ENHANCE Your Endothelial Function

As humans age, their risk of a cardiovascular event escalates, even if traditional vascular risk values are in "normal" ranges.

An underappreciated factor in the development of cardiovascular disease is endothelial dysfunction.

Our inner arterial lining is called the endothelium. It loses youthful function in response to normal aging.

The consequences of endothelial dysfunction are diminished circulation, high blood pressure, thrombosis, and atherosclerosis—the major causes of stroke and heart attack.¹⁴

Fortunately, astute scientists and formulators have discovered potent natural methods to tackle the underlying causes of endothelial dysfunction.
Despite your physician’s reliance on standard lipid/glucose testing to determine if you are at risk of heart disease, there is an equally, if not more important, factor involved in the development of arterial blockage: **endothelial dysfunction.**

The **endothelium** is an ultra-thin, one-cell-thick layer of cells that lines your arteries. As you age, your endothelium faces increased vulnerability due to **reduced nitric oxide**, exposing you to increased cardiovascular disease risk.

**Nitric oxide** plays a key role in the healthy functioning of the endothelium. Increasing nitric oxide production can revitalize endothelial function and prevent a host of cardiovascular disease risks.

Fortunately, researchers have discovered an extract from the rind of sweet oranges that has been shown to **increase** nitric oxide production. One way it does this is to **reduce** destruction of the enzyme that is needed to produce nitric oxide. This enzyme is called **endothelial nitric oxide synthase** (eNOS). The name of the natural orange peel extract that boosts nitric oxide is CORDIART™.

---

**Why Cordiart™ Is Superior**

You might find other preparations of hesperidin on the market, so it’s important to understand why Cordiart™ is different. It has to do with bioavailability, the measure of how much a substance you take truly gets into your bloodstream and is delivered to its sites of action in your body.

A human study shows that the hesperidin in Cordiart™ is far superior to other forms of citrus extract containing hesperidin.37 When volunteers took a single 500 mg dose of either Cordiart™ or commercially sourced hesperidin, blood sampling proved that Cordiart™ produced **108% greater absorption** (bioavailability) compared with the commercial product.

This increased bioavailability comes as a result of Cordiart™’s unique formulation. Cordiart™ has been specially formulated to contain a very high ratio of the active form of the molecule (the “S” form) compared with the less active form (the “R” form). This mimics natural oranges, which contain 100% “S”—and is distinctly different from conventional hesperidin supplements, which contain nearly equal amounts of “S” and “R” forms.35

---

**Nitric Oxide: The Key To Endothelial Health**

Endothelial cells **regulate** the amount of blood flow through the arterial system.5 With age, the endothelium gradually loses its responsiveness, which leads to a reduction of the amount of blood that flows through the body.6

Declining endothelial function is the process that underlies a major cause of cardiovascular disease—atherosclerosis.23

The key to youthful endothelial responsiveness is **nitric oxide**. Aging people synthesize much less nitric oxide, which can **accelerate endothelial dysfunction** as well as additional cardiovascular factors including increased blood pressure and reduced blood flow.7,8

When nitric oxide concentrations are increased, smooth muscle cells of the arterial wall relax and allow increased blood flow and lower blood pressure.3

In order to produce nitric oxide, endothelial cells **require** a specific enzyme called **endothelial nitric oxide synthase** (eNOS).

---

**Cordiart™: A Multi-Targeted Endothelial Defender**

Medical options to enhance and protect the endothelium are limited, yet researchers have identified a unique extract, Cordiart™, derived from sweet orange peels as a novel endothelial protection agent.

Cordiart™ is rich in **hesperidin-2S** (hesperetin-7-O-rutinoside-2S), a rutinoside molecule.9-11 Studies show that hesperidin-2S can change the way endothelial cells communicate with smooth muscle cells to permit natural dilatation and control of blood flow and pressure. In isolated endothelial cells in culture, hesperidin stimulates expression and production of eNOS, the nitric oxide-producing enzyme that triggers arterial dilatation to increase healthy blood flow.12,13
How Nitric Oxide Is Created

Arginine → Nitric Oxide Synthase → Nitric Oxide

The typical American ingests 4-5 grams of arginine a day from dietary sources.*

Arginine is broken down in the body by multiple enzymes, one of them being nitric oxide synthase. The acronym “eNOS” is used to describe endothelial nitric oxide synthase, which is the enzyme that converts arginine into nitric oxide in the arteries.

