# HEALTH INGREDIENT OF POMEGRANATE

**Maqsood Ahmad**
The University of Faisalabad, Faisalabad
**PAKISTAN**
**&**
**Muhammad Waqas Hussain & Mudasser Ali,** Institute of Homes Science Nutrition and Technology
GCU, Faisalabad, **PAKISTAN**

## ABSTRACT

Pomegranate (Punica granatum L.) is an ancient fruit that is widely consumed as fresh fruit and juice. The use of pomegranate fruit dates from ancient times and reports of its therapeutic qualities have echoed throughout the ages. Both in vitro and in vivo studies have demonstrated how this fruit acts as antioxidant, antidiabetic, and hypolipidemic and shows antibacterial, antiinflammatory, antiviral, and anticarcinogenic activities. The fruit also improves cardiovascular and oral health. These beneficial physiological effects may also have preventive applications in a variety of pathologies. The health benefits of pomegranate have been attributed to its wide range of phytochemicals, which are predominantly polyphenols, including primarily hydrolyzable ellagitannins, anthocyanins, and other polyphenols. The aim of this review was to present an overview of the functional, medical, and physiological properties of this fruit.

**Keywords:** Pomegranate, In Vitro, Antioxidant, Antidiabetic, Hypolipidemic, Anti-Inflammatory, Antiviral, Anticarcinogenic.

## INTRODUCTION

Pomegranate (Punica granatum L. Punicaceae; the common name is derived from Latin words ponus and granatus), a seeded or granular apple, is a delicious fruit consumed worldwide. The fruit is native to Afghanistan, Iran, China and the Indian subcontinent. The ancient sources of pomegranate linked Iran to Pakistan, China and eastern India, where pomegranates had been under cultivation for thousands of years. From the west of Persia (modern day Iran), pomegranate cultivation stretched through the Mediterranean region to the Turkish European borders and American southwest, California and Mexico (Celik et al., 2009; Lansky and Newman, 2007). Several studies have demonstrated the antimicrobial, antihelminthic, and antioxidant potential of the active ingredients of pomegranate extracts (PoMx), suggesting their preventive and curative role in gastro-mucosal injuries, cancer chemoprevention, ethanol- and acetone-induced ulceration and diabetic oxidative damage (Al-zoreky and Nakahara, 2003; Arun and Singh, 2012; Negi et al., 2003).

Pomegranate (Punica granatum) and its juices and extracts are currently being widely promoted, with or without scientific support, to consumers as one of the new super foods, capable of addressing a variety of health ailments. This fruit, which has been consumed and used as a medicinal food in the Middle East for thousands of years, has recently gained popularity in the United States. The potential capabilities of pomegranate as listed on a number of Web sites selling pomegranate products include its use as an antioxidant, an anti-inflammatory, an antiviral, an antibacterial, and an antifungal. Specific health benefits listed on these Web sites include anticancer properties, improvement in cardiovascular health, diabetes prevention and management, relief of menopausal symptoms, hormone balance, increased libido in both genders, improved male virility and erectile function, skin

nourishment including anti-wrinkle effects, and protection against Alzheimer's disease and rheumatoid arthritis. The high antioxidant activity of the fruit and juice as compared with other fruits and antioxidant beverages (Halvorsen et al. 2002, Gil et al. 2000, Stangeland et al. 2007, Wolfe et al. 2008, Seeram et al. 2008a, Chidambara Murthy et al. 2002, Guo et al. 2008) has been the basis for much of the purported health benefits and has stimulated interest in research on potential nutraceutical and functional food applications.

## Health Effects

Pomegranate has reportedly been used medicinally by the peoples of many cultures for centuries to treat conditions such as diabetes and to combat malarial parasites (Xu et al. 2009, Dell'Agli et al. 2009). However, it is just within the past decade that scientific research related to the health effects of pomegranate has increased substantially. Because of the high in vitro antioxidant activity of pomegranate products, a wide variety of diseases and health conditions that appear to have some relationship to the body's ability to ward off oxidative stresses have been investigated. Of note, many pomegranate products are being marketed for specific health effects, despite limited scientific data. Human clinical trials are relatively few in number but have shown positive effects of pomegranate juice consumption on prostate cancer prevention and cardiovascular health. Beneficial effects of pomegranate products have also been observed in animal models for prostate, colon, breast, and skin cancers, as well as for hyperlipidemia, atherosclerosis, and diabetes prevention and treatment. Although the weight of evidence is not sufficient for any one health claim, there is some preliminary evidence that shows promise.

