

LE Magazine February 2007

## REPORT

### Pomegranate Reverses Atherosclerosis and Slows the Progression of Prostate Cancer

By Dave Tuttle



Research from around the globe confirms that pomegranate is one of nature's most concentrated sources of antioxidants.<sup>1-3</sup> Extraordinary new findings indicate that compounds in pomegranate can do what scientists previously thought to be virtually impossible—namely, reverse the process of atherosclerosis.

These studies indicate that pomegranate confers unprecedented cardiovascular protection by restoring endothelial health, lowering blood pressure, and protecting low-density lipoprotein (LDL) from damaging oxidation. Pomegranate also appears to fight several of the most common forms of cancer, slowing the progression of prostate cancer and suppressing the growth of colon, breast, and lung cancer cells. Pomegranate even appears to shield against unsightly signs of aging by supporting the health of the skin's underlying matrix.

The good news for consumers is that pomegranate's remarkable health benefits can now be obtained in the form of affordable, highly concentrated extracts.

#### POMEGRANATE ENHANCES NITRIC OXIDE, IMPROVES ENDOTHELIAL FUNCTION

Pomegranate protects cardiovascular health by augmenting nitric oxide, which supports the functioning of endothelial cells that line the arterial walls. Nitric oxide signals vascular smooth muscle to relax, thereby increasing blood flow through arteries and veins. Nitric oxide reduces injury to the vessel walls, which also helps prevent the development of atherosclerosis.<sup>4</sup>

Scientists have known for some time that oxidized low-density lipoprotein (LDL) can reduce the expression of nitric oxide synthase, the enzyme that produces nitric oxide. Recently, they discovered that pomegranate juice enhances the bioactivity of nitric oxide synthase in endothelial cells.<sup>5</sup> Furthermore, pomegranate's antioxidant properties protect nitric oxide from oxidative destruction, thus augmenting its biological actions.<sup>6,7</sup>

An Italian study examined the role of pomegranate juice in nitric oxide synthase activity in artery sections that had already developed atherosclerosis.<sup>8</sup> In these segments, blood forcing its way around atherosclerotic plaque buildup exerts significant stress on arterial walls. This stress reduces nitric oxide synthase expression and sets the stage for the formation of yet more plaque.

The researchers selected mice with a genetic predisposition to developing atherosclerosis. They put the mice on a high-fat diet, let arterial disease develop for six months, and then added pomegranate juice to the experimental group's drinking water for 24 weeks. The placebo group was given plain drinking water.<sup>8</sup>

Pomegranate juice not only increased the expression of nitric oxide synthase in both healthy and atherosclerotic blood vessels, but increased it the most in blood vessels with the most plaque buildup, as shown below.<sup>8</sup>

#### *Increase in Nitric Oxide Synthase Expression by Pomegranate*

- Low-prone atherosclerotic areas +26.1%
- High-prone atherosclerotic areas +46.7% Healthy blood vessel areas +3.3%

Pomegranate's ability to increase nitric oxide synthase resulted in a significant reduction in atherosclerotic lesions:<sup>8</sup>

#### REDUCTION IN ATHEROSCLEROTIC LESIONS BY POMEGRANATE



- Low-prone atherosclerotic areas -20.2%
- High-prone atherosclerotic areas -19.3%
- Healthy blood vessel areas -25.6%

In other words, in healthy parts of the blood vessels, pomegranate juice reduced lesion volume by nearly 26%, while in areas with much more plaque, pomegranate reduced the volume of lesions by approximately 20%.<sup>8</sup> Pomegranate's ability to enhance nitric oxide synthase and protect nitric oxide from destruction may facilitate longer-lasting concentrations of nitric oxide in endothelial cells, thus enhancing endothelial function and conferring profound cardiovascular protection.

## REVERSING PLAQUE BUILDUP AND LOWERING HEART DISEASE RISK

For years, scientists have believed that while antioxidants and other nutrients can slow additional atherosclerotic plaque buildup, they do little to reverse the process once plaque has already formed on the arterial walls. Now, a remarkable study from Israel indicates that pomegranate can actually reduce existing plaque formations in the arteries.

