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File: ■ Pomegranate (*Punica granatum*)
■ Urologic Health
■ Prostate Cancer
■ Erectile Dysfunction
■ Benign Prostatic Hyperplasia

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RE: Review of the Research on Pomegranate Use for Male Urologic Health

Kroeger N, Belldegrun AS, Pantuck AJ. Pomegranate extracts in the management of men's urologic health: scientific rationale and preclinical and clinical data. *Evid Based Complement Alternat Med*. 2013;2013:701434. doi: 10.1155/2013/701434.

Urologic diseases such as prostatitis, benign prostatic hyperplasia (BPH), and prostate cancer increase in incidence as men go into their fifth decade and beyond; 30% of these patients seek alternative medical remedies in addition to standard treatment.[1] Indeed, there has been much research on polyphenols and their health benefits via anti-inflammatory and gene-nutrient interactions. Pomegranate (*Punica granatum*) has been studied over the last decade, both in animals and humans, for its effects on inflammatory pathways. This review discusses both the mechanism of action and the use of pomegranate in the prevention and treatment of erectile dysfunction (ED), BPH, and prostate cancer.

The rationale for studying pomegranate for urological disorders is based on the fact that many of pomegranate's actions are involved in the development of these disorders. Pomegranate has been shown to curb inflammation, increase nitric oxide (NO) production, reduce oxidative stress, and increase blood flow. Inflammation has been implicated in the development of lower urinary tract symptoms (LUTS) and BPH. Regarding prostate cancer, 80-98% of biopsies show inflammation, and a meta-analysis showed a 15-20% reduction in the risk of prostate cancer among those using nonsteroidal anti-inflammatory drugs (NSAIDs) or aspirin on a regular basis. Oxidative stress also plays a role in the development of prostate cancer, as well as ED. ED can also be a result of decreased NO production and compromised blood flow.

Pre-clinical evidence exists for the effect of pomegranate on prostate cancer and ED. In vivo and in vitro studies have demonstrated pomegranate's ability to inhibit tumor cell proliferation, migration, and invasion, and also to induce apoptosis (programmed cell death). Both punicic acid, a fatty acid from the pomegranate seed (the white seed inside each red aril), and POMx®, a pomegranate extract with standardized ellagitannin content (37% punicalagins; POM Wonderful, LLC; Los Angeles, California), have been shown to induce apoptosis and inhibit growth in LAPC4 prostate cancer cell lines. Pomegranate extracts have also been shown in a number of studies to inhibit nuclear factor kappa-B (NF-kB) and

valosin-containing protein (VCP [p97]), which are known to be involved in the metastasis of prostate cancer cells. In a mouse model of spontaneous prostate tumor development, 2 doses (comparable to 250-500 ml for humans) of pomegranate juice (PJ; Wonderful variety of pomegranate; POM Wonderful, LLC) added to the drinking water reduced tumor incidence by 70-80%; compared to 100% tumor incidence in control mice that were drinking plain water.

Regarding ED, 2 studies in rabbits with atherosclerosis-induced ED showed that PJ increased blood flow in the penis, smooth muscle relaxation, and erectile activity compared to controls. One study showed improvement in penile tissue fibrosis; while the other study did not.

Studies in humans have also shown benefits for prostate cancer and ED. In a Phase II study (n=46) using 8 oz of PJ, prostate-specific antigen (PSA) doubling time increased from 5 months at baseline to 54 months after treatment ($P<0.001$). Serum taken from those consuming PJ showed a decrease in the proliferation of LNCaP prostate cancer cells by 12% compared to baseline ($P<0.0048$) and an increase in apoptosis by 17.5% ($P<0.0004$). A second Phase II study (n=104) using POMx at levels equivalent to 8 oz of PJ also showed an increase in PSA doubling time from 11.9 months at baseline to 18.8 months after 6 months of treatment ($P<0.001$), with a decline in PSA observed in 13% of patients.

Both of these studies did not have a placebo control or show a dose response. In addition, the fact that other studies have shown a decrease in PSA doubling time with placebo treatment and that PSA doubling time may not be as appropriate of an end point as something like survival have challenged these results. A phase III, double-blind, placebo-controlled study (n=180) has been completed, with results due in the first quarter of 2013. In addition, a randomized, placebo-controlled trial of POMx for 4 weeks showed that it reduced benign prostate tissue 8-OHdG (8-hydroxy-2'-deoxyguanosine), a marker of DNA oxidation, by 33% ($P=0.003$), and provided evidence for the accumulation of pomegranate extracts in prostate tissues. These studies may help to fill in the gaps of the previous studies.

Regarding ED, 1 crossover study of moderate ED (n=60) using 8 oz of PJ showed a trend towards an improvement of the Global Assessment Questionnaire (GAQ; $P=0.058$) and did not upgrade the erectile function domain. The study was small and additional larger studies are needed to show efficacy.

Given the NO-increasing activity of pomegranate and the role of NO in the development of LUTS, a randomized, double-blind, placebo-controlled pilot study is currently underway by the authors to examine the efficacy of POMx on BPH-related LUTS.

The authors summarize by saying that research shows that pomegranate extracts are able to: (1) inhibit proliferation, invasion, metastatic spread, development of castration-resistant prostate cancer growth, and angiogenesis; (2) modulate inflammatory pathways; and (3) reduce oxidative stress.

—Risa Schulman, PhD

Reference

[1]Bishop FL, Rea A, Lewith H, et al. Complementary medicine use by men with prostate cancer: a systematic review of prevalence studies. *Prostate Cancer Prostatic Dis*. 2011;14(1):1-13.

Referenced article can be downloaded at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3622365.