JPP Journal of Pharmacy and Pharmacology

JPP 2008, 60: 139–144

Received August 2, 2007
Accepted September 12, 2007
DOI 10.1211/jpp.60.2.0001
ISSN 0022-3573

Review Article

Ellagic acid, pomegranate and prostate cancer — a mini review

Carolyn Bell and Susan Hawthorne

Abstract

There is currently a shifting focus towards finding natural compounds that may prevent or treat cancer, due to the problems that exist with current chemotherapeutic regimens. The fruit of the *Punica granatum* (pomegranate) contains hundreds of phytochemicals and pomegranate extracts have recently been shown to exhibit antioxidant properties, thought to be due to the action of ellagic acid, the main polyphenol in pomegranate. In this mini review the effects of pomegranate extracts and ellagic acid on the proliferation of prostate cancer cells and their future potential are discussed.

Introduction

Prostate cancer is the most common male-only cancer in the UK with an individual having a 1 in 13 probability of developing the disease at some point in his lifetime. Over 20 000 new cases are diagnosed every year in the UK, with 10 000 existing patients succumbing to the disease annually (www.prostate-cancer.org.uk). These statistics demonstrate that the UK has one of the lowest survival rates in Europe for prostate cancer. Alarmingly, 30% of men over 50 and 80% of men over 80 years of age are reported to have some histological prostate abnormalities, thus the identification of novel targets for the prevention and treatment of prostate cancer presents us with an urgent challenge.

The prostate and prostate cancer

The prostate gland is one of the male sex glands and is located in the pelvic region of the abdomen, just below the bladder and in front of the rectum. It is composed of glandular and fibromuscular tissue with urothelium, secretory, basal, neuroendocrine and ejaculatory duct type cells (Bostwick 1990; Marchant 1995).

The prostate undergoes significant growth at puberty when luteinising hormone from the anterior pituitary gland stimulates the testes to produce testosterone, and androgens continue to be essential for normal growth and development of the prostate throughout life (Bostwick 1990; Marchant 1995). It is common for the prostate to enlarge with increasing age, a condition known as benign prostatic hyperplasia (BPH), and BPH affects more than half of men in their sixties and up to 70% of men aged 70 years and older (www.prostate-cancer.org.uk). Although rarely life threatening, this growth causes voiding problems as the enlarged prostate presses on the bladder and urethra, blocking the flow of urine (Teillac & Scarpa 2006). While BPH does not cause prostate cancer there is increasing evidence linking the two conditions due to the role of androgens in the development of both conditions (Roehrborn 2006).

Prostate cancer can often be asymptomatic in the earliest stages but symptoms in more advanced disease are those of bladder outlet obstruction, slow urinary stream, hesitancy, frequency, nocturia, haematuria and dysuria (McCance & Huether 2002). Many of these symptoms are also common to non-malignant conditions, such as BPH, prostatitis and prostate stones, but continual back pain or pain in the pelvis,

School of Pharmacy, Medical Biology Centre, Queens University of Belfast, 97 Lisburn Road, Belfast, BT9 7BL, UK

Carolyn Bell, Susan Hawthorne

Correspondence: S. Hawthorne, School of Pharmacy, Medical Biology Centre, Queens University of Belfast, 97 Lisburn Road, Belfast, BT9 7BL, UK.
E-mail: s.hawthorne@qub.ac.uk

hips or upper thighs may be an indication that the disease has metastasised. Other symptoms of advanced prostate cancer include weight loss, poor appetite and impotence (Marchant 1995).

Aetiology of prostate cancer

Despite being the most common cancer among men in developed countries, the aetiology of prostate cancer is not as well understood when compared with other common cancers such as lung and breast cancer (Kumar et al 2005). The known risk factors are older age, race and ethnicity, dietary factors, family history and hormones (Pienta & Esper 1993; Schaid 2004).