Nineteen patients from the Vascular Surgery Clinic in Haifa, Israel, were selected to participate in this three-year trial.<sup>9</sup> All were non-smokers between the ages of 65 and 75, with asymptomatic severe carotid artery narrowing (stenosis) ranging from 70% to 90%. In other words, their arteries were so occluded by plaque buildup that only 10-30% of the original artery volume was available to permit blood flow. Ten of the 19 patients consumed 50 mL (1.7 ounces) of pomegranate juice daily, while the other nine received a placebo beverage. Both groups had similar blood pressure, cholesterol, and glucose levels at baseline, and continued their ongoing drug regimens. Dietary and lifestyle practices were kept constant during the study.



Despite the patients' advanced atherosclerosis, ingesting pomegranate juice produced statistically significant reductions in the thickness of their carotid artery walls, which is correlated with decreased risk for heart attack and stroke. After only three months, the average thickness declined by 13%, and after 12 months, the thickness dropped 35% compared to baseline. During this same 12-month period, the average carotid artery thickness of the placebo group increased by 9%.

This study also measured various other parameters of cardiovascular health. One year of pomegranate supplementation reduced the peak systolic velocity of the blood in the carotid arteries, while systolic blood pressure itself dropped by 21%. Systolic blood pressure refers to the maximum arterial pressure when the heart beats. Pomegranate intake appears to clear so many obstructions in the carotid arteries that the blood encounters less resistance, enabling the heart to pump at a reduced pressure. Less pressure through a wider "pipe" results in less speed, or velocity.<sup>9</sup>

Pomegranate consumption did not change blood levels of glucose, LDL, or high-density lipoprotein (HDL). Standard markers of heart, kidney, and liver function, as well as homocysteine and blood cell counts, also remained unchanged.<sup>9</sup> However, the Israeli researchers noted a number of improvements in blood markers that help to explain why pomegranate so effectively supports cardiovascular health.

For example, total antioxidant status in the blood was increased by 130% after 12 months of pomegranate use, while serum lipid peroxidation was reduced by 59%. Also contributing to the improvements was an 83% increase in serum paraoxonase-1, an enzyme that can reduce harmful lipid peroxides in arterial cells and in lipoproteins in coronary and carotid lesions.<sup>9-11</sup> In addition, one year of pomegranate use more than doubled the time it took for the initiation of LDL oxidation, from 30 minutes to 65 minutes. Since LDL must be oxidized before it can adhere to the arterial wall, delays in oxidation and increasing levels of antioxidants in the blood keep new plaque from building up, while paraoxonase-1 may help break up existing plaque, leading to overall reductions in plaque formation over time.<sup>9</sup>

While all these one-year improvements are remarkable, some of the parameters continued to show improvement until the end of the three-year study. For example, there was a further 16% reduction in lipid peroxidation at 36 months. It appears, however, that continued use of pomegranate is required to sustain these enhancements. One month after stopping supplementation, the study participants saw their average total antioxidant status drop by 35%, while their serum paraoxonase-1 activity declined by 18%.<sup>9</sup> As a result, pomegranate should be incorporated in a long-term program for enhancing cardiovascular health and longevity.

Another Israeli study confirmed that pomegranate reduces both systolic blood pressure and serum angiotensin converting enzyme (ACE) activity.<sup>12</sup> After only two weeks, 50 mL of pomegranate juice daily lowered systolic pressure by 5%, while producing a 36% drop in ACE activity. Since a reduction in ACE activity has been shown to help prevent atherosclerosis independent of its effects on blood pressure, the researchers noted that pomegranate juice appears to offer broad-spectrum protection against cardiovascular disease.

## POMEGRANATE: WHAT YOU NEED TO KNOW

- Pomegranate is now recognized as a powerful source of phytonutrients that can help prevent and reverse cardiovascular disease, avert cancer, and promote healthy skin.
- Pomegranate contains high levels of punicalagins, which are powerful antioxidants used to standardize the potency of pomegranate juice and extracts.
- Pomegranate increases the synthesis of nitric oxide, a key factor required for healthy endothelial function of the inner arteries. Pomegranate's antioxidant effects protect nitric oxide from oxidative degradation.
- New human studies offer dramatic evidence that consuming pomegranate can help reduce coronary plaque buildup and thus reverse existing atherosclerosis. Pomegranate further benefits cardiovascular health by inhibiting LDL oxidation, reducing blood pressure, and quenching oxidative stress.
- Laboratory studies show that pomegranate slows the proliferation of prostate cancer cells and increases cancer cell death. In men treated for prostate cancer, pomegranate dramatically slows PSA doubling time, significantly delaying disease progression. Pomegranate may also help reduce the risk of colon, lung, and breast cancers.
- Topically applied pomegranate extract helps protect the skin from damaging ultraviolet radiation, reduces inflammation, speeds wound healing, and promotes healthy, youthful-looking skin.
- Pomegranate's numerous health-promoting benefits can now be obtained in the form of highly concentrated liquid and powdered extracts.



