

Arginine & Citrulline

TECHNICAL SUMMARY

Arginine and citrulline are two amino acids that are integral to protein metabolism and utilization, as well as to the maintenance of muscle tissue and nitric oxide production.* Both are key intermediates in the urea cycle, where they participate in the detoxification of ammonia via the production of urea.* In addition, any arginine not converted to urea enters general circulation where it is distributed to various tissues and metabolized for other uses such as protein synthesis.*

Structure Formula:



Figure 1: L-Arginine (left) and L-Citrulline (right)

Chemical Name:

Arginine: 2-amino-5-guanidinovaleric acid.

Citrulline: 2-Amino-5-ureidovaleric acid

Allergen and Additive Disclosure: Not manufactured with wheat, gluten, soy, milk, egg, fish, shellfish or tree nut ingredients. Produced in a GMP facility that processes other ingredients containing these allergens.

Delivery Form: Vegetable Capsule

ROLE AS NUTRIENT/FUNCTION

L-arginine is a conditional amino acid involved in many important physiological processes including urea metabolism and excretion, DNA synthesis, protein production, oxidative defense and hormone secretion.* Arginine is also a nitric oxide (NO) precursor; its role in this process will be detailed here.*

NO is synthesized using arginine and oxygen via various nitric oxide synthase enzymes.* NO generated from L-arginine is a highly reactive gas and an important messenger molecule that is involved in functions as diverse as neurotransmission, vasodilation, biological stress regulation, and modulation of gene expression.* At low concentrations, NO produced in the blood vessel wall (endothelium) also mediates several biological processes such as vasodilation, platelet activation, regulation of monocyte and leukocyte adhesion, regulation of smooth muscle cell proliferation and the control of vascular oxidative stress, as well as the expression of redox-regulated genes.*

Citrulline is a non-essential amino acid which derives its name from *Citrullus vulgaris* (watermelon). Citrulline is an immediate precursor for arginine.* While it is involved in many physiological functions in the body, it is the main endogenous source of arginine and is an essential part of the urea cycle which rids the body of toxic ammonia.*

Citrulline is also involved in the maintenance of muscle protein synthesis and supports a healthy nitrogen balance.*

Supplement Facts

Serving Size 1 Veg Capsule

Amount Per Serving

L-Arginine (Free-Form)	500 mg*
L-Citrulline (Free-Form)	250 mg*

* Daily Value not established.

Other ingredients: Hypromellose (cellulose capsule), Silicon Dioxide, Stearic Acid (vegetable source), Magnesium Stearate (vegetable source) and Microcrystalline Cellulose.

- Nitric Oxide Precursors*
- Helps Maintain Muscle Tissue*

SUGGESTED USAGE: Take 1 capsule 2 times daily, or as directed by your healthcare practitioner.

NATUROKINETICS®

Liberation: The disintegration of the vegetable capsule using a USP testing method of disintegration occurs between zero and 60 minutes.

Absorption: Orally administered arginine is rapidly and almost completely absorbed by the intestinal brush border membrane via active uptake by the intestinal transporter system for cationic amino acids.

After oral administration citrulline is rapidly and extensively absorbed in the small intestine (median and lower ileum).

Several clinical studies suggest that citrulline ingestion generates higher arginine blood levels than ingesting arginine alone. This indicates that the combination of arginine and citrulline increases plasma arginine levels more effectively than ingestion of either arginine or citrulline alone.

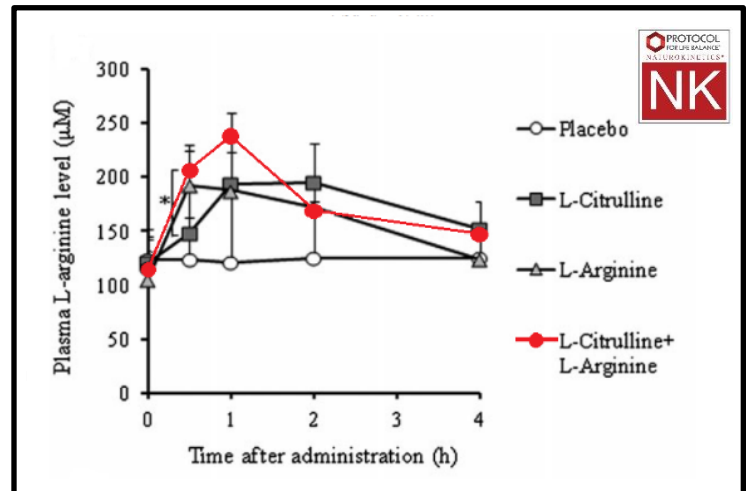


Figure 3: plasma arginine levels measured after oral ingestion of placebo, 2g citrulline, 2g L-arginine or a combination of 1g arginine+1g citrulline. n=45 healthy volunteers. * p<0.05.

Distribution: Pre-clinical data suggest that arginine is mainly found in the skin, liver, small intestine and stomach.