Age

Age is the most important risk factor for prostate cancer. It is predominantly a disease of the elderly, with incidence rising more steeply with age than for any other cancer. It usually affects men whose life expectancy is short and who are likely to be afflicted by other potentially fatal conditions. In the USA, prostate cancer incidence is 0.005% in those under 39 years old and almost 14% in the 60–79 age group (www.cancer.gov). A similar trend is evident in the UK population although higher emphasis on prostate-specific antigen (PSA) screening in the USA probably explains why its incidence data is double that of the UK for some age groups. Different theories exist about the time at which initiation events in prostate cancer occur, with some evidence suggesting that changes occur around puberty as a result of the increases in sex hormones (Diamandis & Yu 1996).

Race and ethnicity

The incidence of prostate cancer varies widely between ethnicities with its incidence being much greater in developed countries (Grönberg 2003). The lowest rates are in China, and generally all Asian countries are considered to have a low risk of prostate cancer incidence (1–9 cases per 100 000 population per year). The highest rates are in Scandinavia and North America, with incidence among African-American men being as high as 137 cases per 100 000 population per year (Schaid 2004). African ethnicity is an undisputed risk factor for prostate cancer and this is clearly seen in the USA, where the disease is 66% more common and twice more likely to be fatal in African-Americans than in Caucasians. It has been shown that greater mortality amongst African-Americans is due to the disease being more advanced when it is first detected, rather than an actual difference in the number of tumours (www.cancer.gov).

Dietary factors

The high incidence of prostate cancer found in developed countries has been associated with the 'western diet', which includes a high intake of dairy and saturated fats (Giovannucci et al 1998; Kirby et al 1998).

Prostate cell proliferation is influenced by vitamin D levels, as well as testosterone levels, with its metabolite 1,25 dihydroxyvitamin D_3 (1,25 D) inhibiting cellular proliferation and inducing differentiation of normal cells in-vitro, reducing the risk of prostate cancer (Chan et al 1998; Chan & Giovannucci 2001). It has been found that older men with higher circulating 1,25 D levels are at reduced risk of clinically advanced prostate cancer, so a diet supplemented with vitamin D could have a possible role in the prevention and treatment of prostate cancer (Giovannucci et al 1998). High intake of calcium in a dairy-rich diet may increase prostate cancer risk by suppressing 1,25 D levels and statistically significant positive associations have been found between dairy intake and prostate cancer (Chan & Giovannucci 2001). While high dairy intake is one of the most widely accepted dietary risk factors for prostate cancer in the published literature, a recent study concluded that there was no increased risk associated with calcium or dairy intake (Koh et al 2006), so further study is warranted before discouraging calcium intake.

High saturated fat intake is widely implicated in the development of prostate cancer, although it is not yet accepted as a risk factor (Kolonel 2001). High dietary fat will affect testosterone synthesis, so it may indirectly control the growth and function of the prostate (Wynder et al 1994).

Diets rich in plant antioxidants and phytochemicals may help to reduce the incidence of cancers, including prostate cancer (Reddy et al 2003). Evidence from epidemiological studies and large clinical prevention trials suggests that oxidative stress and DNA damage play an important role in prostate cancer carcinogenesis (reviewed in Klein 2004). Reactive oxygen species are generated intracellularly during cell metabolism and it is thought that they mediate cytotoxicity by reacting with lipids, DNA and proteins to cause cell damage (Lansky & Newman 2007). Lower levels of oxidative damage in normal secretory prostatic epithelium than in metastatic prostate cancer suggest that antioxidants could prevent primary prostate cancer progression to the metastatic state.

Recent research suggests that antioxidant levels have an inverse relationship with prostate cancer incidence (Reddy et al 2003; Kumar et al 2005; Aggarwal & Shishodia 2006; Bemis et al 2006; Lotito & Frei 2006; Adhami et al 2007), with phytochemicals being one of the main sources of antioxidants in the diet (Reddy et al 2003; Mazzanti 2006). This review will discuss the role that pomegranate antioxidants may play in the progression of prostate cancer.