# REPORT

## **Pomegranate Reverses Atherosclerosis and Slows the Progression of Prostate Cancer**

By Dave Tuttle

### **POMEGRANATE PROTECTS AGAINST PROSTATE AND OTHER CANCERS**

For many years, scientists have used phytonutrients with antioxidant properties, such as curcumin and green tea, to help fight cancer. New evidence suggests that pomegranate may be similarly effective in countering cancer's growth and spread.

For example, University of Wisconsin researchers investigated pomegranate's benefits against several types of aggressive prostate cancer cells. A laboratory study found that pomegranate extract inhibits human prostate cancer cell growth while increasing programmed cancer cell death (apoptosis). Pomegranate increases the expression of a protein that promotes cancer cell death, while decreasing the expression of a protein that inhibits the demise of cancer cells.<sup>13</sup>

A study in mice by the same researchers found that oral consumption of pomegranate extract inhibits prostate cancer cell growth while markedly decreasing serum levels of prostate-specific antigen (PSA). Rising levels of PSA are associated with the progression and recurrence of prostate cancer. The researchers concluded that pomegranate consumption might similarly help prevent prostate cancer or slow its progression in humans, thus prolonging survival and quality of life for patients.<sup>13</sup>

A study at the University of California at Los Angeles found similar benefits of pomegranate consumption.<sup>14</sup> When eight ounces of pomegranate juice was given each day to prostate cancer patients, the average PSA doubling time rose from 15 months at baseline to 54 months in more than 80% of the study subjects. Since a longer PSA doubling time signifies slower disease progression, this 3.6-fold increase in doubling time is a dramatically positive result. Laboratory analysis of the patients' pre- and post-treatment serum showed a 12% decrease in cell proliferation and a 17% increase in cancer cell death, demonstrating pomegranate's cancer-fighting effects.

Pomegranate may also help to fight colon cancer. Pomegranate supplementation reduced the number and size of experimentally induced colon tumors in animal subjects.<sup>15</sup> In the laboratory, pomegranate juice inhibited the proliferation and increased programmed cell death (apoptosis) of human colon cancer cells.<sup>16,17</sup> Pomegranate juice may exert some of its effects by suppressing the activity of nuclear factor-kappa beta (NF-kB), a significant contributor to cancer and age-related disease.<sup>16</sup> The expression of cyclooxygenase-2 (COX-2), an inflammatory enzyme associated with colon cancer risk, was also dramatically reduced by pomegranate.<sup>16</sup>

Pomegranate similarly shows promise in averting deadly lung cancer. In the laboratory, pomegranate inhibited the growth and replication of human lung cancer cells. Additionally, administering pomegranate extract to animals implanted with human lung cancer cells suppressed tumor growth. Scientists believe that pomegranate may fight lung cancer through its inhibitory effects on NF-kB.<sup>18</sup>

Breast cancer may also respond to pomegranate's anti-cancer effects. In the laboratory, pomegranate extracts inhibited human breast cancer cells' ability to proliferate and spread to other areas (metastasize) and induced programmed cell death. Pomegranate displayed efficacy against both estrogen-dependent and estrogen-independent breast cancer cells.<sup>19</sup>

Pomegranate thus holds promise in fighting several of the most common cancers threatening aging adults today.

### **POMEGRANATE SUPPORTS THE SKIN'S UNDERLYING STRUCTURE**

Topical application of pomegranate has been shown to promote skin health via several mechanisms. For example, by suppressing lipid peroxidation in the skin, pomegranate helps shield against damage induced by ultraviolet light.<sup>20</sup> In animal studies, pomegranate seed and fruit extracts significantly reduced the incidence and number of skin tumors in the animals after an experimental cancer-provoking challenge.<sup>21,22</sup> Pomegranate inhibits two inflammatory enzymes, cyclooxygenase and lipoxygenase, which may help protect the skin against the age-accelerating effects of inflammation.<sup>23</sup> Pomegranate extract also protected human skin cells against the increase in NF-kB induced by ultraviolet-A light, suggesting a role for pomegranate in preventing skin cancer.<sup>24</sup>