Aging and other factors create a deficiency of eNOS, and a corresponding deficit of nitric oxide that is required for healthy endothelial function. Boosting levels of eNOS and nitric oxide are crucial components of a program aimed at preventing vascular disorders.


Hesperidin also reduces elevated CRP and serum amyloid A. Both of these inflammation-promoting factors impair eNOS function and contribute to decreased endothelial function.1,5-11,14,15 Cordair® also lowers levels of E-selectin, an adhesion molecule that can initiate inflammatory infiltration of endothelial tissue.

Animal studies demonstrate that supplementation with hesperidin improved nitric oxide-mediated arterial relaxation, which significantly lowered the animals' blood pressure.16 In other animal research, hesperidin reduced inflow of calcium ions into arterial smooth muscle cells that can lead to arterial calcification, a major factor in the development of angina (chest pain) and acute coronary syndrome, precursors to an all-out heart attack.17

Measuring Increased Nitric Oxide

The most impressive findings about Cordair® come from studies documenting the moment-to-moment changes in endothelial function in living human subjects. Scientists can measure the effects of increased nitric oxide production in humans by measuring flow-mediated dilation (FMD).

Here’s how it works: Flow-mediated dilation is a real-time measure of how well your blood vessels respond to endothelial signaling. It is also one of the best predictors of the progressive arterial stiffening that can later lead to heart attacks and strokes.18 More nitric oxide means better endothelial function, which is indicated by increased flow mediated dilation. This indicates the ability of blood vessels to dilate (widen) as a result of an increase in the amount of blood needing to flow through a vessel.
In a group of adults with metabolic syndrome (the combination of hypertension, central obesity, insulin resistance, and lipid disturbances), researchers found that the flow-mediated dilation in hesperidin-supplemented patients increased by a significant 32% over three weeks when compared to patients on a placebo. This demonstrates the immediate risk-reducing effects of hesperidin—improving flow-mediated dilation now prevents dangerous arterial thickening later.

In another report of real-time endothelial function, 24 adults (averaging 52 years old) with metabolic syndrome took 500 mg of Cordiart™ per day or a placebo for three weeks. Prior to the study, the subjects' flow-mediated dilation and endothelial function were at levels that indicated increased cardiovascular risk. The placebo patients showed a worsening of vascular risk over the time of the study. They had an average decrease in flow-mediated dilation of 6% compared with their baseline values, which means that their risk of heart attack elevated. The Cordiart™ recipients, on the other hand, had an 18% improvement in flow-mediated dilation, which lowered their risk into the normal range.

As an added benefit, subjects in the Cordiart™ group had a significant 13% reduction in levels of E-selectin, which are the potent adhesion molecules that trigger platelets and white blood cells to stick to arterial walls, where they can start to form clots and inflammation.

In other words, subjects who took Cordiart™ showed a significant improvement in markers of nitric oxide production by their endothelial cells. At the same time, Cordiart™ made the endothelial surface slippery, which reduced the attachment by platelets and white blood cells, thereby reducing the risk of atherosclerosis and thrombosis (arterial clotting). Add to that the evidence that Cordiart™'s active ingredient reduces dangerous inflammation that impairs nitric oxide production and you can understand how this orange peel extract protects and improves endothelial function.

Magnitude Of Vascular Disease Epidemic

Cardiovascular disease remains the leading cause of death and a major cause of disability worldwide. In the United States, vascular diseases account for over 30% of all deaths and are a major cause of rising health care costs.

Increased adherence to protective lifestyle changes is crucial for effective prevention.

Life Extension® readers take extraordinary measures to guard against heart attack, stroke, and other vascular disorders. Most members supplement with standardized pomegranate extract or drink pomegranate juice daily. Pomegranate has demonstrated impressive improvements in markers of endothelial function.