Family history

The occurrence of prostate cancer in families can be influenced by a number of factors, including genetic susceptibility and exposure to common environmental factors (Grönberg 2003). Ten to fifteen per cent of men who have prostate cancer have at least one relative who is affected (Hayes et al 1995: Whittemore et al 1995) and first-degree relatives of an affected man are 2–3 times more likely to develop the disease (Spitz et al 1991). Candidate susceptibility genes in hereditary disease include HPC1 (Smith et al 1996), PCAP (Berthon et al 1998) and BRCA1 and 2 (Ford et al 1994; Sigurdsson et al 1997).

Hormones

As mentioned previously, androgens play an important role in the normal growth and development of the prostate but they may also play a role in the development of the cancerous state

(Kirby et al 1998) since men with decreased androgen production have minimal risk of developing the disease (Haas & Sakr 1997). High levels of testosterone before diagnosis are associated with increased risk (Gann et al 1994), and withdrawal of testosterone by chemical or surgical means is a common treatment for prostatic disease (Kirby et al 1998). The exact role that androgens play in the development of prostate cancer has yet to be identified.

Chemoprevention of prostate cancer

Prostate cancer is an ideal candidate for chemoprevention by natural products because it is typically diagnosed in men over 50 years of age, and so a delay in disease progression achieved through nutritional intervention could significantly impact a patient's quality of life (Saleem et al 2003). Also, traditional chemotherapies possess a number of unwanted and often distressing side effects that may lead to poor patient compliance, a problem not normally seen with natural products.

Pomegranate

Pomegranate *(Punica granatum)* is a fruit-bearing deciduous shrub that, while native to Iran, grows throughout the Mediterranean region and the USA. The plant has narrow, glossy, oblong leaves and produces bright red flowers. Rounded fruits are large in size (5–12 cm) and have a thick reddish skin that encapsulates hundreds of small red seeds. When the seeds are crushed and dried they produce a unique oil, 80% of which is punicic acid, a rare 18-carbon fatty acid. The oil also contains the isoflavone genistein, found in soy beans, and coumestrol, a phytoestrogen. It is also one of the only plants in nature known to contain the sex steroid estrone (Pantuck et al 2006).

The pomegranate has recently been termed a 'superfruit', along with others such as blueberry and cranberry, for its proposed superior antioxidative quality (Pratt & Matthews 2003). The fruit is a rich source of polyphenol compounds, such as anthocyanins (which give the red colour to juice and seeds) and hydrolysable tannins, such as ellagic acid (Figure 1) and punicalagin, which account for the majority of the fruit's antioxidant activity (Gil et al 2000). In fact the antioxidative activity of pomegranate extracts surpasses that of green tea, which is currently undergoing clinical trial evaluation for treatment of prostatic disease (Bettuzzi et al 2006).

Biological effects of pomegranate and ellagic acid

The pomegranate has been of health-related interest since 1999 when Israeli researchers demonstrated the antioxidant potency of pomegranates. They showed that daily consumption of pomegranate juice dramatically lowered oxidation of LDL cholesterol, leading to the elimination of plaques in coronary arteries (Schubert et al 1999). The beneficial effects of pomegranate juice in atherosclerotic disease in animal models has since been ascribed to the presence of ellagic acid (Yu et al 2005).

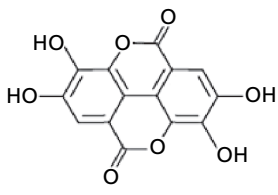

Figure 1 The chemical structure of ellagic acid.

Albrecht et al (2004) extracted crude polyphenols from various parts of the pomegranate fruit and found that proliferation and invasion of LNCaP, DU145 and PC3 prostate cancer cells in-vitro could be significantly reduced in the presence of these polyphenols. Malik et al (2005) evaluated a crude pomegranate fruit extract (PFE), containing ellagic acid among others, for its anti-proliferative and pro-apoptotic properties and found that it caused both cell growth inhibition and apoptosis in a dose-dependent manner in androgen-insensitive PC3 cells via modulation of the cyclin kinase inhibitor–cyclin–cdk machinery. This was achieved by induction of Bax and Bak, down-regulation of Bcl-X_L and Bcl-2 and decreasing the expression of cyclins D1, D2 and E and cdk2, 4 and 6 (Malik et al 2005; Malik & Mukhtar 2006). Oral administration of PFE (0.1% and 0.2% w/v) to mice implanted with androgen-sensitive cells resulted in inhibition of tumour growth with a significant decrease in serum PSA levels. Additionally, a blend of pomegranate juice, seed and peel, again containing ellagic acid, was found to reproducibly kill MCF-7 and MB-MDA-231 breast cancer cells in culture (Kim et al 2002).

