NOx Synergy™ is a comprehensive formula designed to optimize nitric oxide (NO) levels in the body.

**NOx Synergy™ works by:**
- increasing the body's production of NO
- extending the half-life of NO in the body
- protecting NO from producing peroxynitrites (harmful free radicals)
- enhancing the production of ATP

**Arginine and Citrulline**

Arginine is a critical substrate for the synthesis of NO, a compound that relaxes endothelial cells throughout the cardiovascular system. NO also inhibits platelet aggregation and superoxide radical generation. Arginine supplementation has been shown to reverse the endothelial dysfunction associated with common cardiovascular risk factors and also ameliorates symptoms of certain cardiovascular disorders, including coronary and peripheral arterial disease, ischemia/reperfusion injury and heart failure.1

Supplemental arginine may be beneficial due to high arginase activity in the small intestine, where approximately 40% of arginine is degraded during digestion, and only 50% of dietary arginine enters the systemic circulation.1

Citrulline is included as an adjunct to arginine, as citrulline is not metabolized in the intestine or liver and does not induce tissue arginase. In fact, it inhibits arginase, and citrulline entering peripheral tissues—particularly the kidneys and vascular endothelium—may be readily converted to arginine, thus raising arginine levels and enhancing NO production.2 Studies show that citrulline raises plasma arginine levels significantly higher than arginine itself and has a longer half-life in the body, so citrulline can be thought of as a potent “time-released arginine.”3 Research suggests that one of citrulline’s primary physiological roles is serving as a precursor to arginine in the kidneys.4,5

in regards to the influence of citrulline on increasing NO synthesis and stimulating a positive downstream effect, a study involving men with mild erectile dysfunction demonstrated that 1.5g/day of citrulline improved erectile function in 50% of participants.3

**Benefits of NOx Synergy™**

**Cardiovascular health:** by increasing NO production, endothelial cell function is improved, which causes blood vessel relaxation; supports the normalization of blood pressure; supports sexual health by improving erectile function.

**Athletic performance:** by increasing blood flow to muscles and enhancing ATP production, exercise can be performed at a higher intensity for a longer duration; muscle contraction may be more efficient, potentially leading to a greater anabolic effect. Additionally, antioxidants in NOx Synergy™ may help aid recovery from intense athletics.

**Folate (as 5-MTHF)**

Folate, as 5-MTHF, is included as a precursor to tetrahydrobiopterin (BH4), a required cofactor for activity of the enzyme nitric oxide synthase (NOS).6 Inadequate levels of BH4 result in the generation of superoxide radicals, rather than NO, from endothelial NOS (eNOS).7 When low BH4 bioavailability occurs, oxygen activation is “uncoupled” from arginine oxidation, and NOS produces superoxide instead of NO. NOS-derived superoxide reacts with NO to produce highly reactive peroxynitrite radicals, which rapidly oxidize BH4 and trigger uncoupling of NOS. Depletion of BH4 and uncoupling of NOS may result in hypertension, ischemia/reperfusion injury, overload-induced heart failure and atrial fibrillation.8 Sufficient folate is also required for proper metabolism of homocysteine.9

**Grape (Vitis vinifera) and Apple (Malus pumila) Extracts**

A proprietary combination of apple and grape polyphenols are included for their potent antioxidant and vasodilating properties. These polyphenols have been shown to enhance vasodilation by increasing the activation of the eNOS enzyme. Animal models have shown grape-derived polyphenols to be effective in increasing NO synthesis and availability by enhancing eNOS activity.10 Studies using red wine polyphenols demonstrate that these compounds—most potently, the tannins and anthocyanins—cause vasorelaxation in rat aortas.11 Studies in humans confirm the health benefits of wine and grape polyphenols.12,13
Phloretin, a polyphenol most commonly found in apples, has been shown to inhibit the expression of inflammatory cytokine-induced adhesion molecules in aortic endothelial cells. It has also been demonstrated to reduce platelet aggregation, suggesting that phloretin could be protective against the onset and progression of cardiovascular disease. Other apple polyphenols inhibit expression of pro-inflammatory genes in human cells in vitro in a dose-dependent manner.