What has to be realized, however, is that aging causes a progressive loss of endothelial function that too often results in accelerated atherosclerosis. While a cure for endothelial dysfunction is not yet available, there exist a number of validated strategies to partially reverse it.
Those currently using pomegranate may consider adding CordiART to their daily regimen to further combat endothelial dysfunction by enhancing nitric oxide synthesis and reducing adhesion and inflammatory factors that are known to contribute to arterial occlusion.

Those with significant vascular risks may also consider incorporating a specialized form of enteric-coated superoxide dismutase (SOD) that protects the endothelial nitric oxide synthase (eNOS) from oxidative damage.

We conclude this article with a brief review of the vascular restorative effects of enteric-coated SOD and pomegranate.

**Protecting eNOS From Oxidation**

The endothelium is constantly exposed to oxygen-rich arterial blood, making it an easy target for oxidative reactions that destroy endothelial nitric oxide synthase (eNOS), which is required to make vital nitric oxide.

Oxidation is one of the chief chemical stresses faced by the endothelial enzyme eNOS. **Superoxide dismutase** (SOD) is one of the body's strongest endogenous protectors against damage to eNOS. SOD acts by scavenging free oxygen radicals that otherwise destroy eNOS and resulting production of nitric oxide.4

SOD used to only be available in an injectable form because it would otherwise be broken down by stomach acid before it could be absorbed. Several years ago, scientists created an innovative way to ingest SOD orally and protect it from the stomach's powerful acid. Called GliSODin®, this oral form of SOD can be delivered intact to the intestines where it can be safely absorbed without the need of injections.21,22

When GliSODin® was given to animals in a lab, they showed significant elevations in SOD activities and increased cellular resistance to oxidative damage.22 Lab studies show that GliSODin® prevents oxidative destruction of mitochondria, the intracellular powerhouses that "burn" food molecules to release energy.22

SOD has been shown to reduce activity of serum amyloid A, the inflammatory molecule that impairs eNOS function and simultaneously boosts HDL-cholesterol levels, two factors that promote a healthy, youthful endothelium.11

Clinical studies reveal that GliSODin® is effective in reducing carotid intima-media thickness (CIMT), a proven measure of cardiovascular risk.23 CIMT is a direct measurement by ultrasound of the thickness of carotid artery walls—the thicker those walls, the greater the risk for a stroke or heart attack.

---

**Determining Your Cardiovascular Risk**

Researchers use two different, but complementary, methods to discern a person's risk for cardiovascular disease. **Carotid intima-media thickness** (CIMT) is a static, long-term measure of arterial thickening (a pathological process) in response to poor endothelial function. Carotid intima-media thickness is a structural measure of how much vascular damage has already arisen from endothelial dysfunction; it is a powerful predictor of future cardiovascular events.36

Another measure of arterial responsiveness is flow-mediated dilation, or FMD. FMD is of growing importance in understanding endothelial function; it measures real-time, dynamic responses of blood vessels to endothelial signal, and has recently been shown to be the best predictor of progressive arterial stiffening, as measured by carotid intima-media thickness (CIMT).18

Think of FMD as the natural complement of carotid intima-media thickness; the former measures minute-by-minute changes in endothelial function, while the latter measures the cumulative effects of years of endothelial dysfunction. Good endothelial defense mechanisms must provide both improvement in FMD (short-term function) to reduce future increases in carotid intima-media thickness (long-term damage. Doing so helps maintain the best possible arterial responses to threats, and optimally lowers cardiovascular risk.
In a revealing study, subjects at risk of future cardiovascular disease took GliSODin® in the dose of 500 IU a day, while control subjects continued their regular heart-healthy diet. The study lasted for two years. Subjects' carotid intima-media thickness was measured at baseline, at 365 days, at 545 days (1.5 years) and at 730 days (2 years). During this time, the control group's carotid intima-media thickness increased steadily, which indicates an increasing risk for stroke or heart attack. Subjects who supplemented with GliSODin® had a steady decline in carotid intima-media thickness.

**Heart-Protective Benefits Of Pomegranate Extracts**

Pomegranate extracts (from fruit, flower, and seed oil) have long been known to enhance cardiovascular health through a variety of complementary mechanisms. Both lab and human studies demonstrate multiple heart-protective benefits of pomegranate extracts, including reducing blood pressure, lowering triglyceride levels, and boosting beneficial HDL cholesterol.