Not only has crude pomegranate fruit extract been shown to have a biological effect on prostate cancer cells both in-vitro and in-vivo but also purified ellagic acid exerts an effect. It has been shown to initiate cell cycle arrest, apoptosis and anti-tumorigenic activity in animal models (Castonguay et al 1997; Longtin 2003; Seeram et al 2005) and is the active ingredient responsible for over 50% of the antioxidative activity of pomegranate juice (Pantuck et al 2006). It can also induce cell-cycle arrest and apoptosis in other cancer types, such as human bladder and leukaemia cells maintained in culture (Li et al 2005; Khanduja et al 2006)

The occurrence of free ellagic acid in dietary foodstuffs is uncommon; it is usually conjugated with a glycoside moiety, such as glucose, or forms part of the polymeric ellagitannins (Larrosa et al 2006). Ellagitannins are hydrolysable molecules with hydroxybenzoic acid components. The most abundant ellagitannin in the pomegranate fruit is punicalagin and during processing it is extracted into pomegranate juice in quantities reaching levels of over 2 g per litre of juice (Seeram et al 2005). On hydrolysis, punicalagin produces ellagic acid by spontaneous lactonisation of hexahydroxydiphenic acid (Larrosa et al 2006). Results from studies done in colon cancer found that punicalagin could be considered an apoptotic precursor, as it releases its hydrolysis product ellagic acid to the medium, which triggered apoptosis in cancer cells but not in normal colon cells (Larrosa et al 2006).

Ellagic acid is thought to modulate subcellular signalling pathways by various methods, including decreasing nuclear factor kappa, cyclooxygenase-2 and cyclin D_1 levels, inducing p53 and p21 expression as well as lowering levels of vascular endothelial growth factor (VEGF) (Li et al 2005;

Table 1 Effects of pomegranate crude extract and elllagic acid

		Reference
Key components		
Ellagic acid	Metabolite of ellagitannin	Gil et al 2000
Punicic acid	Fatty acid	Pantuck et al 2006
Genistein	Isoflavone	
Coumestrol	Phytoestrogen	
Biological effects		
Crude fruit extracts in-vitro	Inhibition of prostate cancer cell proliferation and induction of apoptosis	Albrecht et al 2004; Malik et al 2005; Malik & Mukhtar 2006
	Kills breast, bladder and leukaemia cancer cells	Khanduja et al 2006; Kim et al 2002; Li et al 2005
Crude fruit extracts in-vivo	Initiates cell cycle arrest and apoptosis in animal models	Castonguay et al 1997; Longtin et al 2003;
	Decrease in serum PSA levels in mice	Seeram et al 2005 Kim et al 2002
Ellagic acid in-vitro	Triggers apoptosis in colon cancer cells	Larrosa et al 2006
	Decreases NFκB, COX-2 cyclin D1 and VEGF levels	Li et al 2005; Aggarwal & Shishodia 2006
	Induces p53 and p21	Li et al 2005; Aggarwal & Shishodia 2006

Aggarwal & Shishodia 2006). The key effects of both crude pomegranate extracts and purified ellagic acid are summarised in Table 1.

Ellagic acid: a new chemotherapeutic?

One issue with pomegranate is that despite ellagic acid being widely implicated as the key compound, it is possible that its action could be supplemented by the presence of all the other polyphenols in pomegranate juice. While standard single-compound agents influence a single pathway, complex botanical therapies have a multi-factorial effect that can influence multiple cellular pathways at once. Single cytotoxic agents mean that cells can more readily switch to a backup pathway and become resistant to the drug, as is the problem with chemotherapy (Longtin 2003).

