

# Citrulline

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## summary

Citrulline, specifically L-citrulline, is a non-essential ~~amino~~ amino acid crucial in various physiological processes, notably in the production of nitric oxide (NO), which is vital for vasodilation and blood flow regulation.[\[1\]\[2\]](#) Characterized by the molecular formula  $C_6H_{14}N_2O_4$ , citrulline plays a significant role in the urea cycle, facilitating the detoxification of ammonia and linking it to several metabolic pathways involving other amino acids such as arginine and ornithine.[\[3\]\[4\]\[5\]](#) Its presence in dietary sources like watermelon, cucumbers, and pumpkins has made it a popular supplement among athletes and health enthusiasts aiming to enhance performance and improve overall health outcomes.[\[6\]\[7\]](#)

The notable health benefits of citrulline include improved cardiovascular health, exercise performance, and metabolic function. Research indicates that citrulline supplementation can lead to lower blood pressure and enhanced blood flow during physical activity, which is particularly beneficial for older adults and those engaged in high-intensity workouts.[\[8\]\[9\]](#) Furthermore, citrulline may aid in reducing perceived fatigue, improving endurance, and enhancing recovery, thereby establishing its relevance in sports nutrition and exercise science.[\[10\]\[11\]](#)

Controversies surrounding citrulline primarily focus on the variability of its effects, which can differ based on individual factors such as fitness level, dosage, and the specific nature of the exercise performed.[\[12\]\[13\]](#) While many studies report positive outcomes from citrulline supplementation, some have shown minimal or no significant benefits, highlighting the need for further research to clarify its efficacy and establish standardized guidelines for use.[\[14\]\[15\]](#) Additionally, safety concerns are minimal, with most individuals tolerating citrulline well, though potential mild side effects, including gastrointestinal discomfort, have been noted in some cases.[\[16\]\[17\]](#)

Overall, citrulline is recognized for its multifaceted role in promoting health and enhancing physical performance, making it a subject of growing interest in both clinical and athletic settings.[\[18\]\[19\]](#)

## Chemical Structure

Citrulline, specifically L-citrulline, is an ~~amino~~ amino acid characterized by its molecular formula  $C_6H_{14}N_2O_4$  and a molar mass of 175.19 [g/mol](#)[\[1\]\[2\]](#). The chemical structure of citrulline features a carboxyl group (-COOH), an amino group (-NH<sub>2</sub>), and a side chain containing a secondary amine, which is integral to its classification as an ~~amino~~ amino acid[\[3\]\[4\]](#). The compound exists as 2-amino-5-(carbamoylamino)pentanoic acid and is recognized for its stability under physiological conditions, facilitating its incorporation into various dietary supplements and formulations[\[5\]\[2\]](#).

Citrulline belongs to the class of organic compounds known as L-alpha-amino acids, which are defined by the L-configuration of the alpha-carbon atom[\[4\]](#). It is classified under the broader categories of carboxylic acids and amino acids, emphasizing its

significance in biochemical pathways[3][4]. The structural characteristics of citrulline are crucial for its biological functions, particularly in metabolism and cell signal transduction[3][6].

The presence of a secondary amine in its structure allows citrulline to effectively participate in biochemical reactions, contributing to various physiological processes, including the production of nitric oxide (NO), which plays a vital role in vasodilation and blood flow regulation[6].

## Biosynthesis

Citrulline is synthesized through several interconnected pathways, primarily within the urea cycle, which is crucial for the detoxification of ammonia in mammals. The process begins with the conversion of ammonia and carbon dioxide into carbamoyl phosphate by carbamoyl phosphate synthetase, a reaction that consumes ATP. This carbamoyl phosphate then combines with ornithine, catalyzed by ornithine transcarbamylase, to form citrulline[7][8].

## Key Enzymes in Citrulline Biosynthesis

Among the pivotal enzymes involved in citrulline biosynthesis, argininosuccinate synthetase (ASS) plays a significant role. It catalyzes the reaction between citrulline and aspartate, leading to the formation of argininosuccinate, which is subsequently cleaved by argininosuccinate lyase (ASL) to produce arginine and fumarate[9][10]. This sequence of enzymatic actions showcases the intricate regulation of citrulline production and its conversion to arginine, which is vital for numerous physiological processes, including protein synthesis and nitric oxide production[3][11].

## Alternative Pathways of Citrulline Synthesis

In addition to its classical biosynthesis via the urea cycle, citrulline can also be derived from arginine as a byproduct of the nitric oxide synthase (NOS) reaction, where arginine is oxidized to produce citrulline and nitric oxide (NO)[12][13]. This pathway not only contributes to citrulline levels but also highlights its role in the broader context of nitric oxide signaling, which is crucial for various physiological functions, including muscle contraction and blood flow regulation during exercise[13][3].