One of the most intriguing, and most recent, findings about pomegranate juice is its ability to protect the nitric oxide-producing eNOS enzyme from the chemical stresses that damage it, resulting in sustained higher levels of nitric oxide in endothelial cells. These effects have been demonstrated in live animal studies as well as cultured human coronary (main heart) arteries. Pomegranate juice also slows the oxidative degradation of nitric oxide, helping to sustain normal signaling from endothelial cells to the smooth muscle cells that must dilate in order to widen the artery and improve blood flow.

But pomegranate juice has many other endothelial-protecting mechanisms.

When lab mice with atherosclerosis were given pomegranate juice, it increased the flow of cholesterol through the arteries.

**Serum Amyloid A Causes Endothelial Dysfunction**

Recent discoveries show that a molecule called serum amyloid A (SAA) is connected to poor cardiovascular health and strokes. The serum amyloid A enzyme exerts a destructive influence on eNOS, thereby reducing nitric oxide production. In fact, serum amyloid A is now recognized as an independent and significant threat, not only to the nitric oxide system, but to other crucial cardiovascular protective factors.

Serum amyloid A (SAA) is a little known but important marker of cardiovascular risk. For those with acute coronary artery disease, the presence of serum amyloid A is often the sign of a poor prognosis. Serum amyloid A can wreak havoc on the cardiac vascular system by affecting reverse cholesterol transport, increasing endothelial dysfunction, promoting clotting, and activating inflammatory cells. Reducing the levels of serum amyloid A in the body is now thought to be likely to benefit patients with acute coronary artery disease.

Serum amyloid A causes endothelial dysfunction partly by reducing the protective activities of superoxide dismutase (SOD).

Fortunately, SOD has been shown to reverse the serum amyloid A-induced contraction of vessels in lab studies, while raising HDL levels that may inhibit some of serum amyloid A's destructive effects.

Another problem with serum amyloid A is that it binds to the protective high density lipoprotein (HDL) particles, reducing its ability to carry cholesterol away from the arteries. Reverse cholesterol transport is a feature of HDL cholesterol particles, and it is critical in reducing the amount of cholesterol that builds up in the endothelium and inflammatory cells that produce atherosclerotic plaque.

Leading researchers from around the world are now calling for development of new strategies to lower serum amyloid A levels and reduce cardiovascular risk from poor endothelial function.
out of inflammatory white blood cells by 39%, while lowering those cells' oxidized LDL cholesterol uptake by 31%. The reduction brought cellular cholesterol levels in these mice down to below that of young, untreated control mice. Remarkably, supplemented mice also experienced a 17% reduction in the size of their atherosclerotic plaques when compared to placebo.

When lab mice are fed a high-cholesterol diet, they develop coronary heart disease (atherosclerosis affecting the main heart arteries). However, researchers found that when these mice were supplemented with pomegranate extract, they experienced numerous heart-protective benefits, including a reduction in the size of the atherosclerotic plaques in their major blood vessels, reduced oxidation, lower levels of inflammatory signaling molecules, and reduced numbers of inflammatory cells in the plaques. In addition, while un-supplemented mice developed ECG abnormalities, the pomegranate-supplemented mice were protected from developing these abnormalities.

Human studies on pomegranate extracts are equally promising. In one study, hypertensive patients who drank 5 oz. of fresh pomegranate juice per day for two weeks had reductions in both systolic (top) and diastolic (bottom) blood pressures. Blood tests on supplemented subjects also revealed significant reductions in VCAM-1, an adhesion molecule that triggers white blood cells to stick to arterial walls, causing blood clots and inflammation.

A separate study published in the British Journal of Nutrition found that people who were supplemented with 400 mg of pomegranate seed oil twice daily experienced reduced lipid abnormalities. Specifically, their mean triglyceride levels fell from 306 mg/dL to 244 mg/dL, while their protective HDL cholesterol levels rose by 5 mg/dL (they fell by 1 mg/dL in placebo subjects). This resulted in a reduction in the ratio of triglyceride-to-HDL cholesterol, a known cardiovascular risk factor, from 7.5 to 5.7.