Studies have found that synergy appears to affect the results found with pomegranate and this needs to be taken into account when isolating a purified compound from just one part of the fruit. Sestili et al (2006) found that while rind extract conferred greater cytoprotection than fruit juice, a combination of the two saw increased survival of oxidatively damaged U937 and HUVEC cells. In another study, different combinations of the phytochemicals within pomegranate were investigated for their anti-carcinogenic properties. Purified ellagic acid was compared with its precursor punicalagin, and also the total pomegranate tannins found within pomegranate juice. While they all decreased the viable cell number of human oral and colon tumour cells, pure pomegranate juice had superior activity and was found to be the most active antioxidant sample tested. Pomegranate juice also stimulated apoptosis when concentrations of isolated tannins that were equalized to amounts found in pomegranate juice had no effect. The superior bioactivity of the juice over its separated and individual polyphenols is suggestive of synergistic or additive effects from the other phytochemicals present in pomegranate juice. This is perhaps unsurprising as the juice also contains phytochemicals such as anthocyanins and flavonoids, that have been shown to have antioxidant and anti-proliferative activity (Seeram et al 2005). While pure pomegranate juice has enhanced bioactivity, it contains, along with ellagic acid, a number of oestrogenic and pro-oestrogenic compounds, such as coumestrol and estrone (Pantuck et al 2006), which may influence the growth and spread of hormone-dependent prostate tumours. For this reason it may be beneficial to develop a one-compound agent based on ellagic acid, which does not display oestrogenic properties, particularly if the compounds were to be used as a treatment for hormone-dependent disease.

While in-vitro studies with ellagic acid show promise, the bioavailability of ellagitannins and ellagic acid in man has not been extensively studied. One recent study has shown that ellagic acid and its metabolites are found in human plasma after ingestion of pomegranate and that antioxidant capacity was retained in ex-vivo studies (Mertens-Talcott et al 2006). Further studies could determine whether the presence of free ellagic acid was due to its release from ellagitannins by gut microflora or physiological pH (Seeram & Heber 2004). Poor absorption from the gut or metabolism plus lack of transport to the prostate may limit the bioavailability and clinical usefulness of ellagic acid but much more research on the pharmacokinetics is required before this can be determined.

Since the amount of information available on the properties and roles of pomegranate extracts, and particularly ellagic acid, is very limited, their potential as cancer-chemopreventive and cancer-chemotherapeutic agents should be thoroughly investigated. A number of clinical trials are currently ongoing focusing on the potential of other phytochemicals, such as green tea catechins, curcumin, resveratrol and genistein, in the treatment of various cancers (Bemis et al 2006; Busby & Kamat 2006; Kumar et al 2007). Pomegranate and ellagic acid exhibit superior antioxidant activity and therefore may have the ability to surpass them all.

References

Adhami, V. M., Malik, A., Zaman, N., Sarfaraz, S., Siddiqui, I. A., Syed, D. N., Afaq, F., Pasha, F. S., Saleem, M., Mukhtar, H. (2007) Combined inhibitory effects of green tea polyphenols and

selective cyclooxygenase-2 inhibitors on the growth of human prostate cancer cells both *in vitro* and *in vivo*. *Clin. Cancer Res.* **13**: 1611–1619

Aggarwal, B. B., Shishodia, S. (2006) Molecular targets of dietary agents for prevention and therapy of cancer. *Biochem. Pharmacol.* **71**: 1397–1421

Albrecht, M., Jiang, W., Kumi-Diaka, J., Lansky, E. P., Gommersall, L. M., Patel, A., Mansel, R. E., Neeman, I., Geldof, A. A., Campbell, M. J. (2004) Pomegranate extracts potently suppress proliferation, xenograft growth and invasion of human prostate cancer cells. *J. Med. Food* **7**: 274–283

Bemis, D. L., Katz, A. E., Buttyan, R. (2006) Clinical trials of natural products as chemopreventive agents for prostate cancer. *Expert Opin. Invest. Drugs* **15**: 1191–1200