**Pomegranate (Punica granatum) Extract**

Pomegranate is a rich source of antioxidants, and has demonstrated impressive results regarding cardiovascular function. Pomegranate juice compounds have reduced angiotensin-converting enzyme (ACE) activity by over 30% in vivo and in vitro. Although this was accompanied by only a 5% reduction in systolic blood pressure, reductions in ACE activity—even in the absence of a reduction in blood pressure—have been shown to attenuate atherosclerosis. Human studies have shown pomegranate juice to be effective in reducing the degree of lipid peroxidation, while animal models indicate it reduces the size of atherosclerotic lesions and the number of foam cells.

**Ginkgo Biloba**

In a study investigating the effects of Ginkgo biloba extract (GBE) on patients with coronary artery disease, GBE increased NO by nearly 13% and decreased endothelin-1 (ET-1, a potent vasoconstricting peptide produced by endothelial cells) by almost 6%, increasing the NO/ET-1 ratio by almost 20%. All three factors—the increase in NO, decrease in ET-1, and increase in the NO/ET-1 ratio—had a linear correlation with increased blood flow through the distal left anterior descending coronary artery (LAD). Researchers believe the primary beneficial effect of GBE on cardiovascular function is the reduction of ET-1 and subsequent increase in coronary blood flow.

Animal models of hypertension suggest there are additional mechanisms behind GBE’s effects on vascular health. Hypertensive rats treated with GBE showed increased activity of the enzyme glutathione peroxidase, inhibition of ACE, and reduced norepinephrine-induced vasoconstriction. In addition, GBE-treated rats showed improved endothelial function induced by vasorelaxing acetylcholine.

**Taurine**

This sulfonic acid derivative of cysteine has been shown to affect cardiovascular function through multiple mechanisms. It is anti-arrhythmic, hypotensive, and may decrease platelet aggregation. It also has a normalizing effect on cardiac muscle function with regard to calcium status, as it may strengthen contraction at low calcium levels, and beneficially relax the force of contraction at high calcium levels. Human and animal studies have shown taurine to reduce intimal thickening, arteriosclerosis, oxidative stress, and inflammation associated with diabetes, hypertension, and smoking-induced vascular events. Taurine supplementation in hypertensive patients has been shown to alleviate hypertension symptoms, as well as reverse arterial stiffness in type 1 diabetics.

**Chelated Creatine/Magnesium Complex**

The combination of creatine and magnesium is a synergistic pairing of two compounds with powerful effects on cardiovascular health and muscle performance. The production of ATP involves the transfer of a phosphate group from creatine to ADP, and this transfer is dependent on the availability of magnesium ions. The chelated creatine/magnesium complex in this formula provides a stable, highly effective form of creatine with the presence of magnesium, wherein magnesium replenishment facilitates the anabolic activity of creatine.

Magnesium is well-regarded for its hypotensive and relaxing effects, and a magnesium deficiency is associated with several conditions related to blood vessel function and blood flow. Creatine has long been recognized for its beneficial effects on muscle performance. Supplemental creatine stimulates strength and muscle mass, but its efficacy is limited by the lactation reaction, which transforms some creatine into anabolically inert creatinine. Pairing creatine with magnesium inhibits this conversion, thus increasing the amount of creatine available for supporting muscle cells.

Supplementing with this creatine/magnesium chelate helps increase muscle strength as well as the speed of muscle mass growth, since larger amounts of ATP may facilitate greater force stimuli and muscle contraction. Creatine has also been demonstrated to increase muscle anaerobic capacity and aerobic recovery by stimulating mitochondrial activity. According to research, the effects of a combined magnesium/creatine chelate are significantly more potent than the administration of creatine and magnesium from separate sources.

---

*For a list of references cited in this document, please visit [http://mkt.s.designsforhealth.com/techsheets/NoxSynergyReferences.pdf](http://mkt.s.designsforhealth.com/techsheets/NoxSynergyReferences.pdf)

To contact Designs for Health, please call us at (800) 847-8302, or visit us on the web at [www.designsforhealth.com](http://www.designsforhealth.com)