]

While citrulline initiates NO production, the stability and bioavailability of NO in the body are often compromised by oxidative stress. This is where glutathione plays a critical role. As the body's principal intracellular antioxidant, GSH mitigates oxidative degradation of NO and supports the redox environment necessary for eNOS coupling.[17] Additionally, glutathione forms S-nitrosoglutathione, a stable NO reservoir that facilitates controlled release and extends the vasodilatory effect of NO beyond the initial production burst.[16,27] This mechanism offers a reason for combining the two compounds, although the clinical evidence is still early. This stabilization is particularly relevant during prolonged or repeated bouts of exercise when oxidative stress is elevated and NO bioavailability declines.

Emerging clinical data suggest that combining citrulline with glutathione enhances plasma nitrite levels, a surrogate marker for NO, more effectively than citrulline alone. For instance, some studies observed increases in plasma nitrites, lean mass, and flow-mediated dilation, while others found no significant changes in vessel diameter, time-to-exhaustion, or muscle strength.[21-24] Therefore, although there may be an additive or synergistic effect where citrulline enhances NO production and glutathione maintains bioactivity, these findings should be interpreted cautiously due to small sample sizes, short intervention periods, and inconsistent results.

From a mechanistic perspective, this dual-nutrient strategy targets both the supply and the sustainability of NO. In athletes, this could translate to improved exercise efficiency, faster recovery due to better metabolite clearance, and potentially enhanced muscular adaptations via improved perfusion and nutrient delivery. Furthermore, the antioxidant support from glutathione may attenuate exercise-induced oxidative damage, contributing to better recovery and reduced inflammation post-exercise.

Despite these promising insights, several gaps remain. Longitudinal studies evaluating performance adaptations, recovery markers (e.g., creatine kinase, inflammatory cytokines), and muscle oxygenation following chronic use of citrulline-glutathione combinations are limited. Additionally, sex-based and sport-specific differences in responsiveness have not been adequately explored. Standardizing dosing protocols, examining timing (e.g., pre- vs. post-workout), and identifying responder subgroups (e.g., endothelial dysfunction, aging athletes) will be critical to refining practical recommendations.

While these four double-blind, placebo-controlled trials provide encouraging evidence that citrulline plus glutathione may support NO-mediated outcomes, the results are mixed. Future research with this combination should include larger, long-term studies to examine its effects on markers of muscle damage and recovery, such as creatine kinase, lactate dehydrogenase, myoglobin, C-reactive protein, interleukin-6, and delayed onset muscle soreness measured through visual analog scoring.

Conclusions

The combination of glutathione and l-citrulline at a 1:10 ratio represents a physiologically rational and evidence-informed strategy to enhance NO-mediated vasodilation, improve blood flow, and support both acute performance and long-term recovery in an athletic population. However, the limited number of available studies justifies further research across different populations.

Acknowledgements and Conflicts of Interest

The K.E. is a researcher and employee of Kyowa Hakko USA INC., which produces and supplies Setria® glutathione globally. D.E.G. has no conflicts of interest to disclose.

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