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# Citrulline – The Powerhouse Nutrient for Cardiometabolic and Brain Health

**Authors**:

1. Daria Pedrycz

- affiliation: Department of Family Medicine, Medical University of Białystok

- ORCID: 0009-0001-4988-5992

- corresponding author: e-mail: daria.pedrycz@op.pl

2. Mateusz Drabczyk

- affiliation: Bonifrater Medical Center Branch in Katowice

- ORCID: 0000-0003-3354-5982

3. Emilia Pedrycz

- affiliation: Wojewodzki Szpital Zespolony w Kielcach

- ORCID: 0009-0006-2751-2227

4. Karolina Karoń

- affiliation: Municipal Hospital in Zabrze

- ORCID: 0009-0005-0356-8907

5. Grzegorz Drapała

- affiliation: Wojewodzki Szpital Zespolony w Kielcach

- ORCID: 0009-0008-1492-1544

6. Wojciech Grabowski
- affiliation: Municipal Hospital in Zabrze
- ORCID: 0009-0006-9238-1411
7. Łukasz Karoń
- affiliation: Department of Pathology and Molecular Diagnostics, Medical University of Silesia in Katowice
- ORCID: 0009-0009-5083-8307
8. Anna Zygmunt
- affiliation: Department of Pathology and Molecular Diagnostics, Medical University of Silesia in Katowice
- ORCID: 0009-0002-5849-6347
9. Sławomir Karoń
- affiliation: Wojewódzki Szpital Specjalistyczny nr 5 w Sosnowcu im. św. Barbary
- ORCID: 0009-0003-2551-4745

**Abstract**

Citrulline, a non-essential amino acid and precursor to L-arginine, plays a pivotal role in nitric oxide (NO) synthesis, with profound implications for vascular health and neuroprotection. By enhancing NO production, citrulline supports endothelial function, vasodilation, and cerebral circulation, thereby mitigating cognitive decline associated with aging and neurodegenerative diseases. Unlike direct arginine supplementation, citrulline offers superior bioavailability, bypassing first-pass metabolism and achieving sustained plasma levels of arginine. Furthermore, citrulline's antioxidant properties counteract oxidative stress by modulating reactive oxygen species (ROS), reducing lipid peroxidation, and protecting neuronal integrity. Emerging evidence suggests its potential in delaying endothelial senescence and preventing ferroptosis, establishing its role in vascular and neuroprotective strategies. Dietary sources, such as watermelon juice, further enhance citrulline’s accessibility, combining its bioactivity with additional antioxidants like lycopene. While existing studies underscore its promise, targeted research is needed to confirm its direct impact on cognitive function and explore its application in neurodegenerative populations. This review synthesizes current knowledge on citrulline's mechanisms, therapeutic potential, and broader implications for aging and vascular health.

Keywords: Citrulline, Watermelon juice, Cognitive function, Vascular health, Neuroprotection, Neurodegenerative diseases, Oxidative stress

## Introduction

Citrulline, amino acid with distinct metabolic properties, has garnered significant interest for its potential role in enhancing cognitive function through mechanisms tied to vascular health and oxidative stress reduction. Unlike other amino acids, citrulline serves as a precursor to L-arginine, a substrate for nitric oxide (NO) synthesis. NO is a critical molecule in vascular homeostasis, mediating vasodilation, enhancing blood flow, and supporting endothelial function. These vascular benefits are particularly relevant for brain health, where efficient blood flow and reduced oxidative damage are pivotal for maintaining cognitive performance and mitigating age-related decline. As highlighted by Tsuboi et al. , citrulline supplementation has been shown to reduce endothelial senescence and enhance NO production, thereby mitigating oxidative damage and promoting vascular health [3]. This unique profile positions citrulline as a promising candidate for addressing neurovascular dysfunction, a key contributor to cognitive impairment.

The growing interest in dietary and supplement-based neuroprotective strategies reflects the urgent need to counter the increasing prevalence of cognitive disorders, particularly those associated with aging. As demonstrated by Bahri et al., citrulline's antioxidant properties and its ability to attenuate oxidative stress by reducing reactive oxygen species (ROS) further bolster its potential as a neuroprotective agent [2]. Mechanistic studies have revealed that citrulline supplementation can restore endothelial NO levels, modulate oxidative stress pathways, and improve vascular function, creating a foundation for its application in preventing and treating cognitive decline. Additionally, Papadia et al. emphasized citrulline’s therapeutic potential in age-related health conditions due to its ability to enhance vascular NO levels and reduce oxidative damage [1]. These findings are particularly compelling given the safe and well-tolerated nature of citrulline, even with long-term use, making it an attractive option for widespread application.

