AngiNOX™ Elite

Vascular Performance Enhancer*

Available in 30 stick packs

Clinical Applications

- Optimize Flow of Blood and Oxygen to Peripheral Tissues*
- Supports Vascular Health Linked to Healthy Male Sexual Function*
- Supports Athletic Performance*
- Supports Healthy Dilation of Blood Vessels*
- Supports the Healthy Flow of Blood and Oxygen to the Brain*

***AngiNOX™ Elite** is designed to boost the generation of nitric oxide, a naturally occurring biological compound produced in the vascular endothelium that supports healthy blood flow and vascular function. This formula contains a unique combination of beneficial ingredients delivered in a lightly flavored powder that easily mixes into water.**

Discussion

Nitric oxide (NO) is produced cellularly from the amino acid arginine through the enzymatic action of nitric oxide synthase (NOS) and has critical roles in regulating the function of organs and systems throughout the body. Production of NO by vascular endothelium is vital to blood flow regulation, and inadequate production can adversely affect blood flow, vascular tone, delivery of nutrients and oxygen, and other vascular functions.*[1,2]

L-Arginine

Arginine is a conditionally essential amino acid and the principal substrate for the family of NOS enzymes that catalyze NO biosynthesis. It is synthesized in the body from the amino acid citrulline and can also be obtained from dietary protein. Oral L-arginine supplementation can affect vasodilation, decrease platelet aggregation, and reduce endothelial monocyte adhesion.[2-4] The effect of L-arginine and its underlying mechanism can vary according to arginine plasma concentration range, administration route, and vascular functionality.*[2]

Vascular endothelial dysfunction is a hallmark of increased cardiometabolic risk and results from impairment to the synthesis or bioavailability of NO. In a randomized, double-blind trial comparing the effects of oral L-arginine (4.5 g/d) with placebo and assessing postprandial endothelial function, researchers concluded that L-arginine plays a role in alleviating endothelial dysfunction when baseline arginine is low.[5] However, orally administered L-arginine is hampered by extensive metabolic processes that impair its ability to reach the circulatory plasma and be available as a substrate for NOS. Another contributing factor to arginine not being available in circulatory plasma as a substrate is the accumulation of a naturally occurring byproduct of metabolism, known as asymmetric dimethylarginine (ADMA), which impairs NO formation as it competes with endogenous L-arginine for NOS binding.[6] Further research is needed to elicit the contributive effect of lower dosages of oral L-arginine.*

L-Citrulline

Citrulline, a precursor to arginine, readily permeates the intestinal wall and enters the bloodstream. It is processed by the kidney, where it is partially converted to arginine. L-citrulline supplementation in humans has been shown to increase plasma arginine availability for NO synthesis, thereby enhancing blood flow.*[7]

In a double-blind, randomized, placebo-controlled, crossover study, subjects (N = 20) with impaired NO activity and secondary-to-elevated ADMA concentrations were given 6 different dosing regimens of L-arginine, L-citrulline, and placebo to assess pharmacokinetic and pharmacodynamic effects. While a benefit was noted at lower dosages for both L-arginine and L-citrulline, oral administration of 3 g of L-citrulline twice daily was found to most efficiently increase arginine plasma and augment NO-dependent signaling to benefit endothelial function in healthy humans. Additional studies are needed to elicit the same effect in subjects with endothelial dysfunction.*[6]

Supplementing with L-citrulline increases plasma arginine and elicits a positive influence of NO-mediated responses that contribute to vascular function. A double-blind evaluation was conducted to determine the short-term effect of L-citrulline (5.6 g/d) supplementation on arterial stiffness in healthy volunteers (N = 15). L-citrulline was found to have a significant functional effect on the improvement of arterial stiffness independent of blood pressure. Further research is needed in a larger population group and with varying dose levels to determine the optimal dose of L-citrulline for arterial benefit.*[1]

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Folate
High levels of homocysteine (Hcy) can impair the bioavailability of NO.[8] Folate has been researched for its ability to moderate plasma Hcy levels, an effect widely linked to its vascular benefits. Studies have suggested that folic acid and 5-methyltetrahydrofolic acid (5-MTHF), supplemental forms of folate, are equivalent in reducing Hcy. However, folic acid bioavailability is impaired in individuals with a 5,10-methylenetetrahydrofolate reductase genetic polymorphism, rendering 5-MTHF necessary to alter Hcy levels.*[9-11]

It has also been suggested that folate has a direct effect on vascular function and oxidative stress through the regulation of NO synthesis. Folate influences the coupling of endothelial NOS and its cofactor tetrahydrobiopterin (also known as BH4), enhancing NO bioavailability. In a placebo-controlled study, subjects (N = 56) were randomized to receive 400 mcg of folic acid, 5 mg of folic acid, or placebo per day for 7 weeks before coronary artery bypass grafting to assess the effect of low versus high doses of folic acid on human blood vessels. Improved vascular function was observed and equal in both low- and high-dose groups. This benefit was attributed to the improved availability of BH4 for NOS and reduced vascular oxidative stress.*[12]

