

REPORT

Pomegranate

Favorably Modulates Gene Expression

By Julius Goepp, MD

When we consume fewer calories, one *proven* benefit is favorable changes in the expression of our *genes*. Favorable changes occur when “youth genes” that promote cellular vitality are “turned on,” while “senescence genes” that rob cellular functionality are “turned off.” **Resveratrol** has become popular because like **calorie restriction**, it favorably alters **gene expression** in ways that have been shown to protect against age-related disease. Several years ago, **researchers discovered significant** health benefits in response to pomegranate ingestion. **New studies show that one way pomegranate protects against cancer, atherosclerosis, type 2 diabetes, and other disorders is by inducing beneficial alterations in gene expression.**

This article discusses the many **mechanisms** that enable **pomegranate** to combat degenerative disease, including its newly discovered ability to modulate **gene expression**.



A MULTI-PRONGED APPROACH TO PREVENTING ATHEROSCLEROSIS

Atherosclerosis (hardening of the arteries) is a leading killer of older adults. Pomegranate extracts work at every step in the deadly atherosclerosis cascade to prevent or reverse the damage, thereby extending life.^{1,2}

Pomegranate juice contains powerful antioxidant polyphenols called ellagitannins and ellagic acid.^{3,4} Early animal and human studies established that pomegranate juice consumption reduces oxidative stress, low-density lipoprotein (LDL) aggregation and oxidation, and platelet clumping associated with atherosclerosis.⁵⁻⁸ It also inhibits a serum enzyme called angiotensin-converting enzyme (ACE) that can produce high blood pressure, helping to lower systolic blood pressure in humans.⁹

Another **vascular-protective mechanism of pomegranate extracts is inhibition of the inflammatory actions of NF-kappaB** in vascular endothelial (vessel lining) cells.¹⁰ Israeli researchers found that pomegranate wine powerfully inhibited NF-kappaB that had been activated by blood flow disruptions—a step in development of the inflammatory atherosclerotic plaque.¹¹ Cholesterol-lowering statin drugs have also been found to down regulate inflammatory NF-kappaB. However, these medications have side effects that many people find intolerable.^{12,13}

Pomegranate researchers later found that they could **reduce carotid artery wall thickness** (a major risk factor for stroke) with three years of pomegranate juice supplementation.¹⁴ Excitingly, they discovered that this effect was accompanied by **lower blood pressure and reduced LDL oxidation**, vividly demonstrating pomegranate’s multi-pronged approach to stroke prevention.



Pomegranate juice exerts powerful control over atherosclerosis-related **genes**.¹⁵ For example, disrupted blood flow (shear stress) in arteries increases expression of oxidation-sensitive genes causing **endothelial damage**. Pomegranate juice concentrate **reduced activation of those dangerous genes** in cultured human coronary artery cells exposed to shear stress and **blocked progression of atherosclerosis** in mice with elevated cholesterol.^{16,17} Pomegranate juice also markedly increases the stability and activity of the vital paraoxonase-1 (PON-1) complex in humans.¹⁸ PON-1 is a component of high-density lipoprotein (HDL) that prevents lipid oxidation.¹⁹

Its extraordinary ability to support vascular health extends even further. The vital protective cytokine called **prostacyclin** prevents platelet clumping and clot formation. When human aortic endothelial cells were exposed to pomegranate juice, their prostacyclin production increased by **61%**, a benefit that would be expected to significantly reduce arterial clotting risk (a major cause of heart attack and stroke).^{20,21} And pomegranate flower extracts **radically improved heart muscle metabolism of excess lipids** in diabetic rats.²² Human studies confirm this benefit—concentrated pomegranate juice consumption **significantly lowered total**

CANCER

Nearly **one-third of all cancer deaths in the United States could be prevented** through appropriate dietary modification.²⁴ Pomegranate's broad-spectrum antioxidant and anti-inflammatory powers, plus its proven safety record, make it a natural for cancer prevention.²⁵ Compelling evidence details how **pomegranate juice and extracts prevent a variety of common cancers**.

PROSTATE CANCER

Prostate cancer is a **devastating malignancy**, accounting for about 25% of all the newly diagnosed cancers in American men. Although it is highly survivable when detected early, the American Cancer Society estimates that prostate cancer was responsible for more than 29,000 deaths in 2008.²⁶⁻²⁸ Pomegranate and its extracts are **potent suppressors of prostate cancer** at virtually every phase of its development.²⁵ Pomegranate extracts powerfully **suppressed** proliferation, growth, invasion, and blood vessel formation of **human prostate cancer cells** in culture and when implanted in experimental animals.²⁹⁻³² Pomegranate juice also helps stimulate the programmed "cellular suicide" called **apoptosis** that often stops incipient cancer cells from developing into full-blown tumors.^{33,34} Dramatic **synergistic effects** were discovered by Israeli researchers, who found that extracts from various parts of the whole fruit acted in concert to **block prostate cancer invasion** in the laboratory.³⁵ And pomegranate juice blocks activity of carcinogen-activator enzymes called cytochrome P450 in the liver.³⁶