Furthermore, enterocytes in the small intestine also produce citrulline, illustrating its importance in amino acid metabolism and nutrient absorption[12][3]. This emphasizes the diverse biosynthetic routes through which citrulline can be generated, depending on the metabolic demands and physiological contexts of the organism.

## Interconversion with Other Amino Acids

Citrulline is metabolically interrelated with other amino acids, notably arginine and ornithine. The conversion of citrulline to arginine involves the sequential action of ASS and ASL, emphasizing the dynamic nature of amino acid metabolism[9][14].

Conversely, citrulline can be converted back into ornithine, highlighting its role as a key intermediate in nitrogen metabolism and homeostasis within the body[8][15].

## Sources

Citrulline is a non-essential amino acid that is found naturally in various fruits and vegetables, with watermelon being one of the most notable sources. It is particularly rich in citrulline, making it a popular choice among athletes and health-conscious individuals looking to enhance their performance and overall health.[3][16] Other dietary sources include cucumbers, pumpkins, and muskmelons, all of which contribute to citrulline intake in the diet.[2]

The consumption of watermelon has been linked to various health benefits, including improvements in inflammation and antioxidant capacity, particularly when incorporated into the diets of individuals consuming atherogenic diets.[17] Citrulline can also be supplemented in the form of L-citrulline malate, which combines citrulline with malic acid to enhance absorption and effectiveness.[18]

Supplementation protocols typically use a dosage of around 8 grams of citrulline malate, which has shown significant effects on reducing perceived exertion and improving muscle performance during exercise.[19][20] Additionally, the bioavailability of citrulline from dietary sources and supplements plays a crucial role in its effectiveness, influencing parameters such as blood pressure and exercise responses.[20]

## Physiological Functions

Citrulline plays a critical role in various physiological processes, primarily through its involvement in nitric oxide (NO) production. NO is a gaseous signaling molecule essential for numerous bodily functions, including the regulation of vascular tone and blood flow. Citrulline acts as a precursor in the citrulline-arginine-NO pathway, whereby it is converted into arginine, which is subsequently metabolized by nitric oxide synthase (NOS) to produce NO[20][21]. This process is vital for enhancing blood flow and oxygen delivery during physical activity, thus improving overall exercise performance[22][23].

## Cardiovascular Health

Research indicates that supplementation with citrulline can lead to significant reductions in arterial blood pressure (BP) and heart rate during exercise, particularly in older adults[20]. This effect is largely attributed to the increased bioavailability of NO, which facilitates vasodilation—widening of blood vessels—and enhances blood flow to muscles and the brain[20][22]. Improved blood flow helps meet the heightened oxygen demand during physical exertion, thereby contributing to better exercise performance and cardiovascular health[13][24].

## Muscle Function and Metabolism

Citrulline also plays a pivotal role in muscle metabolism. During exercise, the demand for energy and amino acids increases, necessitating enhanced citrulline catabolism[7]. The metabolism of citrulline is intricately linked to muscle performance, as it provides ornithine, which can be converted into creatine, an important molecule for energy production in muscle cells[7]. Furthermore, citrulline supplementation has been shown to buffer ammonia levels through the urea cycle, leading to decreased lactate production and improved aerobic utilization of energy substrates during exercise[17].

## Neurovascular Regulation

Beyond its cardiovascular and muscular effects, citrulline is also involved in neurovascular regulation. NO produced from citrulline plays a role in cerebral blood flow auto-regulation and neurovascular coupling, ensuring that sufficient blood reaches active brain regions during physical activity[20]. This function highlights citrulline's importance in both physical and cognitive performance, particularly under conditions of increased metabolic demand.

## Aging and Health Implications

As individuals age, the metabolic pathways involving citrulline can become less efficient due to declining enzymatic activity, potentially leading to increased risks of cardiovascular diseases and other age-related health issues[7][17]. Thus, understanding the metabolic shifts of citrulline across the lifespan is crucial for developing strategies to mitigate these risks and promote healthier aging.

## Health Benefits

Citrulline, a non-essential amino acid, has garnered attention for its wide-ranging health benefits, particularly in cardiovascular health, exercise performance, and metabolic function.