Vascular endothelial function is attenuated in healthy older adults, as evidenced by a vasodilation mechanism that reduces endothelium-derived NO activity. Consequently, interventions such as folate that target the NO pathway have been studied for their effectiveness in supporting vascular health and function. In 2 separate studies comparing young subjects (N = 11, with an average age of 22) with older subjects (N = 11, with an average age of 71), both age groups were given intradermal and oral folic acid. In both studies, an increased vasodilatation response attributable to NO-dependent mechanisms was noted to have occurred in the older individuals but not in the younger participants.*[13]

Pomegranate Extract
Pomegranate juice, seeds, inner membranes, and husks contain active compounds linked to many health benefits, including cardiovascular health. Punicalagin, the primary polyphenol in pomegranate, has been credited with much of the antioxidant activity and health benefits associated with pomegranate. In experimental animal research, the biological mechanism considered to benefit vascular health points was attributed to an increase in the activity of NOS in the endothelium cells, which triggers the release of NO in plasma.*[14]

The importance of glucocorticoids in maintaining vascular reactivity and their vital role in regulating blood flow is well established in the literature, and pomegranate may support this function. In an exploratory randomized, double-blind, placebo-controlled trial in human subjects (N = 29), participants consumed pomegranate extract (standardized to 210 mg of punicalagin per dose) or placebo daily for 4 weeks to assess the cardiometabolic effects of pomegranate extract consumption. Blood pressure, fasting glucose, and stress hormone (salivary cortisol/cortisone) levels were compared at baseline and after the study duration, with results indicating a significant effect of pomegranate extract in improving various risk factors. This study was important for setting a foundation for future large trials.*[15]

Hawthorn Extract
Animal studies using extracts of hawthorn suggest it may have endothelium-dependent vasodilatory properties. Traditional use of hawthorn indicates benefits for lowering blood pressure, increasing blood flow, and addressing issues with heart rhythms.[16,17] Using human and animal vascular tissue, laboratory researchers investigated the influence of hawthorn extract on vasorelaxation and presented findings that attributed the increased blood flow in human tissue to the activation of endothelial NOS.*[16]

A randomized, double-blind study was conducted on subjects (N = 92) with mild hypertension. Participants were given 20 drops of hawthorn extract or placebo 3 times daily for 4 months, and a significant decrease in both systolic and diastolic blood pressure was demonstrated after 3 months.[17] Additional human trials are needed to further elicit the benefit and effective dose of hawthorn extract to support endothelial health.*

AngiNOX™ Elite provides key ingredients selected for their role in promoting the production of nitric oxide, a naturally occurring biological compound that functions at the cellular level to signal responses beneficial to circulatory and vascular health.*

AngiNOX™ Elite Supplement Facts

Serving Size: 1 Stick Pack (about 4.5 g)

	Amount Per Serving	%Daily Value
Calories	20	
Total Carbohydrate	less than 1 g	< 1%†
Folate (as (6S)-5-methyltetrahydrofolic acid, glucosamine salt)[S1]	680 mcg DFE	170%
L-Citrulline	1.5 g	**
L-Arginine	500 mg	**
Pomegranate Extract (*Punica granatum*)(whole fruit)(30% punicalagins A+B and punicalins A+B)[S2]	375 mg	**
Hawthorn Extract (*Crataegus monogyna*)(leaves and flowers)	50 mg	**

†Percent Daily Values are based on a 2,000 calorie diet.
** Daily Value not established.

Other Ingredients: Natural flavors, citric acid, red beet powder, malic acid, monk fruit extract, stevia leaf extract, and sea salt.

DIRECTIONS: Dissolve the contents of one stick pack in 8-10 oz of water according to preferred taste. Consume once daily, or use as directed by your healthcare professional.

Consult your healthcare professional prior to use. Individuals taking medication should discuss potential interactions with their healthcare professional. Do not use if stick pack is damaged.

STORAGE: Keep closed in a cool, dry place out of reach of children.

FORMULATED TO EXCLUDE: Wheat, gluten, yeast, soy, animal and dairy products, fish, shellfish, peanuts, tree nuts, egg, sesame, ingredients derived from genetically modified organisms (GMOs), artificial colors, and artificial sweeteners.

Quatrefolic® S1. Quatrefolic is a registered trademark of Gnosis S.p.A. Produced under U.S. patent 7,947,662.

pomanox® S2. Pomanox is a registered trademark of Euromed S.A.

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