Other studies have demonstrated that pomegranate helps reverse visible signs of aging by promoting a moderate thickening of the skin's outer layer, known as the epidermis.<sup>25</sup> Pomegranate fruit extract also provides nutritional support for fibroblast cells in the skin's dermis, which lies below the epidermis; fibroblasts produce collagen and elastin, the critical structural fibers that provide the skin with support and flexibility. Pomegranate extract also increased dermal cell proliferation and collagen synthesis at the same time.<sup>25</sup>

In addition, pomegranate's phenolic compounds effectively promote wound healing. Indian researchers noted that a topical pomegranate cream produced an average 35% reduction in the number of days required for complete recovery from an excision wound.<sup>26</sup>

Pomegranate extract thus helps protect the skin against the threats of ultraviolet light and inflammation, while supporting its underlying structure and helping to restore its youthful appearance and function.

## CONCLUSION

Pomegranate is fast becoming one of today's most talked-about nutrients. With emerging evidence indicating that it works via several mechanisms to remove plaque from human arteries, retard cancer growth, and promote more youthful-looking skin, pomegranate may soon be regarded as an essential nutrient. Its concentrated blend of powerful phytonutrients appears to confer profound protection against atherosclerosis, cancer, and other degenerative conditions. Health-conscious adults seeking to optimize their defense against these and other lethal diseases of aging should consider making pomegranate a part of their daily anti-aging regimen.

---

## References

---

1. Aviram M, Dornfeld L, Rosenblat M, et al. Pomegranate juice consumption reduces oxidative stress, atherogenic modifications to LDL, and platelet aggregation: studies in humans and in atherosclerotic apolipoprotein E-deficient mice. *Am J Clin Nutr.* 2000 May;71(5):1062-76.
2. Gil MI, Tomas-Barberan FA, Hess-Pierce B, Holcroft DM, Kader AA. Antioxidant activity of pomegranate juice and its relationship with phenolic composition and processing. *J Agric Food Chem.* 2000 Oct;48(10):4581-9.
3. Singh RP, Chidambara Murthy KN, Jayaprakasha GK. Studies on the antioxidant activity of pomegranate (*Punica granatum*) peel and seed extracts using in vitro models. *J Agric Food Chem.* 2002 Jan 2;50(1):81-6.
4. Ignarro LJ, Cirino G, Casini A, Napoli C. Nitric oxide as a signaling molecule in the vascular system: an overview. *J Cardiovasc Pharmacol.* 1999 Dec;34(6):879-86.
5. de Nigris F, Williams-Ignarro S, Botti C, Sica V, Ignarro LJ, Napoli C. Pomegranate juice reduces oxidized low-density lipoprotein downregulation of endothelial nitric oxide synthase in human coronary endothelial cells. *Nitric Oxide.* 2006 Nov;15(3):259-63.
6. Ignarro LJ, Byrns RE, Sumi D, de Nigris F, Napoli C. Pomegranate juice protects nitric oxide against oxidative destruction and enhances the biological actions of nitric oxide. *Nitric Oxide.* 2006 Sep;15(2):93-102.
7. de Nigris F, Williams-Ignarro S, Sica V, et al. Effects of a pomegranate fruit extract rich in punicalagin on oxidation-sensitive genes and eNOS activity at sites of perturbed shear stress and atherogenesis. *Cardiovasc Res.* 2006 Sep 1; [Epub ahead of print].
8. de Nigris F, Williams-Ignarro S, Lerman LO, et al. Beneficial effects of pomegranate juice on oxidation-sensitive genes and endothelial nitric oxide synthase activity at sites of perturbed shear stress. *Proc Natl Acad Sci USA.* 2005 Mar 29;102(13):4896-901.
9. Aviram M, Rosenblat M, Gaitini D, et al. Pomegranate juice consumption for 3 years by patients with carotid artery stenosis reduces common carotid intima-media thickness, blood pressure and LDL oxidation. *Clin Nutr.* 2004 Jun;23(3):423-33.
10. Aviram M, Rosenblat M, Bisgaier CL, Newton RS, Primo-Parmo SL, La Du BV. Paraoxonase inhibits high-density lipoprotein oxidation and preserves its functions. A possible peroxidative role for paraoxonase. *J Clin Invest.* 1998 Apr 15;101(8):1581-90.
11. Aviram M, Hardak E, Vaya J, et al. Human serum paraoxonases (PON1) Q and R selectively decrease lipid peroxides in

human coronary and carotid atherosclerotic lesions: PON1 esterase and peroxidase-like activities. *Circulation*. 2000 May 30;101(21):2510-7.

