

CitraNOX®



CLINICAL APPLICATIONS

- *Multidimensional Support for Optimal Blood Pressure*
- *Helps Maintain Endothelial Cell Elasticity*
- *Helps Preserve Coronary Arteries*
- *Enhances Circulating Nitric Oxide Levels*

CARDIOVASCULAR HEALTH

CitraNOX® is formulated specifically to maintain healthy blood pressure levels by enhancing endothelial cell and arterial function. Using a combination of high-dose L-citrulline, quercetin and grape seed extract, CitraNOX® delivers full-spectrum support to help maintain normal inflammatory balance, arterial elasticity, optimal nitric oxide levels, and blood flow. CitraNOX® provides a powerful formula for those seeking to optimize several mechanisms of cardiovascular health.

Overview

Stress placed on coronary arteries as a result of normal cardiac function is an expected part of the aging process. This stress can lead to disruptions in arterial function, proliferation of vascular smooth muscle, decreases in circulating nitric oxide (NO) levels, and eventually vasoconstriction of key coronary arteries.^{1,2} CitraNOX® provides a blend of targeted nutrients designed to help dampen this stress by maintaining normal inflammatory balance, balancing NO levels, maintaining smooth muscle integrity, and optimizing vasodilation of key coronary arteries.

L-Citrulline†

L-citrulline is one of three dietary amino acids in the urea cycle responsible for converting ammonia into urea as well as for the production of NO, an important cellular signaling molecule. In this process, L-citrulline is the natural precursor of L-arginine, the substrate used by endothelial nitric oxide synthase (eNOS) to produce NO.

As a signaling molecule, NO has been shown to have a very powerful effect on vasodilation and blood flow.³⁻⁵ Because of

this, optimizing circulating NO levels has long been a target of aerobic and anaerobic athletes. In fact, numerous clinical trials have been conducted showing that L-citrulline and L-arginine supplementation have a profound effect on exercise performance and power output.⁶⁻¹⁰

The benefits of circulating NO levels stretch far beyond exercise performance. As a vasodilator, NO improves arterial elasticity, decreases platelet adhesion, scavenges free radicals, and prevents oxidation of LDL cholesterol.¹¹⁻¹³ Studies show low levels of NO are associated with endothelial cell dysfunction, vasoconstriction, and blood flow challenges.¹³⁻¹⁵ Unfortunately, supplemental L-arginine has a small, transient effect, with no long-term benefit on circulating NO levels because liver metabolism restricts excess arginine from the blood to avoid long-term physiological consequences.^{14,16,17}

However, recent research shows that supplementing L-citrulline bypasses liver metabolism, thus making it more bioavailable in the blood stream and allowing it to significantly impact circulating NO levels.¹⁸ In a direct comparison, a recent study showed 3,000 mg of L-citrulline supplementation increased circulating NO levels 1.6-fold higher than 3,200 mg of L-arginine.¹⁹ Another direct comparison study showed L-citrulline supplementation significantly sustained peak plasma NO levels for upwards of four hours, and NO levels in the L-arginine group begin to decline at 1.5 hours.²⁰

Quercetin Dihydrate†

A flavonoid found in a variety of botanicals, vegetables and fruits, quercetin is a potent antioxidant that inhibits inducible ICAM-1 expression, an important pathway for maintaining

† 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.

normal inflammatory balance.²¹ Quercetin has been shown to support normal inflammatory balance by directly inhibiting the activity of NFκB, similar to turmeric.²² Quercetin is also known for its ability to improve endothelial cell dysfunction by maintaining normal inflammatory balance in specific pathways.²³

MegaNatural® BP Grape Seed Extract†

MegaNatural® BP is a premium grape seed extract made in California from a special seed blend extracted with water from a variety of white wine grape seeds. Grapes and grape products contain phenolic compounds found to have health-promoting properties, particularly in cardiovascular wellness.²⁴ Grape seed extract has a high concentration of phenolic compounds, which have been found to support healthy arterial dilation and blood flow. These polyphenols have been shown to activate NOS, the enzyme that facilitates NO production.²⁵

A study examining the effects of MegaNatural® BP grape seed extract in 27 volunteers found that after four weeks of supplementation with either 150 mg or 300 mg, the participants were able to maintain healthy blood pressure levels.²⁶ The participants taking 300 mg also had a significant reduction in oxidized low-density lipoprotein when compared to placebo.

Directions

4 capsules per day or as recommended by your health care professional.

Does Not Contain

Gluten, corn, yeast, artificial colors or flavors.

Cautions

If you are pregnant or nursing, consult your health care professional before taking this product.

Supplement Facts ^{v1}		
Serving Size 4 Capsules		
Servings Per Container 30		
	Amount Per Serving	% Daily Value
L-Citrulline	3 g	*
Grape Seed Extract (MegaNatural®-BP)	200 mg	*
Quercetin Dihydrate	200 mg	*
* Daily Value not established		