Pomegranate extracts can also enhance the benefits of lipid-lowering drugs (statins). For example, when the drug simvastatin was used alone in one study, it reduced reactive oxygen species (ROS) by 18% compared with baseline. However, when subjects took a pomegranate extract in addition to simvastatin, that reduction reached 30%. In addition, triglyceride levels fell by a significant 48% in the pomegranate group, while the drug-only group experienced no change at all.

The beneficial effects of pomegranate extracts have also been demonstrated in studies that specifically evaluated major artery wall structures through carotid intima-media thickness (CIMT). This is a long-term measure of arterial thickening as a result of endothelial dysfunction. An increase in CIMT indicates narrowing of the carotid arteries.

When people with increased CIMT took a pomegranate juice supplement, they experienced an average 30% reduction in CIMT (hence a widening of the area for blood flow). This was in stark contrast to the

---

Nitric Oxide Enhancement Restores Erectile Function

Nitric oxide is a vital arterial dilator beyond those involved in heart attacks and strokes. Normal function of the eNOS enzyme and adequate amounts of nitric oxide are required to achieve a normal erection in males; to develop an erection, arteries in the penis must dilate to allow rapid infusion of blood. In fact, animal studies show that, in individuals with erectile dysfunction, levels of eNOS and nitric oxide are well below normal, while blood within the cavities of the penis contain an abundance of reactive oxygen species that further damage eNOS. Among the properties of erectile dysfunction drugs like sildenafil is the ability to restore normal eNOS function; such drugs were originally developed for use in patients with angina, who needed the ability to dilate their coronary arteries. Studies in animals now demonstrate that long-term pomegranate juice supplementation can reverse the diminished penile blood flow, inhibit oxidative processes within the penis, and restore proper erectile function.
control patients, who had an average increase in CIMT of 9%, demonstrating further narrowing the arteries. Supplemented patients also experienced a 12% reduction in systolic (top number) blood pressure and a beneficial 83% increase in concentration of a native enzyme called PON1, which forms an important functional role of the protective HDL cholesterol complex.

**Summary and Recommendations**

Healthy arteries have good **endothelial function** that enables them to expand and contract with youthful elasticity.

Good endothelial function requires ample supplies of **nitric oxide**, which is formed in the arteries by **nitric oxide synthase** (eNOS).

Normal aging, along with chemical and metabolic stresses damage eNOS. The resulting **endothelial dysfunction** creates a host of vascular disorders including diminished circulation, hypertension, and occlusive arterial disease.

While mainstream medicine has little to offer in terms of **endothelial dysfunction**, researchers have identified **three** nutrients that provide multi-targeted protection. These nutrients increase clinical markers of endothelial **nitric oxide** and provide other vascular protective effects.

The best studied of these nutrients is **pomegranate**, which protects endothelial **nitric oxide** and fosters **reverse cholesterol transport** by HDL, which can result in shrinking of atherosclerotic plaques.

**Cordiart**, an extract from sweet oranges, has been shown to **increase endothelial nitric oxide synthase**, which stimulates **nitric oxide** production in the body. **Cordiart** also suppresses **inflammatory** reactions associated with circulatory disorders and has shown significant improvement in blood flow in human subjects.

**GliSODin**, a specialized form of superoxide dismutase, further protects **endothelial nitric oxide synthase** (eNOS) from oxidative destruction.

Each of these nutrients has shown improvements in clinically validated markers of vascular health in human studies.

The dilemma for the health and pocketbooks of aging humans is how many of these endothelial-protecting nutrients are required to achieve **optimal** protection against vascular disorders.

Those already taking **pomegranate** may consider adding low-cost **Cordiart** to further boost endothelial **nitric oxide** levels that is crucial to arterial health.

Individuals with particular vascular concerns may consider utilizing all three of these nutrients, **pomegranate, Cordiart**, and **GliSODin**, which can now be obtained in one formula.

The objective of supplementing with these nutrients is to restore as much youthful endothelial responsiveness as possible by boosting **nitric oxide**, suppressing proinflammatory factors, and enhancing HDL functionality.

**References**


35. BioActor: Cordat(TM) formulation has a >100% improved bioavailability compared to standard hesperidin. Bioactor B.V.; 2013.


