

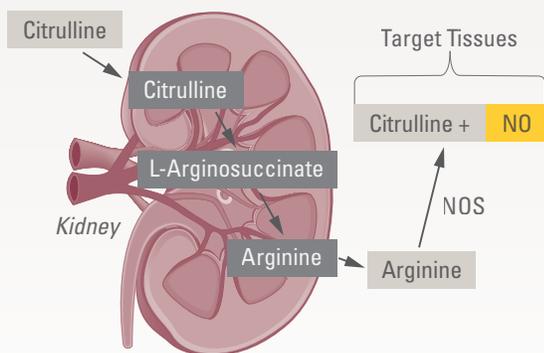
VASOPHIL™ ARGININE AND CITRULLINE COMBINATION

Arginine is a semi-essential amino acid involved in many biochemical pathways in the human body. It is involved in immune function, ammonia metabolism, and the secretion of hormones. Arginine is perhaps best known as a biochemical precursor to nitric oxide (NO).

Citrulline acts as an arginine precursor for NO synthesis (see Figure 1 below)¹ and plays an important part in NO metabolism and regulation.² In combination these amino acids support efficient NO synthesis for healthy cardiovascular function, vasodilation, and blood flow.* As with other amino acids, the effective dose range for arginine and citrulline is 3 grams or more of each.

Vasophil from Integrative Therapeutics™ is designed to support nitric oxide (NO) production and healthy peripheral circulation.* This great-tasting sour apple-flavored drink mix contains 3 grams of free-form arginine and 3 grams of free-form citrulline.

FIGURE 1



wheat free



gluten free



corn free



soy free



dairy free



1. Wu G. *J Nutr* 1998;128:1249-52.

2. Romero MJ, Platt DH, Caldwell RB, Caldwell RW. *Cardiovasc Drug Rev* 2006;24:275-90.



VASOPHIL™

Introduction: Arginine and Citrulline

Arginine is a semi-essential amino acid involved in many biochemical pathways in the human body. It plays a role in immune function, ammonia metabolism, and the secretion of hormones. Arginine is perhaps best known as a biochemical precursor to nitric oxide (NO) which functions as part of Endothelial-Derived Relaxing Factor (EDRF). EDRF is a messenger molecule that mediates physiological effects in the cardiovascular system. Because of arginine's NO-stimulating and other effects, it can be used as a supplement to support numerous physiological functions, including supporting normal blood flow to the heart, extremities, and male sexual organs.* In addition, arginine has been studied for supporting immune function, athletic performance, healthy cell proliferation, normal blood sugar metabolism,[†] gastrointestinal function, healthy sexual and reproductive function, urinary bladder structure and healthy cognition in the elderly.*¹ When taken in conjunction with omega-3 fatty acids, supplemental arginine may support healthy weight maintenance in people trying to keep weight on.²

Citrulline was first identified and isolated from the juice of the watermelon (*Citrullus vulgaris*).³ This amino acid initially attracted little interest because it is a non-protein amino acid that was considered solely an intermediate metabolite in the formation of urea.^{4,5} However, newer research has accumulated because of its unusual metabolism.⁶ Citrulline is a non-essential amino acid, donor of arginine and NO, and (similar to glutamine) a conditionally essential amino acid in intestinal health.* Its major actions include: reduces oxidative stress, vasodilatation, decreases leukocyte migration, restores nitrogen balance, increases muscle protein content and muscle protein synthesis, improves endothelial function, increases arginosuccinate synthase expression in cells, and preserves healthy cell mediator responses during immune challenge.*⁷

Metabolism of Arginine and Citrulline

Arginine is synthesized in mammals from glutamine in a multi-step metabolic conversion process.⁸ In adults, most endogenous arginine is derived from citrulline, a by-product of glutamine metabolism in the gut or liver. Citrulline is released into the circulation and taken up primarily by the kidney for conversion into arginine.⁹ Oral arginine taken as a supplement is readily absorbed.¹⁰ About half of ingested arginine is rapidly converted in the body to ornithine, primarily by the enzyme arginase.¹¹ Besides its most well known role as a precursor for NO, arginine is also a precursor for the synthesis of proteins as well as urea, creatine, and agmatine.¹²