## Cancer

Inhibition of cancer by pomegranate products has been studied for prostate, breast, colon, skin, lung, and cervical cancers, as well as leukemia. Of these, prostate cancer has been the most well studied, and positive effects of pomegranate juice consumption have been demonstrated in humans.

## Prostate

In a study of 46 men with rising prostate-specific antigen (PSA) levels following treatment for prostate cancer, consumption of 8 oz per day of pomegranate juice significantly delayed the rise in PSA, increasing the PSA doubling time from 15 months to 54 months based on baseline versus post-treatment measurements. Plasma analysis before and after treatment with pomegranate juice showed the treated subjects' plasma to have higher antioxidant and antiproliferative activities (Pantuck et al. 2006). At the time of publication, these authors indicated that a placebo-controlled trial to study these effects in more detail was underway. Furthermore, several studies in cell culture and animal models have reported inhibition of prostate cancer by pomegranate juice and extracts (Seeram et al. 2005, 2007; Albrecht et al. 2004; Lansky et al. 2005a,b; Malik et al. 2005; Sartippour et al. 2008; Rettig et al. 2008; Hong et al. 2008), and a number of mechanisms have been proposed. In vitro, pomegranate ellagitannins and their urolithin metabolites were shown to inhibit CYP1B1, a cytochrome P450 (CYP450) enzyme associated with prostate cancer initiation and progression. However, only urolithins A and B at higher concentrations inhibited this enzyme in prostate cancer cell cultures (Kasimsetty et al. 2009). Furthermore, urolithin A glucuronide, urolithin B glucuronide, and dimethyl ellagic acid were the only ellagitannin metabolites detected in human prostate tissues after three days of pomegranate juice or walnut consumption prior to

fasting for surgery (Gonzalez-Sarr ´ ´ ıas et al. 2010a). Given that these ellagitannin entities have beendemonstrated to accumulate in prostate tissues in vivo, inhibition assays in cell cultures using these compounds may add to our knowledge of the underlying mechanisms.

**Colon**

Prevention of colon cancer with pomegranate products is mostly theoretical, with only a few studies in animal models and cell cultures for support. The number of azoxymethane-induced aberrant crypt foci in rats, an animal model for colon cancer, was significantly decreased by consumption of pomegranate juice (Boateng et al. 2007) and punicic acid–rich pomegranate seed oil (Kohno et al. 2004). Additionally, in human colon cell cultures, pomegranate juice inhibited proliferation and induced apoptosis (Seeram et al. 2005), possibly via an inflammatory cell signaling mechanism (Adams et al. 2006). Punicalagin, the primary ellagitannin in pomegranate was shown to release ellagic acid in cell culture media, which actively induced apoptosis of colon cancer–derived Caco-2 cells (Larrosa et al. 2006). It has also been shown that specific ellagitannins from pomegranate and the corresponding urolithin metabolites inhibited proliferation and induced apoptosis of HT-29 human colon cancer cells (Kasimsetty et al. 2010).

**Breast**

In breast cancer cell cultures, growth was inhibited by pomegranate extracts via apoptosis (Jeune et al. 2005). Similarly, a breast cancer mouse model showed reduction in lesions when treated with fermented pomegranate juice polyphenols, a purified unknown compound from the fermented pomegranate, and pomegranate seed oil (Mehta & Lansky 2004). Further research with these pomegranate components indicated that the inhibition observed in breast cancer models may be due to an antiangiogenic mechanism of action (Toi et al. 2003) and inhibition of nuclear factorkappa-B (NF-κB) (Khan et al. 2009). Additionally, differentiation-promoting ability was shown for fermented pomegranate juice and peel extracts in a leukemia cell model (Kawaii & Lansky 2004). Given the intestinal metabolism of pomegranate polyphenols, several ellagitannin metabolites were tested in vitro for their antiproliferative and antiaromatase activities. Urolithin B displayed the greatest inhibition of both aromatase (an enzyme that interconverts testosterone and estrogen hormones) activity and proliferation (Adams et al. 2010), indicating that the bioactive components of the polyphenolic pomegranate extracts may be the microbially derived metabolites. Punicic acid, a major component of pomegranate seed oil, also inhibited breast cancer cells, but this effect was dependent on lipid peroxidation (Grossmann et al. 2010). Taken together, there appears to be some evidence in animal and cell culture models that a variety of bioactive compounds may exist in pomegranate extracts and oil that could have anticarcinogenic properties.