Berthon, P., Valeri, A., Cohen-Akenine, A., Drelon, E., Paiss, T., Wohr, G., Latil, A., Millasseau, P., Mellah, I., Cohen, N., Blanche, H., Bellane-Chantelot, C., Demenais, F., Teillac, P., Le Duc, A., de Petriconi, R., Hautmann, R., Chumakov, I., Bachner, L., Maitland, N. J., Lidereau, R., Vogel, W., Fournier, G., Mangin, P., Cohen, D., Cussenot, O. (1998) Predisposing gene for early-onset prostate cancer, localized on chromosome 1q42.2-43. *Am. J. Hum. Genet*. **62**: 1416–1424

Bettuzzi, S., Brausi, M., Rizzi, F., Castagnetti, G., Peracchia, G., Corti, A. (2006) Chemoprevention of human prostate cancer by oral administration of green tea catechins in volunteers with high grade prostate intraepithelial neoplasia. *Cancer Res.* **66**: 1234–1240

Bostwick, D. G. (1990) *Pathology of the prostate*. Churchill Livingstone Publishers, NY

Busby, J. E., Kamat, A. M. (2006) Chemoprevention for bladder cancer. *J. Urol*. **176**: 1914–1920

Castonguay, A., Gali, H. U., Perchellet E. M. (1997) Antitumorigenic and antipromoting activities of ellagic acid, ellagitannins and oligometric anthocyanin and procyanidin. *Int. J. Oncol*. **10**: 367–373

Chan, J. M., Giovannucci, E. L. (2001) Dairy products, calcium, and vitamin D and risk of prostate cancer. *Epidemiol. Rev.* **23**: 87–92

Chan J. M., Stampfer, M. J., Giovannucci, E. L. (1998) What causes prostate cancer? A brief summary of the epidemiology. *Cancer Biol.* **8**: 263–273

Diamandis, E. P., Yu, H. (1996) Does prostate cancer start at puberty? *J. Clin. Lab. Anal*. **10**: 468–469

Ford, D., Easton, D. F., Bishop, D. T., Narod, S. A., Goldgar, D. E. (1994) Risks of cancer in BRCA-1 mutation carriers. Breast Cancer Linkage Consortium. *Lancet* **343**: 692–695

Gann, P. H., Hennekens, C. H., Sacks, F. M., Grodstein, F., Giovannucci, E. L., Stampfer, M. J. (1994) Prospective study of plasma fatty acids and risk of prostate cancer. *J. Natl Cancer Inst*. **86**: 281–286

Gil, M. I., Tomas-Barberan, F. A., Hess-Pierce, B., Holcroft, D. M., Kader, A. A. (2000) Antioxidant activity of pomegranate juice and its relationship with phenolic composition and processing. *J. Agric. Food Chem*. **10**: 4581–4589

Giovannucci, E., Rimm, E. B., Wolk, A., Ascherio, A., Stampfer, M. J., Colditz, G. A., Willett, W. C. (1998) Calcium and fructose intake in relation to risk of prostate cancer. *Cancer Res.* **58**: 442–447

Grönberg, H. (2003) Prostate cancer epidemiology. *Lancet* **361**: 859–864

Haas, G. P., Sakr, W. A. (1997) Epidemiology of prostate cancer. *CA Cancer J. Clin*. **47**: 273–287

Hayes, R. B., Liff, J. M., Pottern, L. M., Greenberg, R. S., Schoenberg, J. B., Schwartz, A. G., Swanson, G. M., Silverman, D. T., Brown, L. M., Hoover, R. N., Fralmeni, J. F. (1995) Prostate cancer risk in U.S. blacks and whites with a family history of cancer. *Int. J. Cancer* **60**: 361–364

Khanduja, K. L., Avti, P. K., Kumar, S., Mittal, N., Sohi, K. K., Pathak, C. M. (2006) Anti-apoptotic activity of caffeic acid, ellagic acid and ferulic acid in normal human peripheral. blood mononuclear cells: a Bcl-2 independent mechanism. *Biochim. Biophys. Acta* **1760**: 283–289