Because it is a precursor of arginine, citrulline is being investigated as a supplement from which arginine can be synthesized. In some cells, arginine can be recycled from citrulline, which is of major importance in the NO cycle. In other words, citrulline acts as an arginine precursor for NO synthesis¹³ and plays an important part in NO metabolism and regulation,¹⁴ which is relevant for men who wish to support healthy sexual function and healthy blood pressure.*[†] Citrulline possesses a highly specific metabolism that bypasses splanchnic extraction because it is not used by the intestine or taken up by the liver. The administration of citrulline may be used to deliver available nitrogen for protein

[†]within normal limits.

homeostasis in peripheral tissues and as an arginine precursor synthesized de novo in the kidneys and endothelial and immune cells.*⁴

Supplemental Use of Arginine

Numerous studies have shown that acute and chronic supplemental L-arginine improves endothelial nitric oxide bioactivity.*¹⁵ It reduces the oxygen cost of aerobic exercise, supports healthy blood pressure,[†] enhances exercise tolerance, increases NO synthesis, and increases plasma concentration of nitrogen dioxide (NO₂), a key marker of NO bioavailability.*

Arginine supports healthy blood flow to the heart.*¹⁶ It has been shown to improve exercise efficiency and exercise tolerance in healthy humans.*¹⁷ Arginine supports cardiac ventricular function and the efficiency of the heart's pumping action.*¹⁸

Arginine also appears to support healthy mood, alleviating occasional anxiety and reducing basal cortisol levels in healthy humans.*¹⁹ Arginine increases free radical scavenging by superoxide dismutase (SOD), increases levels of beneficial thiols and ascorbic acid, decreases lipid peroxidation, decreases the activity of xanthine oxidase, and supports healthy cholesterol metabolism.*¹²⁰

Arginine supports immune function and can positively influence cytokine balance.* For example, high doses of arginine (30 g per day for three days) were shown to significantly enhance natural killer (NK) cell activity, lymphokine-activated killer cell cytotoxicity, and lymphocyte mitogenic reactivity.*²¹

Arginine in Healthy Sexual Function

Most studies using arginine to support healthy sexual function have studied it in combination with other ingredients, such as pyconogenol,²²⁻²⁵ yohimbine,^{26,27} or adenosine monophosphate.²⁸ Only a few studies have looked at arginine by itself for healthy sexual function. In a small, uncontrolled trial, men were given 2.8 g arginine per day for two weeks. Forty percent of the men in the treatment group experienced improvement, compared to none in the placebo group.²⁹ In a double-blind trial, men with concerns about sexual performance took 5 g arginine per day or a matching placebo for six weeks.³⁰ Nine of 29 (31%) patients taking L-arginine reported a significant subjective improvement in sexual function. All nine patients treated with L-arginine and who had subjectively improved sexual performance had had an initially low urinary nitric oxide, and this level had doubled at the end of the study. Men given just 500 mg three times daily in another trial experienced no better improvement than placebo.³¹ These results suggest that higher doses may be needed, and that men with lower nitric oxide levels might benefit the most.

Supplemental use of Citrulline

Indications for citrulline supplementation include supporting nutritional status during intestinal challenge, aging and support of normal muscle mass, and cardiovascular functions that benefit from enhanced NO production, including healthy sexual function.*³² In fact, studies in healthy volunteers show that oral citrulline supplementation raises blood arginine levels more effectively than arginine supplementation itself.*^{33, 42} Other indications include support of healthy red blood cell morphology, support of healthy blood pressure,[†] support of blood lipid metabolism,[†] support of blood sugar metabolism,[†] immunomodulation, arginase-associated T cell function, healthy cellular proliferation, cognitive function in the elderly, improving aerobic function and energy production, urea cycle support, as an antioxidant, and to support intestinal health.*⁵

Citrulline in Healthy Sexual Function

In a single blind, short-term study in men seeking support for healthy sexual function, L-citrulline was given 1.5 g/day for a month. Researchers concluded it was safe and psychologically well-accepted, very satisfying to test subjects, and supported sexual function score improvements.³⁴

[†]within normal limits.

Safety of Arginine

Significant adverse effects have not been observed with arginine supplementation. People with kidney failure or liver disease may be unable to appropriately metabolize and excrete supplemental arginine and should only take arginine supplements under the supervision of a qualified healthcare professional.

It has been suggested, on the basis of older *in vitro* data³⁵ and anecdotal reporting, that arginine supplementation is contraindicated in persons with herpes infections (i.e. cold sores, genital herpes). The assumption is that arginine might stimulate replication of the virus and/or provoke an outbreak; however, this caution has not been validated by controlled clinical trials.