**Skin**

Both pomegranate seed oil and pomegranate fruit extract applied topically to mouse models for skin cancer inhibited the incidence and multiplicity of tumors, as well as delayed their onset (Hora et al. 2003, Afaq et al. 2005b). Sunlight provides UVA, UVB, and UVC radiation, but UVB(290–320 nm) tends to be most carcinogenic. The negative cellular effects of UVB exposure were studied in normal human epidermal keratinocytes in cell culture, and pomegranate fruit extract treatment was found to inhibit changes in NF-κB and mitogen-activated protein kinase (MAPK) pathways that would normally be stimulated by UVB exposure (Afaq et al. 2005a). Pomegranate juice, extract, and oil applied to reconstituted

human skin prior to UVB exposure were equally successful in preventing UVB-mediated damage related to both aging and skin cancer (Afaq et al. 2009). Similarly, pomegranate extract has been shown to inhibit markers for UVB-induced skin damage in cultured human skin fibroblasts (Park et al. 2010, Pacheco-Palencia et al. 2008), with the effects attributed to the content of catechin (Park et al. 2010) and ellagic acid (Bae et al. 2010). Thus, the protective effects of pomegranate extracts on skin cells may be beneficial for both cancer prevention and reduction of photoaging.

**Other**

Pomegranate fruit extract was demonstrated to have an inhibitory effect that was specific to lung cancer cells, having very little effect on normal bronchial cells in cell culture, and that reduced tumor growth and multiplicity in mouse models (Khan et al. 2007a,b). In contrast, pomegranate extract standardized to 50 μg ml−1 gallic acid equivalents was only slightly cytotoxic to cervical cancer cells in vitro and one of the least effective among the fruits tested (McDougall et al. 2008).

**Cardiovascular Health**

Research on effects of pomegranate products on cardiovascular health has been primarily focused on the prevention of atherosclerosis and the management of hyperlipidemia in diabetic individuals. Several human studies have been conducted, most of which have shown benefits of pomegranate products on cardiovascular health in relation to blood pressure, cholesterol, intima media thickness, and endothelial function. Elderly, hypertensive subjects (n = 10) that consumed pomegranate juice containing 1.5 mmol total phenols per day for two weeks experienced a 36% decrease in serum angiotensin II converting enzyme activity and a 5% decrease in systolic blood pressure, both of which are markers for cardiovascular disease risk (Aviram & Dornfeld 2001). After consumption of 50 ml pomegranate juice per day for two weeks, plasma from 13 healthy nonsmoking young men had higher antioxidant activity, decreased lipid peroxides, increased arylesterase activity, and increased resistance to copper sulfate–induced high-density lipoprotein (HDL) oxidation (Aviram et al. 2000). In this same report, it was demonstrated that pomegranate juice consumption decreased the number of foam cells and the size of atherosclerotic lesions by 44% in apolipoprotein E–deficient mice, an animal model for atherosclerosis.

**Diabetes**

Pomegranate flower extract and pomegranate juices and concentrates have been studied for their roles in management of diabetes in both animal models (Zucker diabetic rats) and humans. Pomegranate flower extract consumed by Zucker diabetic rats, a type II diabetes model, decreased the expected glucose load–induced increase in plasma glucose levels but had no effect on Zucker lean rats (Li et al. 2005, Huang et al. 2005a). Authors hypothesized that this effect was due to increased insulin receptor sensitivity via pomegranate flower stimulation of the peroxisome proliferator-activated receptors (PPAR)-γ (Huang et al. 2005a) or inhibition of intestinal α-glucosidase (Li et al. 2005). In addition to glucose metabolism in diabetic states, pomegranate flower extract has also been shown to decrease triglycerides and total cholesterol (Huang et al. 2005b), decrease cardiac fibrosis (Huang et al. 2005c), and reduce fatty liver via upregulation of fatty acid oxidation (Xu et al. 2009) in Zucker diabetic rat model systems. Pomegranate flower extract was also shown to increase HDL cholesterol, glutathione, and antioxidant enzymes in streptozotocin-induced diabetic Wistar rats and