12. Aviram M, Dornfeld L. Pomegranate juice consumption inhibits serum angiotensin converting enzyme activity and reduces systolic blood pressure. *Atherosclerosis*. 2001 Sep;158(1):195-8.
13. Malik A, Afaq F, Sarfaraz S, Adhami VM, Syed DN, Mukhtar H. Pomegranate fruit juice for chemoprevention and chemotherapy of prostate cancer. *Proc Natl Acad Sci USA*. 2005 Oct 11;102(41):14813-8.
14. Pantuck AJ, Leppert JT, Zomorodian N, et al. Phase II study of pomegranate juice for men with rising prostate-specific antigen following surgery or radiation for prostate cancer. *Clin Cancer Res*. 2006 Jul 1;12(13):4018-26.
15. Kohno H, Suzuki R, Yasui Y, Hosokawa M, Miyashita K, Tanaka T. Pomegranate seed oil rich in conjugated linolenic acid suppresses chemically induced colon carcinogenesis in rats. *Cancer Sci*. 2004 Jun;95(6):481-6.
16. Adams LS, Seeram NP, Aggarwal BB, Takada Y, Sand D, Heber D. Pomegranate juice, total pomegranate ellagitannins, and punicalagin suppress inflammatory cell signaling in colon cancer cells. *J Agric Food Chem*. 2006 Feb 8;54(3):980-5.
17. Seeram NP, Adams LS, Henning SM, et al. In vitro antiproliferative, apoptotic and antioxidant activities of punicalagin, ellagic acid and a total pomegranate tannin extract are enhanced in combination with other polyphenols as found in pomegranate juice. *J Nutr Biochem*. 2005 Jun;16(6):360-7.
18. Khan N, Hadi N, Afaq F, Syed DN, Kweon MH, Mukhtar H. Pomegranate fruit extract inhibits prosurvival pathways in human A549 lung carcinoma cells and tumor growth in athymic nude mice. *Carcinogenesis*. 2006 Aug 18; [Epub ahead of print].
19. Kim ND, Mehta R, Yu W, et al. Chemopreventive and adjuvant therapeutic potential of pomegranate (*Punica granatum*) for human breast cancer. *Breast Cancer Res Treat*. 2002 Feb;71(3):203-17.
20. Ashoori F, Suzuki S, Zhou JH, Isshiki N, Miyachi Y. Involvement of lipid peroxidation in necrosis of skin flaps and its suppression by ellagic acid. *Plast Reconstr Surg*. 1994 Dec;94(7):1027-37.
21. Afaq F, Saleem M, Krueger CG, Reed JD, Mukhtar H. Anthocyanin- and hydrolysable tannin-rich pomegranate fruit extract modulates MAPK and NF-kappa B pathways and inhibits skin tumorigenesis in CD-1 mice. *Int J Cancer*. 2005 Jan 20;113(3):423-33.
22. Hora JJ, Maydew ER, Lansky EP, Dwivedi C. Chemopreventive effects of pomegranate seed oil on skin tumor development in CD1 mice. *J Med Food*. 2003 Fall;6(3):157-61.
23. Schubert SY, Lansky EP, Neeman I. Antioxidant and eicosanoid enzyme inhibition properties of pomegranate seed oil and fermented juice flavonoids. *J Ethnopharmacol*. 1999 Jul;66(1):11-7.
24. Syed DN, Malik A, Hadi N, Sarfaraz S, Afaq F, Mukhtar H. Photochemopreventive effect of pomegranate fruit extract on UVA-mediated activation of cellular pathways in normal human epidermal keratinocytes. *Photochem Photobiol*. 2006 Mar-Apr;82(2):398-405.
25. Aslam MN, Lansky EP, Varani J. Pomegranate as a cosmeceutical source: Pomegranate fractions promote proliferation and procollagen synthesis and inhibit matrix metalloproteinase-1 production in human skin cells. *J Ethnopharmacol*. 2006;103:311-8.
26. Murthy KN, Reddy VK, Veigas JM, Murthy UD. Study on wound healing activity of punica granatum peel. *J Med Food*. 2004 Summer;7(2):256-9.

taking any medication, or if you have or suspect you might have a health problem. You should not stop taking any medication without first consulting your physician.