Current data suggest modulating NO synthesis by giving oral arginine supplements has no significant effect on airway response to exercise in asthmatic subjects.³⁶ Until more is known, arginine should be used with caution in persons with asthma.

Since polyamines act as growth factors for cancers, and arginine may stimulate polyamine synthesis, chronic administration of arginine in cancer patients should probably be avoided until information arises regarding the safety of this practice.

Safety of Citrulline

Citrulline is generally recognized as safe (GRAS) for oral use.³⁷ In contrast to arginine or ornithine, which can induce gastrointestinal side effects at high doses (i.e. >10 g in one bolus),³⁸ citrulline is well tolerated.³⁹⁻⁴³ This could be explained by the rapid saturation of the intestinal absorption of arginine and ornithine inducing osmotic diarrhea at high loads.^{14,23} This difference between these amino acids suggests that the intestinal absorption of citrulline is not a limiting step in citrulline bioavailability, even at high citrulline loads.

Short-term administration of citrulline is safe and well-tolerated. No adverse effects were observed in healthy subjects that given different loading doses of 2 g, 5 g, 10 g, or 15 g.¹³ There is a dearth of reliable scientific data regarding its use in pregnancy and lactation, so standard pregnancy cautions apply.

Supplement Facts

Serving Size 1 sachet (8.28 g) Servings per container 30

Amount per sachet		%DV**
Calories	20	
Protein	<1 g	2%**
L-Arginine	3 g	***
L-Citrulline	3 g	***

**Percent Daily Values (DV) are based on a 2,000 calorie diet.

***Daily Value not established.

Other ingredients: Malic acid, citric acid, natural flavors and silicon dioxide.

Contains No: Sugar, salt, yeast, wheat, gluten, corn, soy, dairy products, artificial coloring, artificial flavoring, or preservatives.

Recommendations: Mix the contents of 1 sachet in cold water or juice and drink daily or take as recommended by your healthcare professional.

Caution: If pregnant, nursing, or taking prescription drugs, or if you have a history of genital or oral herpes, asthma, or cancer, consult your healthcare professional prior to use.

Integrative Therapeutics	Natural Partners	Emerson Ecologics
30 CT 10350	30 CT IT0100	30 CT IT03504