decrease fasting blood glucose, TG, LDL cholesterol, VLDL cholesterol, and tissue lipid peroxidation (Bagri et al. 2009). This is in agreement with the previous animal studies and provides additional information on the improvement in oxidative state upon treatment with pomegranate flower extract, a traditional antidiabetic medicine. Similarly, pomegranate juice extract consumed for four weeks was able to ameliorate the biochemical and physiological effects of diabetes and hypertension induced in Wistar rats (Mohan et al. 2009).

**Arthritis**

The effect of pomegranate fruit extract on arthritis has been studied to a limited degree in animal models. Pomegranate fruit extract fed to mice in their drinking water significantly delayed the onset and reduced the incidence and severity of arthritis in a collagen-induced arthritis model, and inflammatory cytokine interleukin 6 (IL-6) was reduced. (Shukla et al. 2008) Similarly, pomegranate juice prevented chondrocyte damage in a mouse model for osteoarthritis in a dose-dependent fashion (Hadipour-Jahromy & Mozaffari-Kermani 2010). Human osteoarthritis cartilage samples (chondrocyte cell cultures) pretreated with an anthocyanin-rich pomegranate fruit extract in vitro resisted interleukin 1-B-induced cytotoxicity, and cartilage degradation was inhibited as evidenced by decreased proteoglycan release (Ahmed et al. 2005) These studies suggest a positive effect of pomegranate Less is known at this time about the beneficial effects of pomegranate toward other cancers.

## CONCLUSION

The consumption of pomegranate has grown tremendously due to its reported health benefits. Pomegranate and derivates, such as juice, peel, and seeds, are rich sources of several high-value compounds with potential beneficial physiological activities. The rich bioactive profile of pomegranate makes it a highly nutritious and desirable fruit crop. Accumulating research offers ample evidence that routine supplementation with pomegranate juice or extract may protect against and even improve several diseases, including diabetes and cardiovascular disease; it may even help to prevent and arrest the development of certain cancers, in addition to protecting the health of the mouth and skin. Side effects are very rare. Using concentrated, low-cost pomegranate juice or standardized pomegranate extract capsules offers consumers a way of reaping the broad spectrum of health benefits of this fruit.

## REFFERENCES

Adams LS, Seeram NP, Aggarwal BB, Takada Y, Sand D, Heber D. 2006. Pomegranate juice, total pomegranate ellagitannins, and punicalagin suppress inflammatory cell signaling in colon cancer cells. J. Agric. Food Chem. 54:980–85.

Adams LS, Zhang Y, Seeram NP, Heber D, Chen S. 2010. Pomegranate ellagitannin–derived compounds exhibit antiproliferative and antiaromatase activity in breast cancer cells in vitro. Cancer Prev. Res. 3:108–13.

Afaq F, Malik A, Syed D, Maes D, Matsui MS, Mukhtar H. 2005a. Pomegranate fruit extract modulates UV-B-mediated phosphorylation of mitogen-activated protein kinases and activation of nuclear factor kappa B in normal human epidermal keratinocytes. Photochem. Photobiol. 81:38–45.

Afaq F, Saleem M, Krueger CG, Reed JD, Mukhtar H. 2005b. Anthocyanin- and hydrolyzable tannin-rich pomegranate fruit extract modulates MAPK and NF-kappaB pathways and inhibits skin tumorigenesis in CD-1 mice. Int. J. Cancer 113:423–33.

Afaq F, Zaid MA, Khan N, Dreher M, Mukhtar H. 2009. Protective effect of pomegranate-derived products on UVB-mediated damage in human reconstituted skin. Exp. Dermatol. 18:553–61.

Ahmed S, Wang N, Hafeez BB, Cheruvu VK, Haqqi TM. 2005. Punica granatum L. extract inhibits IL- 1beta-induced expression of matrix metalloproteinases by inhibiting the activation of MAP kinases and NF-kappaB in human chondrocytes in vitro. J. Nutr. 135:2096–102.

