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Citrulline: A Multifunctional Compound for Health, Performance, and Therapeutic Applications

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Abstract

Introduction:

L-citrulline, a non-proteinogenic amino acid, is predominantly synthesized in the enterocytes of the small intestine, with smaller amounts produced in the kidneys, which plays a critical role in the detoxification of ammonia in the urea cycle, and serves as a precursor for nitric oxide (NO). Recent studies have highlighted citrulline's potential benefits in diverse physiological and pathological contexts, ranging from enhancing physical performance and muscle recovery to supporting cardiovascular health, mitigating endothelial dysfunction, and acting as a therapeutic agent in various health conditions.

Aim of study:

The study aims to provide a comprehensive summary of current knowledge on the biochemical characteristics, physiological functions, and therapeutic potential of citrulline.

Materials and methods:

A comprehensive scientific literature review was conducted using the PubMed database, focusing on studies published up to 2024, reporting experimental, clinical, or in vivo data related to citrulline's synthesis, biological functions, and therapeutic applications. Keywords used in the search included "L-citrulline," "arginine metabolism," "physical performance,"

"vascular health," "neuroprotection," and "citrulline supplementation" in various combinations.

Conclusion:

Emerging evidence highlights citrulline's potential in treating various health conditions, such as erectile dysfunction, neurodegenerative diseases, and intestinal barrier dysfunction, as well as its protective effects in hepatic failure, wound healing, and oxidative stress-related damage. These findings suggest that citrulline may serve as a multifaceted therapeutic agent, meriting further research to optimize its clinical use.

Key words: citrulline;NO;hypertension;sport;neuroprotection

Introduction

Citrulline (L-citrulline) is a non-proteinogenic amino acid first isolated from watermelon juice (Citrullus lanatus), from which its name is derived [1]. Citrulline is primarily synthesized in the enterocytes of the small intestine from ornithine and carbamoyl phosphate through a reaction catalyzed by citrulline synthase [1]. To a lesser extent, it is also produced in the kidneys and can be supplied through dietary intake [2,3]. After its synthesis in enterocytes, citrulline is transported to the liver via the portal circulation, where it is converted into arginine [1]. Arginine derived from citrulline is a key amino acid in the urea cycle, responsible for eliminating toxic ammonia [1]. It is also a precursor of nitric oxide (NO), an essential vasodilator and neurotransmitter [1]. The enzyme nitric oxide synthase (NOS) catalyzes the conversion of arginine into NO and citrulline, completing a cycle in which citrulline can be reutilized for arginine synthesis [1]. Supplementation with citrulline more effectively increases plasma arginine levels than direct arginine administration because citrulline is not extensively metabolized in the liver [2,3].