References

1. Appleton J. *Altern Med Rev* 2002;7(6):512-22.
2. Pichard C, Sudre P, Karsegard V, et al. Swiss HIV Cohort Study. *AIDS* 1998;12:53-63.
3. Mandel H, Levy N, Izkovitch S, Korman SH. *J Inherit Metab Dis* 2005;28:467-72.
4. Moirand C, Cynober L. *J Nutr* 2007;137:1621S-5S.
5. Curis E, Nicolis I, Moirand C, Osowska S, Zerrouk N, Benazeth S, et al. *Amino Acids* 2005;29:177-205.
6. Bahri S. *Nutrition* 2013 Mar;29(3):479-84. doi: 10.1016/j.nut.2012.07.002. Epub 2012 Sep 28.
7. Kaore SN, Amame HS, Navinchandra MK. *Fundamental Clin Pharmacol* 2013;27:35-50.
8. Wu G, Davis PK, Flynn NE, et al. *J Nutr* 1997;127:2342-49.
9. Dhanakoti SN, Brosnan JT, Herzberg GR, Brosnan ME. *Am J Physiol* 1990;259:E437-42.
10. Preiser JC, Berre PJ, Van Gossom A, et al. *JPEN J Parenter Enteral Nutr* 2001;25:182-7.
11. Castillo L, Sanchez M, Vogt J, et al. *Am J Physiol* 1995;268:E360-7.
12. Wu G, Morris SM Jr. *Biochem J* 1998;336:1-17.
13. Wu G. *J Nutr* 1998;128:1249-52.
14. Romero MJ, Platt DH, Caldwell RB, Caldwell RW. *Cardiovasc Drug Rev* 2006;24:275-90.
15. Loscalzo J. *J Nutr*. 2004 Oct;134(10 Suppl):2798S-2800S; discussion 2818S-2819S.
16. Blum A, Porat R, Rosenschein U, et al. *Am J Cardiol* 1999;83:1488-1490.
17. Bailey SJ, Winyard PG, Vanhatalo A, et al. *J Appl Physiol*. 2010 Nov;109(5):1394-403. doi: 10.1152/jap-physiol.00503.2010. Epub 2010 Aug 19.
18. Orozco-Gutiérrez JJ, Castillo-Martínez L, et al. *Cardiol J*. 2010;17(6):612-8.
19. Smirga M et al. *Biomed Res* 2007;28(2):85-90.
20. Tripathi P, Chandra M, Misra MK. *Oxid Med Cell Longev*. 2009 Sep-Oct;2(4):231-7. doi: 10.4161/oxim.2.4.9233.
21. Brittenden J, Park KGM, Heys SD, et al. *Surgery* 1994;115:205-12.
22. Aoki H, Nagao J, Ueda T, Strong JM, Schonlau F, et al. *Phytother Res*. 2012 Feb;26(2):204-7. doi: 10.1002/ptr.3462. Epub 2011 May 27.
23. Ledda A, Belcaro G, Cesarone MR, Dugall M, Schönlaue F. *BJU Int*. 2010 Oct;106(7):1030-3. doi: 10.1111/j.1464-410X.2010.09213.x. Epub 2010 Feb 22.
24. Stanislavov R, Nikolova V. *J Sex Marital Ther*. 2003 May-Jun;29(3):207-13.
25. Stanislavov R, Nikolova V, Rohdewald P. *Int J Impot Res*. 2008 Mar-Apr;20(2):173-80. Epub 2007 Aug 16.
26. Kernohan AF, McIntyre M, Hughes DM, Worcel M, Reid JL. *Br J Clin Pharmacol*. 2005 Jan;59(1):85-93.
27. Lebreton T, Hervé JM, Gorny P, Worcel M, Botto H. *Eur Urol*. 2002 Jun;41(6):608-13; discussion 613.
28. Neuzillet Y, Hupertan V, Cour F, Botto H, Lebreton T. *Andrology*. 2013 Mar;1(2):223-8. doi: 10.1111/j.2047-2927.2012.00046.x. Epub 2012 Dec 26.
29. Zorogniotti AW, Lizza EF. *Int J Impot Res* 1994;6:33-6.
30. Chen J, Wollman Y, Chernichovsky T, et al. *BJU Int* 1999;83:269-73.
31. Klotz T, Mathers MJ, Braun M, Bloch W, Engelmann U. *Urol Int*. 1999;63(4):220-3.
32. Bahri S. *Nutrition* 2013 Mar;29(3):479-84. doi: 10.1016/j.nut.2012.07.002. Epub 2012 Sep 28.
33. Kuhn KP, Harris PA, Cunningham GR et al. *Circulation* 2002;106(III):1-766S.
34. Cormio L, De Sisti M, Lorusso F, et al. *Urology* 2011;77:119-22.
35. Tankersley RW. *J Bacteriol* 1964;87:609-13.
36. de Gouw HW, Marshall-Partridge SJ, Van Der Veen H, et al. *J Appl Physiol* 2001;90:586-92.
37. Romero MJ, Platt DH, Caldwell RB, Caldwell RW. *Cardiovasc Drug Rev* 2006;24:275-90.
38. Grimble GK. *J Nutr* 2007;137:1693S-701S.
39. Collins JK, Wu G, Perkins-Veazie P, Spears K, Claypool PL, Baker RA, Clevidence BA. *Nutrition* 2007;23:261-6.
40. Moirand C, Nicolis I, Neveux N, Darquy S, Benazeth S, Cynober L. *Br J Nutr* 2007;99:855-62.
41. Schwedhelm E, Maas R, Freese R, Jung D, Lukacs Z, Jambrecina A, et al. *Br J Clin Pharmacol* 2007;65:51-9.
42. Smith HA, Canter JA, Christian KG, Drinkwater DC, Scholl FG, Christman BW, et al. *J Thorac Cardiovasc Surg* 2006;132:58-65.
43. Waugh WH, Daeschner CW, Files BA, McConnell ME, Strandjord SE. *J Natl Med Assoc* 2001;93:363-71.

*THIS STATEMENT HAS NOT BEEN EVALUATED BY THE FOOD AND DRUG ADMINISTRATION. THIS PRODUCT IS NOT INTENDED TO DIAGNOSE, TREAT, CURE, OR PREVENT ANY DISEASE.