Albrecht M, Jiang W, Kumi-Diaka J, Lansky EP, Gommersall LM, et al. 2004. Pomegranate extracts potently suppress proliferation, xenograft growth, and invasion of human prostate cancer cells. J. Med. Food 7:274– 83.

Al-Zoreky, N.S., 2009. Antimicrobial activity of pomegranate (Punica granatum L.) fruit peels. International Journal of Food Microbiology 134, 244–248.

Arun, N., Singh, D.P., 2012. Punica granatum: a review on pharmacological and therapeutic properties. International Journal of Pharmaceutical Sciences and Research 3 (5), 1240–1245.

Aviram M, Dornfeld L, Rosenblat M, Volkova N, Kaplan M, et al. 2000. 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. 71:1062–76.

Aviram M, Dornfeld L. 2001. Pomegranate juice consumption inhibits serum angiotensin converting enzyme activity and reduces systolic blood pressure. Atherosclerosis 158:195.

Aviram M, Rosenblat M, Gaitini D, Nitecki S, Hoffman A, et al. 2004. 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. 23:423–33.

Aviram M, Volkova N, Coleman R, Dreher M, Reddy MK, et al. 2008. Pomegranate phenolics from the peels, arils, and flowers are antiatherogenic: Studies in vivo in atherosclerotic apolipoprotein e-deficient (E 0) mice and in vitro in cultured macrophages and lipoproteins. J. Agric. Food Chem. 56:1148–57.

Bae JY, Choi JS, Kang SW, Lee YJ, Park J, Kang YH. 2010. Dietary compound ellagic acid alleviates skin wrinkle and inflammation induced by UV-B irradiation. Exp. Dermatol. 19:e182–90.

Bagri P, Ali M, Aeri V, Bhowmik M, Sultana S. 2009. Antidiabetic effect of Punica granatum flowers: effect on hyperlipidemia, pancreatic cells lipid peroxidation and antioxidant enzymes in experimental diabetes. Food Chem. Toxicol. 47:50–54.

Boateng J, Verghese M, Shackelford L, Walker LT, Khatiwada J, et al. 2007. Selected fruits reduce azoxymethane (AOM)-induced aberrant crypt foci (ACF) in fisher 344 male rats. Food Chem. Toxicol. 45:725–32.

Celik, I., Temur, A., Isik, I., 2009. Hepatoprotective role and antioxidant capacity of pomegranate (Punica granatum) flowers infusion against trichloroacetic acidexposed in rats. Food and Chemical Toxicology: An International Journal Published for the British Industrial Biological Research Association 47, 145–149.

Chidambara Murthy KN, Jayaprakasha GK, Singh RP. 2002. Studies on antioxidant activity of pomegranate (Punica granatum) peel extract using in vivo models. J. Agric. Food Chem. 50:47 91–95.

Davidson MH, Maki KC, Dicklin MR, Feinstein SB, Witchger M, et al. 2009. Effects of consumption of pomegranate juice on carotid intima-media thickness in men and women at moderate risk for coronary heart disease. Am. J. Cardiol. 104:936–42.

de Nigris F, Balestrieri ML, Williams-Ignarro S, D'Armiento FP, Fiorito C, et al. 2007. The influence of pomegranate fruit extract in comparison to regular pomegranate juice and seed oil on nitric oxide and arterial function in obese zucker rats. Nitric Oxide 17:50–54.

de Nigris F, Williams-Ignarro S, Botti C, Sica V, Ignarro LJ, Napoli C. 2006. Pomegranate juice reduces oxidized low-density lipoprotein downregulation of endothelial nitric oxide synthase in human coronary endothelial cells. Nitric Oxide 15:259–63.

de Nigris F, Williams-Ignarro S, Lerman LO, Crimi E, Botti C, et al. 2005. 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 102:4896–901.

Esmaillzadeh A, Tahbaz F, Gaieni I, Alavi-Majd H, Azadbakht L. 2004. Concentrated pomegranate juice improves lipid profiles in diabetic patients with hyperlipidemia. J. Med. Food 7:305–8.

Fuhrman B, Volkova N, Aviram M. 2005. Pomegranate juice inhibits oxidized LDL uptake and cholesterol biosynthesis in macrophages. J. Nutr. Biochem. 16:570–76.