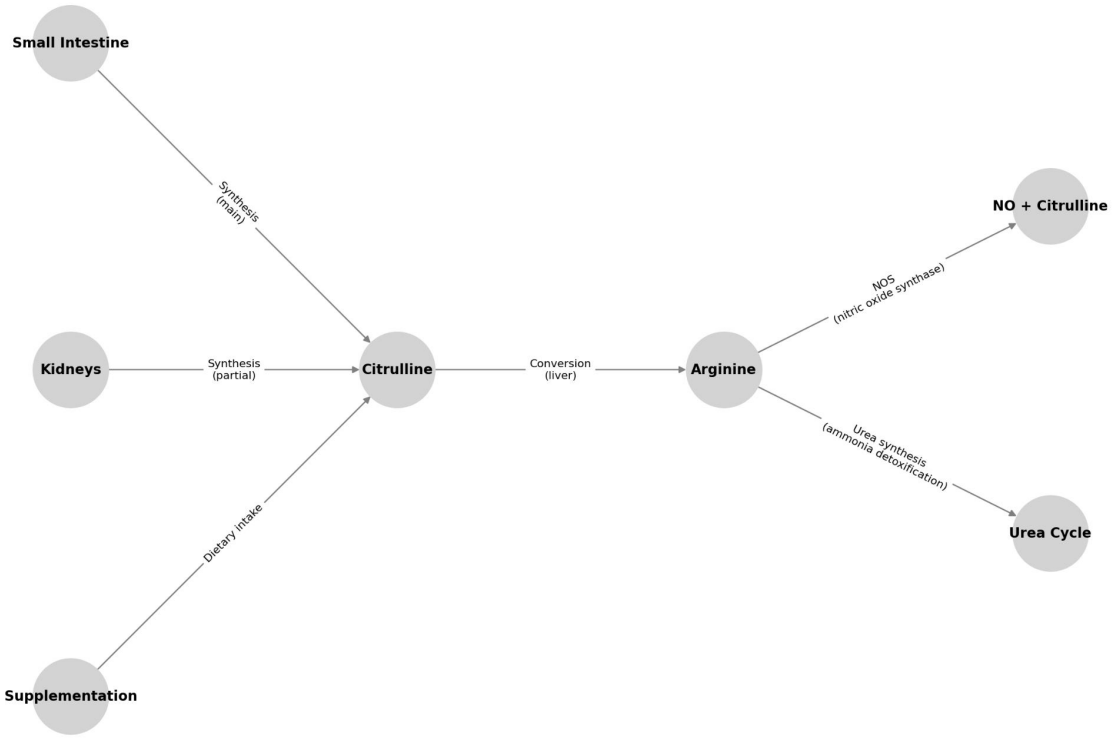

Fig. 1. Synthesis and metabolism of citrulline

Impact on Physical Performance and Muscle Recovery

Citrulline supports physical performance by improving both aerobic and anaerobic muscle metabolism [1]. Its supplementation, which enhances the bioavailability of arginine as a precursor of nitric oxide (NO), leads to increased NO plasma levels, vasodilation, and improved blood flow to muscles. This enhances oxygen and nutrient delivery and facilitates the removal of metabolic byproducts such as lactate and ammonia [1,4]. Studies have shown that supplementation with citrulline malate (a combination of L-citrulline and malate) improves performance in strength and endurance sports, confirmed in both laboratory and real-world exercise tests [4,5]. Citrulline helps reduce muscle fatigue and delayed-onset muscle soreness (DOMS) by promoting the elimination of ammonia generated during protein metabolism and by influencing the acid-base balance, which is particularly important during intense exercise [4,5]. Supplementation also reduces CO2 and hydrogen ion accumulation in muscles, supporting optimal pH maintenance [5,6]. Citrulline aids in ammonia detoxification via the urea cycle and may accelerate phosphocreatine resynthesis, shortening muscle recovery times after intense exercise [1,4,6]. Additionally, it exhibits antioxidant properties, protecting muscle cells from exercise-induced damage [1,7]. Repeated supplementation

increases arginine and NO levels, enhancing mitochondrial biogenesis and adaptive capacity in muscles during prolonged, strenuous training [8,9]. Citrulline may also positively affect the nervous system by reducing central nervous system (CNS) fatigue, potentially via improved cerebral blood flow and oxidative stress reduction [10].