This growing body of research necessitates a deeper exploration of citrulline's molecular pathways and its direct implications for cognitive health. Its ability to synergize vascular benefits with oxidative stress modulation suggests it could serve as an integral part of broader neuroprotective strategies, particularly in addressing age-related cognitive decline and neurodegenerative diseases.

**Citrulline as a key precursor in nitric oxide synthesis**

Citrulline is a non-essential endogenous amino acid frequently found in natural food sources like watermelon. It is synthesized in the body from ornithine through a process that not only adds to the dietary intake but also supports various metabolic functions [1]. In human physiology, citrulline steps into the metabolic pathway as a precursor to arginine, a critical substrate that promotes the production of nitric oxide (NO) [2]. This process is crucial as nitric oxide serves fundamental roles in mediating vascular function, enhancing vasodilation and contributing to the overall cardiovascular health. Furthermore, citrulline's conversion to arginine bypasses the typical liver-first pass metabolism found in direct arginine supplementation, resulting in more sustained and elevated plasma levels of arginine when citrulline is ingested [1].

Comparatively, while both citrulline and arginine serve as precursors to nitric oxide, citrulline offers advantages in terms of absorption and retention within the circulatory system, positioning it as a more potent regulator of NO-mediated processes. In recent studies, citrulline supplementation has shown potential not only in supporting athletic performance by enhancing blood flow and oxygen delivery but also in delaying the onset of endothelial senescence, contributing to healthier aging of the vascular system [3]. This heightened efficacy makes citrulline a valuable supplement in managing conditions related to endothelial aging and dysfunction, as evidenced by therapeutic research demonstrating its role in decelerating the process of endothelial cell senescence and supporting vascular health [3].

**Citrulline's impact on vascular system health**

Citrulline supplementation has been identified as a potent enhancer of nitric oxide (NO) production, which plays a crucial role in vasodilation. Nitric oxide is essential for widening

blood vessels, regulating blood flow and thereby positively influencing cerebrovascular circulation [4]. The enhancement of NO levels can improve blood flow, reduce blood pressure and increase the delivery of nutrients as well as oxygen to the brain which supports overall cardiovascular and cognitive health.

The endothelium, a thin layer of cells lining the blood vessels is essential for regulating vascular tone and blood pressure through the production of NO. By enhancing L-arginine availability, L-citrulline supplementation supports endothelial NO production which is vital for maintaining vascular health and preventing hypertension. Research trials have indicated that L-citrulline can significantly lower resting blood pressure by positively impacting endothelial function [5,6].

Furthermore, studies suggest that L-citrulline supplementation may have a favorable impact on cerebral blood flow, potentially improving cognitive function. While the precise mechanisms are yet to be fully understood, the observed improvements in endothelial function and NO production likely contribute to enhanced blood supply to the brain. Although direct human studies remain limited, the beneficial effects on systemic circulation observed in existing research suggest that similar outcomes may occur in cerebral circulation. Further investigation, including both human and animal studies, is needed to confirm these findings [4,5].

These insights underscore the potential of L-citrulline as an effective supplement for enhancing vascular system health. The mechanisms primarily involve NO production, improved endothelial function and the regulation of blood pressure with promising implications for both systemic and cerebral circulation benefits.

**Role of Citrulline in Oxidative Stress and Neuroprotection**

Oxidative stress plays a crucial role in the decline of cognitive function, particularly within the context of neurodegenerative diseases. It results from an imbalance between the production of free radicals - unstable, reactive oxygen species (ROS) and the brain's capacity to detoxify them through antioxidant mechanisms [7]. This imbalance damages lipids, proteins and nucleic acids, elements highly susceptible within the brain due to its elevated

oxygen consumption and a high concentration of polyunsaturated fatty acids along with iron, which catalyze free radical production [8].

The persistent presence of oxidative stress is noted to catalyze and exacerbate the progression of neurodegenerative diseases such as Alzheimer's and Parkinson's [9]. In these illnesses, increased ROS levels contribute to neuronal damage and cell death, which critically impacts cognitive functions [10]. Moreover, oxidative stress also increases the accumulation of misfolded proteins, a key feature of Alzheimer's, where beta-amyloid plaques are present [11].

Mitochondrial dysfunction, triggered by oxidative stress, worsens these conditions. Since neurons are highly dependent on mitochondrial energy production, dysfunctions associated with oxidative damage heighten neurodegenerative risks [12]. Also, impairments in synaptic plasticity and neurotransmission compromise foundational cognitive processes like learning and memory [13].