Gil MI, Tomas-Barber ´ an FA, Hess-Pierce B, Holcroft DM, Kader AA. 2000. Antioxidant activity of pomegranate juice and its relationship with phenolic composition and processing. J. Agric. Food Chem. 48:4581.

Gonzalez-Sarr ´ ´ ıas A, Gimenez-Bastida JA, Garc ´ ´ ıa-Conesa MT, Gomez-S ´ anchez MB, Garc ´ ´ ıa-Talavera NV, et al. 2010a. Occurrence of urolithins, gut microbiota ellagic acid metabolites and proliferation markers expression response in the human prostate gland upon consumption of walnuts and pomegranate juice. Mol. Nutr. Food Res. 54:311–22.

Grossmann ME, Mizuno NK, Schuster T, Cleary MP. 2010. Punicic acid is an omega-5 fatty acid capable of inhibiting breast cancer proliferation. Int. J. Oncol. 36:421–26.

Guo C, Wei J, Yang J, Xu J, Pang W, Jiang Y. 2008. Pomegranate juice is potentially better than apple juice in improving antioxidant function in elderly subjects. Nutr. Res. 28:72–77.

Hadipour-Jahromy M, Mozaffari-Kermani R. 2010. Chondroprotective effects of pomegranate juice on monoiodoacetate-induced osteoarthritis of the knee joint of mice. Phytother. Res. 24:182–85.

Halvorsen BL, Holte K, Myhrstad MCW, Barikmo I, Hvattum E, et al. 2002. A systematic screening of total antioxidants in dietary plants. J. Nutr. 132:461–71.

Hashemi M, Kelishadi R, Hashemipour M, Zakerameli A, Khavarian N, et al. 2010. Acute and long-term effects of grape and pomegranate juice consumption on vascular reactivity in paediatric metabolic syndrome. Cardiol. Young. 20:73–77.

Hong MY, Seeram NP, Heber D. 2008. Pomegranate polyphenols down-regulate expression of androgensynthesizing genes in human prostate cancer cells overexpressing the androgen receptor. J. Nutr. Biochem. 19:848–55.

Hora JJ, Maydew ER, Lansky EP, Dwivedi C. 2003. Chemopreventive effects of pomegranate seed oil on skin tumor development in CD1 mice. J. Med. Food 6:157–61.

Huang TH, Peng G, Kota BP, Li GQ, Yamahara J, et al. 2005a. Anti-diabetic action of Punica granatum flower extract: activation of PPAR-gamma and identification of an active component. Toxicol. Appl. Pharmacol. 207:160–69.

Huang TH, Peng G, Kota BP, Li GQ, Yamahara J, et al. 2005b. Pomegranate flower improves cardiac lipid metabolism in a diabetic rat model: role of lowering circulating lipids. Br. J. Pharmacol. 145:767–74.

Huang TH, Yang Q, Harada M, Li GQ, Yamahara J, et al. 2005c. Pomegranate flower extract diminishes cardiac fibrosis in zucker diabetic fatty rats: modulation of cardiac endothelin-1 and nuclear factor-kappaB pathways. J. Cardiovasc. Pharmacol. 46:856–62.

Jeune MA, Kumi-Diaka J, Brown J. 2005. Anticancer activities of pomegranate extracts and genistein in human breast cancer cells. J. Med. Food 8:469–75.

Kaplan M, Hayek T, Raz A, Coleman R, Dornfeld L, et al. 2001. Pomegranate juice supplementation to atherosclerotic mice reduces macrophage lipid peroxidation, cellular cholesterol accumulation and development of atherosclerosis. J. Nutr. 131:2082–89.

Kasimsetty SG, Bialonska D, Reddy MK, Ma G, Khan SI, Ferreira D. 2010. Colon cancer chemopreventive activities of pomegranate ellagitannins and urolithins. J. Agric. Food Chem. 58:2180–87.

Kasimsetty SG, Bialonska D, Reddy MK, Ma G, Khan SI, Ferreira D. 2010. Colon cancer chemopreventive activities of pomegranate ellagitannins and urolithins. J. Agric. Food Chem. 58:2180–87.

Kawaii S, Lansky EP. 2004. Differentiation-promoting activity of pomegranate (Punica granatum) fruit extracts in HL-60 human promyelocytic leukemia cells. J. Med. Food 7:13–18.