### Cardiovascular Health

Citrulline is known for its ability to act as a vasodilator, helping to widen blood vessels and improve blood circulation.[25] This effect can lead to lower blood pressure, which is significant in reducing the risk of cardiovascular diseases.[26][6] Several studies indicate that citrulline supplementation may lower blood pressure, although results vary, with some studies reporting minimal or no significant effects.[27][28] Its potential to support endothelial function also contributes to overall cardiovascular health, particularly in populations at risk, such as postmenopausal women.[29]

### Exercise Performance

The use of citrulline supplements is often promoted to enhance exercise performance. Research suggests that citrulline can improve endurance and recovery during physical activities by increasing nitric oxide production, which may enhance

blood flow and oxygen delivery to muscles.[\[30\]](#)[\[31\]](#) Athletes and individuals engaged in high-intensity workouts may benefit from citrulline supplementation as it has been shown to decrease the perception of fatigue and improve performance metrics in various sports.[\[25\]](#)

## Metabolic Health

Beyond its cardiovascular and performance benefits, citrulline may play a role in metabolic health. It has been associated with improved body composition and may help in managing conditions such as insulin resistance and type 2 diabetes. Citrulline's ability to enhance nitric oxide levels can improve insulin sensitivity and blood sugar management, potentially reducing the risk of complications related to high blood sugar and diabetes.[\[28\]](#)[\[24\]](#) Moreover, it has been noted that citrulline acts as an antioxidant, further supporting metabolic functions and reducing oxidative stress.[\[30\]](#)

## Research and Studies

### Health Benefits of Citrulline

Citrulline, a non-essential amino acid, has been the subject of numerous studies due to its potential health benefits, particularly in enhancing physical performance and supporting metabolic health. Research indicates that citrulline supplementation may improve exercise performance, body composition, and cardiovascular health [\[30\]](#)[\[25\]](#)[\[3\]](#). Notably, it has been shown to act as a vasodilator, helping to widen blood vessels, which can contribute to improved blood flow during physical activity [\[6\]](#).

### Mechanisms of Action

The effectiveness of citrulline may be attributed to its role in increasing nitric oxide (NO) production within the body. Increased NO levels can enhance vascular function, thereby supporting endurance exercise performance [\[13\]](#). However, the impact of citrulline on exercise performance is influenced by various factors, including exercise intensity, duration, and individual differences in NO synthesis among sexes and fitness levels [\[13\]](#)[\[20\]](#).

### Systematic Reviews and Meta-Analyses

A systematic review assessing the effects of nitric oxide-related supplements, including citrulline, found significant improvements in time trial (TT) and time-to-exhaustion (TTE) performance. Specifically, significant, moderate improvements were noted in intermittent graded exercise tests (IGXT), while no significant effects were observed in performance tests lasting less than 5 minutes or more than 60 minutes [\[13\]](#)[\[32\]](#). This suggests that citrulline may be particularly beneficial for certain types of endurance activities.



# Clinical Trials and Study Design

Clinical trials have utilized various designs, including crossover and parallel trial formats, to evaluate the benefits of citrulline. Crossover trials generally reported trivial but significant benefits from citrulline supplementation, whereas parallel trials indicated smaller, insignificant improvements [\[13\]](#). This discrepancy highlights the need for careful consideration of study design when interpreting results.

## Current Findings

Research has identified that citrulline not only supports exercise performance but also may enhance muscle function and possess antioxidant properties [\[25\]](#)[\[3\]](#). Some studies have reported that citrulline supplementation may lead to reductions in plasma ammonia levels, which could help in reducing fatigue during prolonged exercise [\[3\]](#)[\[33\]](#). Overall, while the evidence suggests a range of benefits from citrulline supplementation, more extensive and well-controlled studies are needed to fully understand its potential and safety [\[6\]](#)[\[33\]](#).

## Side Effects and Safety

Citrulline, particularly in its L-citrulline form, is generally considered safe and well-tolerated by most individuals. Adverse effects associated with L-citrulline supplementation are rare, and most studies report no significant negative outcomes for participants [\[25\]](#)[\[34\]](#). However, individual responses may vary, and it is crucial to monitor for any unexpected reactions when starting supplementation.

## Potential Side Effects

While serious adverse events are uncommon, there have been reports of mild side effects. In clinical trials, a small percentage of patients experienced adverse events, with no significant differences between those taking L-citrulline and those receiving a placebo [\[35\]](#). Some studies indicate that L-citrulline may cause gastrointestinal discomfort, diarrhea, or an upset stomach in certain individuals [\[25\]](#). Furthermore, the long-term effects of high-dose supplementation remain uncertain, necessitating further investigation to establish comprehensive safety guidelines [\[34\]](#).

## Drug Interactions

L-citrulline may interact with specific prescription medications, particularly those prescribed for hypertension and cardiovascular conditions. Individuals taking medications for these issues should consult with their healthcare provider before beginning L-citrulline supplementation [\[6\]](#). As the FDA does not regulate dietary supplements as rigorously as prescription drugs, it is advisable for consumers to choose reputable products to ensure quality and accurate labeling [\[25\]](#).

## Dosage Considerations

There is currently no standard recommended daily dose for L-citrulline, and previous research suggests that individuals can tolerate doses up to 15 grams over an 8-hour period without experiencing side effects[6]. However, the efficacy and safety of such high doses, particularly for prolonged use, have not been fully established. It is advisable for individuals to discuss appropriate dosages with their healthcare provider, who can provide guidance based on personal health status and specific needs[32][6].

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