**Antioxidant Properties of Citrulline: Modulating Oxidative Stress and Reactive Oxygen Species (ROS)**

L-citrulline has shown significant potential in modulating oxidative stress through its antioxidative properties and its role in nitric oxide (NO) biosynthesis. One of the primary functions of citrulline is to serve as a precursor for arginine synthesis in the kidneys, which in turn is a precursor for NO. Nitric oxide is crucial for maintaining endothelial function and vascular health, enabling it to mitigate the harmful effects of Reactive Oxygen Species (ROS) [14].

Clinical trials demonstrates that citrulline supplementation can help restore NO levels, which might drop in oxidative conditions. It is known to protect brain capillary endothelial cells from glutamate-induced cytotoxicity by enhancing NO production, which facilitates better blood flow and nutrient delivery to the brain [15]. This restoration is particularly beneficial in pathological conditions where vascular dysfunction is a key concern [16].

Additionally, citrulline's contribution to regulating ROS involves modulating enzymatic activities and signaling pathways that can balance oxidative stress and reduce cellular damage. For instance, it aids in reducing the lipid peroxidation levels, thus protecting neuronal

membranes from oxidative stress [12]. Its antioxidant effects are further enhanced when combined with other compounds like glutathione, where recent studies suggest it significantly improves endothelial function and blood pressure response in populations at risk, such as postmenopausal women [17].

Citrulline has also been noted to be effective in preventing ferroptosis - a form of programmed cell death associated with iron and oxidative stress which highlights its role in preserving cellular integrity and function under stress conditions [18]. Furthermore, it helps in modulating oxidative stress markers such as malondialdehyde, superoxide dismutase and catalase, which are crucial in assessing oxidative damage and the antioxidant capacity of cells [9].

Significant findings from both in vitro and in vivo studies reveal citrulline's role in sustaining oxidative balance and protecting cellular functions. Its administration is associated with diminished oxidative and inflammatory biomarkers, evidencing its systemic antioxidant capability [19].

These insights highlight citrulline's antioxidant promise for treating oxidative damage, especially in neurodegenerative contexts. Its modulation of ROS, restoration of NO levels and enhancement of cellular uptake support its therapeutic application for neuroprotection against oxidative stress [10]. Integrating citrulline-based strategies may benefit in counteracting the detrimental effects of free radicals on cognition and neurodegeneration.

**Citrulline therapy**

The therapeutic potential of citrulline is primarily supported by its ability to enhance nitric oxide (NO) production through its role as a precursor to L-arginine, bypassing the metabolic limitations associated with direct L-arginine supplementation. Romero MJ et. al highlights that citrulline is not degraded by intestinal or hepatic metabolism and does not induce arginase activity, making it a more effective and stable option for increasing NO levels. This property suggests indirect neuroprotective implications, as NO is vital for neurovascular health [20]. Rashid J et al. reinforces the pharmacokinetic stability and safety profile of citrulline, which has been shown to be well-tolerated even in long-term use. Both articles underscore its potential to address arginine deficiencies and related health issues, including possible cognitive benefits. While effective doses range between 3–6 grams daily and show minimal adverse effects, inter-individual variability due to genetic and physiological

differences may influence outcomes. However, direct studies linking citrulline to neuroprotection and cognitive enhancement are limited, pointing to a need for focused research, especially in aging and neurodegenerative populations [21].

**Watermelon juice and L-citrulline**

Watermelon juice is a natural and rich source of L-citrulline, an amino acid that serves as a precursor for L-arginine, which is essential for nitric oxide (NO) synthesis. NO plays a critical role in vascular health by promoting vasodilation and improving endothelial function. Studies have highlighted the potential benefits of watermelon juice on cardiovascular and metabolic health due to its high content of L-citrulline. For instance, Volino-Souza et al. (2022) discuss how watermelon-derived L-citrulline effectively improves vascular function, including arterial stiffness and blood pressure, with applications in food technology to enhance its bioactive compound concentration for easier consumption [22]. As highlighted by Burton-Freeman et al., the citrulline content in watermelon juice contributes to its beneficial effects on cardio-metabolic health, including improvements in vascular function and reductions in blood pressure [26]. Beyond its vascular benefits, watermelon juice contains other bioactive compounds, such as antioxidants, which provide additional health advantages by mitigating oxidative stress and inflammation. The antioxidative properties of watermelon juice are particularly relevant for conditions involving oxidative stress and vascular injury, as described by Hrelia et al. Their findings emphasize the role of compounds like citrulline in addressing cellular redox imbalances and supporting neurovascular health, which could have implications for managing neurodegenerative diseases [27]. Additionally, watermelon juice supplementation has been shown to enhance NO bioavailability and alleviate oxidative stress, as described by Bailey et al. (2016), who found improvements in endothelial function after consistent supplementation [23].