Khan GN, Gorin MA, Rosenthal D, Pan Q, Bao LW, et al. 2009. Pomegranate fruit extract impairs invasion and motility in human breast cancer. Integr. Cancer Ther. 8:242–53.

Khan N, Afaq F, Kweon MH, Kim K, Mukhtar H. 2007a. Oral consumption of pomegranate fruit extract inhibits growth and progression of primary lung tumors in mice. Cancer Res. 67:3475–82.

Khan N, Hadi N, Afaq F, Syed DN, Kweon MH, Mukhtar H. 2007b. Pomegranate fruit extract inhibits prosurvival pathways in human A549 lung carcinoma cells and tumor growth in athymic nude mice. Carcinogenesis 28:163–73.

Kohno H, Suzuki R, Yasui Y, Hosokawa M, Miyashita K, Tanaka T. 2004. Pomegranate seed oil rich in conjugated linolenic acid suppresses chemically induced colon carcinogenesis in rats. Cancer Sci. 95:481–86.

Lansky EP, Harrison G, Froom P, Jiang WG. 2005a. Pomegranate (Punica granatum) pure chemicals show possible synergistic inhibition of human PC-3 prostate cancer cell invasion across matrigel. Invest. New Drugs 23:121–22.

Lansky EP, Jiang W, Mo H, Bravo L, Froom P, et al. 2005b. Possible synergistic prostate cancer suppression by anatomically discrete pomegranate fractions. Invest. New Drugs 23:11–20.

Lansky, E., Shubert, S., Neeman, I., 2004. Pharmacological and therapeutic properties of pomegranate. CIHEAM–Options Mediterraneennes xx, 231–235.

Larrosa M, Tomas-Barber ´ an FA, Esp ´ ´ ın JC. 2006. The dietary hydrolysable tannin punicalagin releases ellagic acid that induces apoptosis in human colon adenocarcinoma caco-2 cells by using the mitochondrial pathway. J. Nutr. Biochem. 17:611–25.

Li Y, Wen S, Kota BP, Peng G, Li GQ, et al. 2005. Punica granatum flower extract, a potent alpha-glucosidase inhibitor, improves postprandial hyperglycemia in zucker diabetic fatty rats. J. Ethnopharmacol. 99:239–44.

Malik A, Afaq F, Sarfaraz S, Adhami VM, Syed DN, Mukhtar H. 2005. Pomegranate fruit juice for chemoprevention and chemotherapy of prostate cancer. Proc. Natl. Acad. Sci. USA 102:14813–18.

McDougall GJ, Ross HA, Ikeji M, Stewart D. 2008. Berry extracts exert different antiproliferative effects against cervical and colon cancer cells grown in vitro. J. Agric. Food Chem. 56:3016–23.

Mehta R, Lansky EP. 2004. Breast cancer chemopreventive properties of pomegranate (Punica granatum) fruit extracts in a mouse mammary organ culture. Eur. J. Cancer Prev. 13:345–48.

Mirmiran P, Fazeli MR, Asghari G, Shafiee A, Azizi F. 2010. Effect of pomegranate seed oil on hyperlipidaemic subjects: a double-blind placebo-controlled clinical trial. Br. J. Nutr. 104:402–6.

Mohan M, Waghulde H, Kasture S. 2009. Effect of pomegranate juice on angiotensin II-induced hypertension in diabetic wistar rats. Phytother. Res. 24(Suppl. 2):S196–203.

Negi, P.S., Jayaprakasha, G.K., Jena, B.S., 2003. Antioxidant and antimutagenic activities of pomegranate peel extracts. Food Chemistry 80, 393–398.

Pacheco-Palencia LA, Noratto G, Hingorani L, Talcott ST, Mertens-Talcott SU. 2008. Protective effects of standardized pomegranate (Punica granatum L.) polyphenolic extract in ultraviolet-irradiated human skin fibroblasts. J. Agric. Food Chem. 56:8434–41.

Pantuck AJ, Leppert JT, Zomorodian N, Aronson W, Hong J, et al. 2006. Phase II study of pomegranate juice for men with rising prostate-specific antigen following surgery or radiation for prostate cancer. Clin. Cancer Res. 12:4018–26.