ID# 720120 120 Capsules

References

1. Black PH and Garbutt LD. Stress, inflammation and cardiovascular disease. *J Psychosom Res.* 2002;52:1-23.
2. Tracy R. Emerging relationships of inflammation, cardiovascular disease and chronic diseases of aging. *Int J Obes Relat Metab Disord.* 2003;27.
3. Palmer RM, Ferrige A and Moncada S. Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. *Nature.* 1987.
4. Furchgott R and Jothianandan D. Endothelium-dependent and-independent vasodilation involving cyclic GMP: relaxation induced by nitric oxide, carbon monoxide and light. *Blood Vessels.* 1991;28:52-61.
5. Vallance P, Collier J and Moncada S. Effects of endothelium-derived nitric oxide on peripheral arteriolar tone in man. *Lancet.* 1989;334:997-1000.
6. Pérez-Guisado J and Jakeman PM. Citrulline malate enhances athletic anaerobic performance and relieves muscle soreness. *J Strength Cond Res.* 2010;24:1215-1222.
7. Bailey SJ, Blackwell JR, Lord T, Vanhatalo A, Winyard PG and Jones AM. L-citrulline supplementation improves O2 uptake kinetics and high-intensity exercise performance in humans. *J Appl Physiol.* 2015;119:385-395.
8. Suzuki T, Morita M, Kobayashi Y and Kamimura A. Oral L-citrulline supplementation enhances cycling time trial performance in healthy well-trained males. *J Int Soc Sports Nutr.* 2015;12:P52.
9. Nagaya N, Uematsu M, Oya H, Sato N, Sakamaki F, Kyotani S, Ueno K, Nakanishi N, Yamagishi M and Miyatake K. Short-term oral administration of L-arginine improves hemodynamics and exercise capacity in patients with precapillary pulmonary hypertension. *Am J Respir Crit Care Med.* 2001;163:887-891.
10. Wagenmakers AJ. Amino acid supplements to improve athletic performance. *Curr Opin Clin Nutr Metab Care.* 1999;2:539-544.
11. Cannon RO. Role of nitric oxide in cardiovascular disease: focus on the endothelium. *Clin Chem.* 1998;44:1809-1819.

† 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.

12. Radomski MW, Palmer RM and Moncada S. The role of nitric oxide and cGMP in platelet adhesion to vascular endothelium. *Biochem Biophys Res Commun.* 1987;148:1482-1489.
13. Napoli C and Ignarro LJ. Nitric oxide and atherosclerosis. *Nitric Oxide.* 2001;5:88-97.
14. Romero MJ, Platt DH, Caldwell RB and Caldwell RW. Therapeutic use of citrulline in cardiovascular disease. *Cardiovasc Drug Rev.* 2006;24:275-290.
15. Durante W, Johnson FK and Johnson RA. Arginase: a critical regulator of nitric oxide synthesis and vascular function. *Cardiovasc Drug Rev.* 2007;34:906-911.
16. Pollock JS, Förstermann U, Mitchell JA, Warner TD, Schmidt H, Nakane M and Murad F. Purification and characterization of particulate endothelium-derived relaxing factor synthase from cultured and native bovine aortic endothelial cells. *Proc Natl Acad Sci.* 1991;88:10480-10484.
17. Morris SM. Arginine: beyond protein. *Am J Clin Nutr.* 2006;83:508S-512S.
18. Ryall JC, Quantz MA and Shore GC. Rat liver and intestinal mucosa differ in the developmental pattern and hormonal regulation of carbamoyl-phosphate synthetase I and ornithine carbamoyl transferase gene expression. *Eur J Biochem.* 1986;156:453-458.
19. Schwedhelm E, Maas R, Freese R, Jung D, Lukacs Z, Jambrecina A, Spickler W, Schulze F and Böger RH. Pharmacokinetic and pharmacodynamic properties of oral L-citrulline and L-arginine: impact on nitric oxide metabolism. *Br J Clin Pharmacol.* 2008;65:51-59.
20. Morita M, Hayashi T, Ochiai M, Maeda M, Yamaguchi T, Ina K and Kuzuya M. Oral supplementation with a combination of L-citrulline and L-arginine rapidly increases plasma L-arginine concentration and enhances NO bioavailability. *Biochem Biophys Res Commun.* 2014;454:53-57.
21. Bito T, Roy S, Sen CK, Shirakawa T, Gotoh A, Ueda M, Ichihashi M and Packer L. Flavonoids differentially regulate IFN γ -induced ICAM-1 expression in human keratinocytes: molecular mechanisms of action. *FEBS Letters.* 2002;520:145-152.
22. Min Y-D, Choi C-H, Bark H, Son H-Y, Park H-H, Lee S, Park J-W, Park E-K, Shin H-I and Kim S-H. Quercetin inhibits expression of inflammatory cytokines through attenuation of NF- κ B and p38 MAPK in HMC-1 human mast cell line. *Inflamm Res.* 2007;56:210-215.
23. Sanchez M, Galisteo M, Vera R, Villar IC, Zarzuelo A, Tamargo J, Pérez-Vizcaíno F and Duarte J. Quercetin downregulates NADPH oxidase, increases eNOS activity and prevents endothelial dysfunction in spontaneously hypertensive rats. *J Hypertens.* 2006;24:75-84.
24. Plotnick GD, Corretti MC, Vogel RA, Hesslink R and Wise JA. Effect of supplemental phytonutrients on impairment of the flow-mediated brachialartery vasoactivity after a single high-fat meal. *J Am Coll Cardiol.* 2003;41:1744-1749.
25. Edirisinghe I, Burton-Freeman B and Kappagoda CT. Mechanism of the endothelium-dependent relaxation evoked by a grape seed extract. *Clin Sci.* 2008;114:331-337.
26. Sivaprakasapillai B, Edirisinghe I, Randolph J, Steinberg F and Kappagoda T. Effect of grape seed extract on blood pressure in subjects with the metabolic syndrome. *Metabolism.* 2009;58:1743-1746.

LT-PDN-183-A

† 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.

eFFICACY
the power of e