Role in Supporting Vascular Health

Citrulline is increasingly studied as a potential adjunct in hypertension management [9]. As a precursor of arginine, essential for NO production in endothelial cells, it facilitates smooth muscle relaxation, resulting in vasodilation and decreased peripheral resistance [1,8]. Clinically, this effect translates into improved blood flow and reduced systolic and diastolic blood pressure [8]. Hypertension often involves endothelial dysfunction and impaired NO production [11]. By increasing arginine levels, citrulline supports endothelial repair and improves vascular responsiveness to mechanical stimuli [11]. Supplementation reduces arterial stiffness by mitigating oxidative stress and supporting collagen synthesis with more elastic properties, even in older adults [12]. Citrulline may complement pharmacotherapy for conditions like metabolic syndrome (improving lipid profiles and reducing inflammation), renal insufficiency (enhancing toxic metabolite elimination and renal blood flow), and heart diseases (reducing left ventricular workload) [8,13]. Studies show that citrulline supplementation can alleviate fatigue and improve exercise tolerance in cardiovascular patients, which is critical for rehabilitation after myocardial infarction or surgeries [13]. Additionally, citrulline holds therapeutic potential for Raynaud's phenomenon, possibly reducing ischemic episodes and aiding tissue regeneration in peripheral arterial disease [1,14]. It also supports blood pressure regulation in type 2 diabetes and obesity, conditions often linked to insulin resistance and endothelial dysfunction [15]. Research indicates that citrulline supplementation lowers cardiovascular risk markers in metabolic syndrome patients [16]. It may also benefit pregnancy-related hypertension and preeclampsia by improving placental blood flow and reducing vascular tension, although further studies are needed to confirm its efficacy [8,17]. Citrulline has been investigated for pulmonary hypertension, showing improved respiratory performance and reduced pulmonary artery pressure in children [18].

Erectile Dysfunction and Sexual Health

Nitric oxide (NO) is a key regulator of the erectile process, enabling smooth muscle relaxation in the corpus cavernosum of the penis (increased blood flow), thereby enhancing penile engorgement [17,19,20]. Through these mechanisms, citrulline supplementation improves vascular responses to sexual stimulation [20]. Erectile dysfunction is often associated with endothelial dysfunction. Citrulline improves endothelial function by reducing oxidative stress and inflammation (e.g., lowering markers like IL-6 and IL-10), which increases NO bioavailability [20]. Unlike drugs such as phosphodiesterase type 5 inhibitors (PDE-5 inhibitors), citrulline supplementation avoids excessive vascular stimulation [20,21]. Clinical studies have shown improvements in erection quality, increased hardness scores, and enhanced sexual satisfaction, attributed to improved erection quality and confidence [22,23]. Citrulline may support sexual function in individuals with depression or stress, both of which can contribute to erectile dysfunction [20,23]. While citrulline is less effective than sildenafil for moderate-to-severe erectile dysfunction, it can serve as a natural alternative or adjunct therapy for men with mild symptoms, older individuals at risk of vascular changes, and those with comorbidities (e.g., metabolic syndrome) [21,22,23]. Research suggests that combining citrulline with PDE-5 inhibitors may enhance their efficacy or serve as an alternative for those who cannot tolerate these drugs [22,23].

Applications in Atherosclerosis Treatment

Citrulline acts as an antioxidant, reducing free radicals that accelerate the oxidation of low-density lipoproteins (LDL) into oxLDL [25]. It also reduces the expression of adhesion molecules such as VCAM-1 and ICAM-1, which attract monocytes and lymphocytes to sites of endothelial injury [25]. This decreases inflammatory cell infiltration and slows plaque progression [26,27]. Long-term citrulline supplementation (3–6 g/day) has also been shown to reduce inflammatory markers, including C-reactive protein (CRP) [25,26].

Hepatic Function and Detoxification

In liver failure, ammonia accumulates in the blood, potentially leading to hepatic encephalopathy, manifested clinically by disorientation, seizures, or even coma [27]. As a precursor of arginine, citrulline supports ammonia detoxification by converting it into less toxic intermediates, which can then be excreted via the kidneys [1,17]. Studies have found

that citrulline administration in cirrhosis patients enhances urea production, aiding ammonia detoxification. Additionally, citrulline supplementation may promote hepatocyte regeneration, alleviate encephalopathy symptoms, and improve cognitive function [17,27]. Increased NO production during citrulline supplementation may also improve hepatic blood flow, facilitating repair processes and nutrient delivery to hepatocytes. However, this hypothesis requires further studies, as existing research was conducted on alcohol-induced liver damage models in rodents [28].