Park HM, Moon E, Kim AJ, Kim MH, Lee S, et al. 2010. Extract of Punica granatum inhibits skin photoaging induced by UVB irradiation. Int. J. Dermatol. 49:276–82.

Rettig MB, Heber D, An J, Seeram NP, Rao JY, et al. 2008. Pomegranate extract inhibits androgenindependent prostate cancer growth through a nuclear factor-kappaB-dependent mechanism. Mol. Cancer Ther. 7:2662–71.

Rock W, Rosenblat M, Miller-Lotan R, Levy AP, Elias M, Aviram M. 2008. Consumption of wonderful variety pomegranate juice and extract by diabetic patients increases paraoxonase 1 association with high-density lipoprotein and stimulates its catalytic activities. J. Agric. Food Chem. 56:8704–13.

Rosenblat M, Hayek T, Aviram M. 2006a. Anti-oxidative effects of pomegranate juice (PJ) consumption by diabetic patients on serum and on macrophages. Atherosclerosis 187:363–71.

Rosenblat M, Volkova N, Coleman R, Aviram M. 2006b. Pomegranate byproduct administration to apolipoprotein e-deficient mice attenuates atherosclerosis development as a result of decreased macrophage oxidative stress and reduced cellular uptake of oxidized low-density lipoprotein. J. Agric. Food Chem. 54:1928–35.

Rozenberg O, Howell A, Aviram M. 2006. Pomegranate juice sugar fraction reduces macrophage oxidative state, whereas white grape juice sugar fraction increases it. Atherosclerosis 188:68–76.

Sartippour MR, Seeram NP, Rao JY, Moro A, Harris DM, et al. 2008. Ellagitannin-rich pomegranate extract inhibits angiogenesis in prostate cancer in vitro and in vivo. Int. J. Oncol. 32:475–80.

Seeram NP, Adams LS, Henning SM, Niu Y, Zhang Y, et al. 2005. 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. 16:360–67.

Seeram NP, Aronson WJ, Zhang Y, Henning SM, Moro A, et al. 2007. Pomegranate ellagitannin-derived metabolites inhibit prostate cancer growth and localize to the mouse prostate gland. J. Agric. Food Chem. 55:7732–37.

Seeram NP, Aviram M, Zhang Y, Henning SM, Feng L, et al. 2008a. Comparison of antioxidant potency of commonly consumed polyphenol-rich beverages in the United States. J. Agric. Food Chem. 56:1415–22.

Shiner M, Fuhrman B, Aviram M. 2007. Macrophage paraoxonase 2 (PON2) expression is up-regulated by pomegranate juice phenolic antioxidants via PPAR gamma and AP-1 pathway activation. Atherosclerosis 195:313–21.

Shukla M, Gupta K, Rasheed Z, Khan KA, Haqqi TM. 2008. Consumption of hydrolyzable tannins-rich pomegranate extract suppresses inflammation and joint damage in rheumatoid arthritis. Nutrition 24:733–43.

Stangeland T, Remberg SF, Lye KA. 2007. Antioxidants in some Ugandan fruits. Afr. J. Ecol. 45:29–30.

Sumner MD, Elliott-Eller M, Weidner G, Daubenmier JJ, Chew MH, et al. 2005. Effects of pomegranate juice consumption on myocardial perfusion in patients with coronary heart disease. Am. J. Cardiol. 96:810–14.

Toi M, Bando H, Ramachandran C, Melnick SJ, Imai A, et al. 2003. Preliminary studies on the anti-angiogenic potential of pomegranate fractions in vitro and in vivo. Angiogenesis 6:121–28.

Wolfe KL, Kang X, He X, Dong M, Zhang Q, Liu RH. 2008. Cellular antioxidant activity of common fruits. J. Agric. Food Chem. 56:8418–26.

Xu KZY, Zhu C, Kim MS, Yamahara J, Li Y. 2009. Pomegranate flower ameliorates fatty liver in an animal model of type 2 diabetes and obesity. J. Ethnopharmacol. 123:280–87.

Xu KZY, Zhu C, Kim MS, Yamahara J, Li Y. 2009. Pomegranate flower ameliorates fatty liver in an animal model of type 2 diabetes and obesity. J. Ethnopharmacol. 123:280–8