Daily consumption of watermelon juice has also been associated with improved vascular function among postmenopausal women, highlighting its potential in reducing cardiovascular risks, as reported by Ellis et al. (2021) in a randomized controlled trial [24]. Beyond vascular health, watermelon juice contains other beneficial components, such as lycopene, which exhibits antioxidant and anti-inflammatory properties, though its cognitive benefits remain to be conclusively established [25]. The combination of L-citrulline and lycopene in watermelon juice makes it a functional beverage with broad implications for metabolic, vascular, and

potentially cognitive health, positioning it as an attractive dietary intervention in both general and targeted health strategies.

**Conclusion**

The evidence presented highlights the multifaceted potential of citrulline as a therapeutic agent, particularly in the context of vascular health, oxidative stress modulation, and neuroprotection. Citrulline's role as a precursor to L-arginine and its subsequent enhancement of nitric oxide (NO) production positions it as a key regulator of vascular homeostasis, promoting endothelial function, vasodilation, and efficient cerebral circulation. These properties are critical for maintaining cognitive health, particularly in the aging population, where neurovascular dysfunction and oxidative damage are prominent contributors to cognitive decline and neurodegenerative diseases.

Citrulline's unique pharmacokinetics, including bypassing first-pass metabolism and achieving sustained plasma levels of arginine, underscore its superiority over direct arginine supplementation. Its demonstrated antioxidant effects, ability to reduce reactive oxygen species (ROS), and modulation of oxidative stress pathways further solidify its role in preserving cellular integrity under pathological conditions. Emerging research indicates its capacity to mitigate endothelial senescence, reduce oxidative biomarkers, and support vascular health, with implications for both systemic and cerebral benefits.

The consumption of citrulline through dietary sources, such as watermelon juice, enhances its accessibility while offering additional bioactive compounds like lycopene, which synergistically contribute to vascular and metabolic health. Although direct clinical evidence linking citrulline to cognitive enhancement remains limited, existing data suggest promising outcomes in improving cerebral blood flow and mitigating oxidative damage, foundational to neuroprotection.

Future research is warranted to elucidate citrulline's direct effects on cognitive function, particularly in neurodegenerative contexts. Expanding the scope of human trials and exploring combination therapies with other antioxidants or neuroprotective agents could further enhance its therapeutic application. Overall, citrulline presents a safe, well-tolerated, and effective intervention with significant potential for addressing age-related vascular and neurodegenerative challenges.

**Disclosure**

**Author's contribution:** Daria Pedrycz, Karolina Karoń, Mateusz Drabczyk, Emilia Pedrycz, Grzegorz Drapała, Wojciech Grabowski, Łukasz Karoń, Anna Zygmunt, Sławomir Karoń

**Conceptualisation:** Daria Pedrycz, Emilia Pedrycz, Grzegorz Drapała, Mateusz Drabczyk, Sławomir Karoń

**Methodology:** Daria Pedrycz, Anna Zygmunt, Łukasz Karoń, Karolina Karoń

**Software:** Łukasz Karoń, Wojciech Grabowski, Grzegorz Drapała, Mateusz Drabczyk, Sławomir Karoń

**Check:** Daria Pedrycz, Anna Zygmunt, Karolina Karoń, Emilia Pedrycz, Mateusz Drabczyk

**Formal:** Daria Pedrycz, Łukasz Karoń, Wojciech Grabowski, Mateusz Drabczyk, Sławomir Karoń

**Investigation:** Daria Pedrycz, Karolina Karoń, Wojciech Grabowski, Mateusz Drabczyk

**Resources:** Daria Pedrycz, Emilia Pedrycz, Wojciech Grabowski, Grzegorz Drapała, Sławomir Karoń

**Data curation:** Daria Pedrycz, Wojciech Grabowski, Anna Zygmunt, Karolina Karoń, Mateusz Drabczyk

**Writing - Rough Preparation:** Karolina Karoń, Daria Pedrycz, Łukasz Karoń, Sławomir Karoń

**Writing - Review and Editing:** Daria Pedrycz, Łukasz Karoń, Emilia Pedrycz, Mateusz Drabczyk

**Visualisation:** Daria Pedrycz, Emilia Pedrycz, Wojciech Grabowski, Grzegorz Drapała, Sławomir Karoń

**Supervision:** Daria Pedrycz, Wojciech Grabowski, Grzegorz Drapała, Mateusz Drabczyk, Sławomir Karoń

**Project Administration:** Daria Pedrycz, Karolina Karoń, Wojciech Grabowski, Mateusz Drabczyk, Sławomir Karoń

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