Citrulline is found throughout the body and is mainly concentrated in the kidney where it is converted to arginine.

Metabolism: Arginine is rapidly and extensively metabolized in the intestine (in enterocytes) and to a lesser extent in the liver (via arginase). Arginine is metabolized to citrulline and NO (via arginine deaminase and NOS), ornithine and urea (via arginase as part of the urea cycle in the liver), creatine, agmatine (via arginine decarboxylase), and dimethylarginine (via arginine-N-methyltransferase).

In the kidney, citrulline is metabolized to arginine through a partial urea cycle by argininosuccinate synthetase and argininosuccinate lyase. The arginine produced by this process is released into the renal vein to then reach the systemic blood circulation. Citrulline catabolism also allows for NO production via the NO cycle, most notably in macrophages and endothelial cells. Citrulline is also locally metabolized in the liver by periportal hepatocytes via the urea cycle.

Elimination: The half-life of arginine is 1 to 2 hours after oral administration. Unmetabolized arginine is excreted in urine, but is almost completely reabsorbed.

Studies suggest that citrulline is eliminated in urine and is extensively reabsorbed by renal tubule.

CLINICAL VALIDATION

Arginine supplementation and its impact on endothelial function have been extensively evaluated in clinical studies.

- In a clinical study with 51 healthy male volunteers (four groups divided by age and physical activity) receiving 900 mg of arginine in a one-day study, the skin laser Doppler flux (LD flux) was measured in microvessels before and after ingestion of arginine. In the group of young trained men, authors observed a significant increase in LD flux following ingesting arginine.*

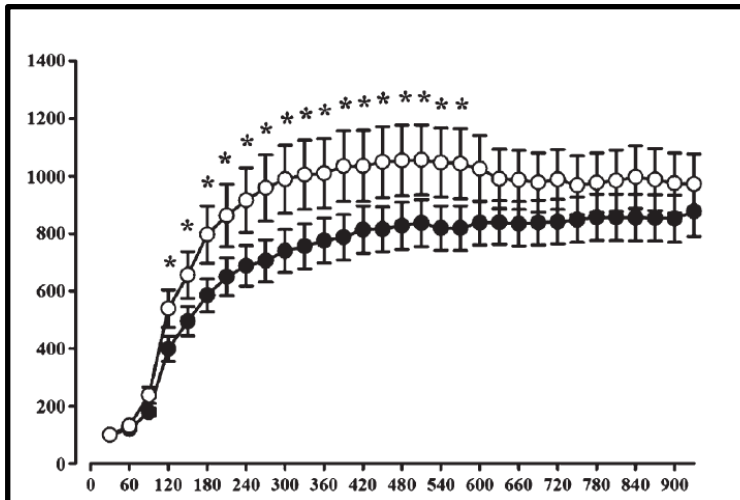


Figure 3: Relative LD flux response in % to acetyl choline applied via iontophoresis before (dark circle) and after ingestion of L-arginine in young trained male volunteers (white circle). * p<0.05 between groups.

SAFETY INFORMATION

Tolerability: Arginine is generally well tolerated when ingested as a supplement in doses up to 30 g/d, in addition to a typical diet that provides

on average at least 5 g/d of arginine through food. Mild GI discomfort may occur in a small subset of individuals ingesting large amounts of arginine as supplement.

Citrulline is generally well tolerated even when more than 10g/d is ingested.

Caution: This product is intended to be used by healthy adults. Caution is advised for use in individuals with asthma, kidney disease, liver disease, herpes virus, glaucoma, established coronary artery disease, low blood pressure and before surgery, as it may lower blood pressure and possibly affect blood coagulation.

Contraindications: Established allergy to arginine. Arginine and citrulline are amino acids normally found in foods (citrulline mainly in watermelon) with daily ingestion from food at levels above the recommended suggested usage for this product. However, for pregnant or nursing women, the safety has not been formally evaluated for a diet supplemented with arginine and citrulline. Therefore, caution and medical supervision is suggested. Do not use in the case of history of myocardial infarction.

INTERACTIONS

Drug Interactions: Because of its function as a NO precursor, blood pressure should be monitored in individuals taking antihypertensive medication.

Pre-clinical data suggest that arginine may affect blood coagulation. Individuals taking anticoagulant medication should have their coagulation monitored when arginine supplementation is implemented.

Preliminary research suggests that arginine may impact glucose metabolism. Individuals taking antidiabetic medication should have their blood sugar levels monitored at the beginning of arginine supplementation.

As citrulline is a precursor of arginine, it may increase blood levels of arginine and therefore may enhance arginine-related drug and supplement interactions.

Supplement Interactions: Supplements affecting blood pressure, coagulation, or blood sugar levels should be used cautiously when combined with -arginine & citrulline.

Interaction with Lab Tests: None known.

STORAGE

Store in cool, dry and dark environment in original sealed container. Temperature 59-86° F. Protect from excessive heat, moisture, air and light.

*These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.