Gastrointestinal Protection and Regeneration

Citrulline is produced in the intestines, primarily in the enterocytes of the small intestine, where glutamine is converted into citrulline, which then travels to the liver and kidneys [1,29]. Its plasma concentration is considered an indicator of active enterocyte mass, correlating with intestinal mucosal damage [30]. Inflammation or mechanical injuries to the intestinal lining increase its permeability, leading to bacterial toxin translocation into the bloodstream [29]. Through its anti-inflammatory properties and promotion of NO production, which regulates epithelial permeability, citrulline supports enterocyte regeneration. Studies have shown that supplementation improves intestinal barrier integrity, accelerates healing, and enhances epithelial function, thereby improving nutrient absorption [1,31,32,34]. In patients with short bowel syndrome (SBS), citrulline supplementation increased blood arginine levels, improved nitrogen balance, and reduced malnutrition symptoms, enhancing tolerance to oral feeding [33,34]. Under conditions of impaired intestinal function, citrulline can act as a nitrogen reservoir, supporting protein synthesis and tissue repair [33,34].

Neuroprotection and Cognitive Function

Citrulline demonstrates potential in improving cognitive function and protecting the nervous system through its ability to enhance NO synthesis, reduce oxidative stress, improve cerebral blood flow, and support neurogenesis and synaptic plasticity [1,35]. Its antioxidant properties and free radical neutralization mitigate neuron damage caused by oxidative stress, a key factor in neurodegenerative disorders such as Alzheimer's and Parkinson's diseases [1,36]. Research indicates that citrulline enhances memory and concentration by increasing blood flow in the prefrontal cortex and promoting neurogenesis in the hippocampus, an area critical for long-term memory [1,8,35]. NO plays a crucial role in synaptic plasticity mechanisms, such as long-term potentiation (LTP), which underpins learning and memory processes. Increasing

arginine availability through citrulline supplementation supports these processes [35]. The cognitive benefits of citrulline supplementation were particularly noticeable in individuals with mild cognitive impairment, where improvements in memory and concentration were observed [35,36].

Future Prospects for Citrulline Utilization

Citrulline may modulate the immune system by regulating NO production in macrophages, which is critical for the immune response [38]. Studies suggest citrulline can enhance immune function under conditions of metabolic stress and chronic diseases [38]. Its ability to stimulate arginine and NO synthesis may support skin repair processes [1,39]. In vitro studies have shown that citrulline accelerates wound healing by promoting fibroblast proliferation, and angiogenesis. Also citrulline improves skin hydration and reduces wrinkles [39,40]. Citrulline may also improve sleep quality through enhanced NO production, although further studies are needed to confirm this hypothesis [1,41]. It is hypothesized that citrulline could influence bone health by regulating nitrogen metabolism and reducing inflammation [1,42]. Experimental animal studies have demonstrated that citrulline supplementation improved bone mineralization and reduced osteopenia risk [42]. Citrulline's chelating properties may also support heavy metal detoxification. Studies on animal models have shown that citrulline could serve as a therapeutic agent for managing heavy metal toxicity, particularly in male reproductive health [43].

Conclusion

Citrulline emerges as a multifunctional compound with significant implications for human health. Its unique metabolic pathways and ability to augment nitric oxide production make it a valuable adjunct in enhancing physical performance, muscle recovery, and vascular health. Citrulline supplementation has shown promise in managing conditions like hypertension, endothelial dysfunction, and cardiovascular diseases by improving blood flow, reducing oxidative stress, and supporting arterial flexibility. Beyond cardiovascular benefits, citrulline also supports sexual health, hepatic detoxification, gastrointestinal integrity, and cognitive function. Emerging evidence highlights its potential in neuroprotection, immune modulation, and skin repair.

While these benefits position citrulline as a therapeutic and performance-enhancing agent, further research is essential to fully understand its mechanisms and optimize its applications in clinical and athletic settings. Continued exploration into dosage, long-term effects, and combinatory treatments will solidify its role in preventive and regenerative medicine.

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The data presented in this study is available upon request from the corresponding author.

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Conflict of Interest Statement

All authors declare that they have no conflicts of interest.

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