A **landmark human clinical trial** was published by urologists at the University of California in 2006.³⁷ This study was conducted in a challenging population, showing the true power of pomegranate. The researchers studied men who had already undergone surgery or radiation treatment, but nevertheless had **rising levels of prostate-specific antigen (PSA)**, the serum marker of tumor growth or reoccurrence. Men drank 8 oz of pomegranate juice daily, and the researchers measured the time it took for their PSA levels to double. The longer the doubling time, the more slowly the disease was progressing and the better the quantity and quality of life.

The mean PSA doubling time increased dramatically and significantly with pomegranate supplementation, rising from 15 months before the study, to 54 months post-treatment. In other words, before supplementation these men's PSA was doubling in less than a year and a half, while it took **four and a half years to double** after supplementation! Lab studies on the men's serum showed that it could drastically cut proliferation of prostate cells in culture while radically increasing the cells' rate of death by apoptosis.

Later studies demonstrated that, by **modulating gene expression**, pomegranate polyphenols down-regulated production of androgens (male hormones) and the androgen receptors that many prostate cancers need to survive and grow.³⁸ In fact, scientists have found that pomegranate is effective at inhibiting both androgen-dependent (often early) **and** androgen-independent (often more advanced) cancers of the prostate.³⁹

WHAT YOU NEED TO KNOW: POMEGRANATE

- Pomegranate juice has long been known to benefit cardiovascular health.
- Exciting new discoveries reveal pomegranate's effects in cancer and diabetes prevention and treatment.
- Pomegranate's multiple benefits may arise from its ability to positively modulate gene expression.
- Oral health is radically enhanced by pomegranate preparations, which can enhance body-wide wellness.
- Not all pomegranate products are the same—beware of store-bought "100% juice" that's mostly apple juice with just a splash of pomegranate.



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BREAST CANCER

Given some of pomegranate's effects on hormone-dependent prostate cancers, it's not surprising that it would also **show promise** in preventing (and even treating) **breast cancers**, which are often reliant on the female hormone estrogen.⁴⁰ Korean researchers discovered a **powerful blocking action of estrogen synthesis** by whole pomegranate seed oil and juice concentrates.⁴¹ The result was dramatic growth inhibition of estrogen-dependent breast cancer cells (but not of healthy breast tissue). The same study showed **inhibition of tumor formation** in rodent cells exposed to known breast carcinogens. Using different methods, another research group found a 42% reduction in tumor formation with whole pomegranate juice polyphenols, and an astonishing 87% reduction with pomegranate seed oil.⁴² A joint Japanese-Israeli partnership showed how powerfully pomegranate extracts **slash production of vascular endothelial growth factor (VEGF)**, a compound tumors use to promote new blood vessel growth.⁴³



COLON CANCER

Colon cancer is one of the **major causes of cancer-related death** in the Western world.⁴⁴ Like prostate cancer, this malignancy can often be treated when caught early, but the effects of chemotherapy are toxic and lose their benefit as the disease becomes advanced. Far better, then, to prevent it in its earliest stages—another natural application for pomegranate juice and extracts! Pomegranate seed oil (rich in healthful linolenic acid) has been shown to **suppress experimentally-induced colon cancer** in laboratory rats.⁴⁵

Inflammation is a powerful trigger for colon cancers, which develop in the toxin-rich environment of the large intestine. Pomegranate juice and several of its concentrated extracts (ellagitannins and punicalagin) **directly suppress inflammatory cell signaling** in colon cancer cells, via several mechanisms involving modulation of gene expression.⁴⁶ Ellagic acid, produced in the colon from ellagitannins in pomegranate juice, **induces apoptosis in colon cancer** cells but not in normal colon cells—another example of the remarkable natural “targeting” system of these supplements.⁴⁷

Pomegranate juice also powerfully **inhibits several of the cytochrome P450 enzymes** that can activate carcinogens, dramatically **lowering the risk that a cancer** could even develop.⁴⁸ Not only that, but ellagic acid from pomegranate juice also **increased the expression of powerful detoxifying enzymes**, tipping the balance even further away from carcinogenesis.⁴⁹

Pomegranate's exciting anticancer potential is now being explored with remarkable effects on lung^{50,51} and skin cancers.^{24,52-57} According to noted cancer expert Dr. Imtiaz Siddiqui, “The prevailing mantra of cancer chemoprevention has been: **‘Find effective agents** with acceptable or no toxicity and **use them in preventing cancer** in relatively healthy people or individuals at high risk for developing cancer.’”⁵⁸ Pomegranate and its extracts fit that bill perfectly.

DIABETES

Mainstream medicine has stood by **virtually powerless** as people eat themselves to death, creating the global epidemic of obesity, metabolic syndrome, and type 2 diabetes.⁵⁹ Pomegranate juice and extracts offer powerful prevention at multiple levels on both diabetic and pre-diabetic states.⁶⁰

For example, **pomegranate extracts lower blood sugar** in diabetic rats by as much as 50% just 12 hours after a first dose.^{61,62} In part this effect results from blocking an important glucose-metabolizing digestive enzyme called **alpha-glucosidase**.⁶³

Diabetics suffer terribly from lipid disturbances and cardiovascular disease. Human studies show that **concentrated pomegranate juice improved lipid profiles** in diabetics with elevated blood lipids.^{23,64} And pomegranate flower extract activates the lipid-lowering receptor protein PPAR-alpha;⁶⁵ this effect also improved cardiac metabolism in diabetic rats.^{22,66} Mainstream physicians can also activate PPAR-alpha with drugs in the **fibrate** category—but these expensive, single-

mechanism drugs have their share of **side effects not seen with pomegranate**. Over time, diabetic hearts develop fibrosis, a reduction in flexibility and contractility of the heart muscle. Pomegranate flower extracts modulate expression of the genes that trigger fibrosis in diabetic rats, **reducing the amount of harmful fibrosis-related** proteins.⁶⁷ The extracts also activate genes in the liver that help diabetics cope with abnormal fat accumulation in the liver.⁶⁸

Diabetics also suffer more than others from **deadly effects of oxidative damage**, which contributes to atherosclerosis and its disastrous consequences.⁶⁹ When diabetics in Israel supplemented with pomegranate juice (just 50 mL or less than 2 oz per day for 3 months), serum **markers of tissue oxidation plunged** as much as **56%**. In diabetics not taking pomegranate, tissue oxidation markers increased by 350%!⁷⁰ This and other studies also showed marked improvements in the way pomegranate-supplemented diabetics' bodies handled dangerous oxidized LDL.^{18,19,71}

Diabetics and people with **metabolic syndrome** often suffer from poor vascular health. Pomegranate juice and extracts **decreased markers of vascular inflammation**, contributing to **improved arterial function**.⁷² Pomegranate seed oil consumption in high fat-fed laboratory rats **reduced weight gain**.⁷³ It also reduced blood levels of the dangerous inflammatory fat-based cytokine **leptin**, while increasing beneficial **adiponectin**. Supplementation in these "metabolic syndrome" animals also **increased their insulin sensitivity**, lowering their risk of developing type 2 diabetes.⁷³

ORAL HEALTH

Gum disease (gingivitis and periodontitis) is unpleasant, unsightly—and **potentially deadly**. Inflamed gums release inflammatory cytokines and dangerous bacteria into the main circulation, radically **increasing risk of cardiovascular disease** and other complications.⁷⁴ An oral pomegranate gel was more effective at inhibiting bacterial adherence (plaque formation) than the antimicrobial drug miconazole, and was effective at **preventing growth** of multiple oral bacteria.⁷⁵ Innovative Thai researchers implanted biodegradable pomegranate-saturated chips into the gum "pockets" of people with periodontitis, finding **dramatic improvement** in clinical signs of periodontal disease.^{76,77} Treated subjects also had lower concentrations of inflammatory cytokines, helping to lower their risk of systemic illness.

A **pomegranate mouth rinse** slashed dangerous bacterial counts in oral plaque by **84%**—compared to a **79%** reduction with the standard medical treatment chlorhexidine rinse.⁷⁸ A similar pomegranate rinse **reduced plaque-inducing protein** in saliva, cut indicators of cell injury, and lowered levels of sugar-degrading enzymes.⁷⁹ The rinse simultaneously increased radical scavenging capacity and antioxidant enzymes in saliva.

SUMMARY

Pomegranate, often called the "**Jewel of Winter**," is turning out to be a crown jewel in our battles against aging. Its antioxidant and anti-inflammatory effects block the development of atherosclerosis and its cardiovascular consequences. It **prevents cancer** at multiple, complementary sites in the cascade of tumor-producing events. Pomegranate's **gene expression-modifying** powers activate natural mechanisms that protect **against diabetes** and its devastating effects—as effectively as and more safely than prescription drugs. And pomegranate **boosts oral health** in ways that promote longevity along with overall health and well-being. If you aren't using concentrated pomegranate products as part of your health-promotion regimen, you are missing some of nature's most generous gifts!

If you have any questions on the scientific content of this article, please call a Life Extension® Health Advisor at 1-866-864-3027.

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