Kim, N. D., Mehta, R., Yu, W. (2002) Chemopreventative and adjuvant therapeutic potential of pomegranate for human breast cancer. *Breast Cancer Res. Treat*. **71**: 203–217

Kirby, R. S., Brawer, M. K., Denis, L. J. (1998) *Fast facts: prostate cancer*. 2nd edn, Health Press, London, pp 7–62

Klein, E. A. (2004) Prostate cancer chemoprevention. In: Klein, E. A. (ed.) *Management of prostate cancer*. 2nd edn, Humana Press, New Jersey, pp 71–106

Koh, K. A., Sesso, H. D., Paffenbarger, R. S., Lee, I.-M. (2006) Dairy products, calcium and prostate cancer risk. *Br. J. Cancer* **95**: 1582–1585

Kolonel, L. N. (2001) Fat, meat, and prostate cancer. *Epidemiol. Rev.* **23**: 72–81

Kumar, R. J., Barqawi, A. B., Crawford, E. D. (2005) Adverse events associated with hormonal therapy for prostate cancer. *Rev. Urol.* **7**: S37–S43

Kumar, N., Shibata, D., Helm, J., Coppola, D., Malafa, M. (2007) Green tea polyphenols in the prevention of colon cancer. *Frontiers Biosci.* **12**: 2309–2315

Lansky, E. P., Newman, R. A. (2007) *Punica granatum* (pomegranate) and its potential for prevention and treatment of inflammation and cancer. *J. Ethnopharmacol.* **109**: 177–206

Larrosa, M., Tomás-Barberán, F. A., Espín, J. C. (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**: 611–625

Li, T. M., Chen, G. W., Su, C. C., Lin, J. G., Yeh, C. C., Cheng, K. C., Chung, J. G. (2005) Ellagic acid induced p53/p21 expression, G1 arrest and apoptosis in human bladder cancer T24 cells. *Anticancer Res*. **25**: 971–979

Longtin, R. (2003) The pomegranate: nature's power fruit? *J. Natl Cancer Inst.* **95**: 346–348

Lotito, S. B., Frei, B. (2006) Consumption of flavonoid-rich foods and increased plasma antioxidant capacity in humans: cause, consequence, or epiphenomenon? *Free Radic. Biol. Med.* **41**: 1727–1746

Malik, A., Mukhtar, H. (2006) Prostate cancer prevention through pomegranate fruit. *Cell Cycle* **5**: 371–373

Malik, A., Afaq, F., Safaraz, S., Adhami, V. M., Syed, D. N., Mukhtar, H. (2005) Pomegranate fruit juice for chemoprevention and chemotherapy of prostate cancer. *Proc. Natl Acad. Sci. USA* **102**: 14813–14818

Marchant, N. (1995) *Diseases of the prostate*. Office of Health Economics, London

Mazzanti, G. (2006) Antioxidants and food. *Phytother. Res.* **20**: 322–332

McCance, K. L., Heuther, S. E. (2002) Alterations of the reproductive systems. In: McCance, K. L., Heuther, S. E. (eds) *Pathophysiology: the biologic basis for disease in adults and children*. 4th edn, Mosby, Missouri, pp 705–780

Mertens-Talcott, S. U., Jilma-Stohlawetz, P., Rios, J., Hingorani, L., Derendorf, H. (2006) Absorption, metabolisn and antioxidant effects of pomegranate polyphenols after ingestion of a standarised extract in healthy human volunteers. *J. Agric. Food Chem*. **54**: 8956–8961

Pantuck, A. J., Leppert, J. T., Zomorodian, N., Aronson W., Hong, J., Barnard, R. J., Seeram N., Liker, H., Wang, H. J., Elashoff, R., Heber, D., Aviram, M., Ignarro, L., Belldegrun, A. (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**: 4018–4026

Pienta, K. J., Esper, P. S. (1993) Risk factors for prostate cancer. *Ann. Intern. Med*. **118**: 793–803

Pratt, S. G., Matthews, K. (2003) *Superfoods Rx*. Harper Collins Press, New York

Reddy, L., Odhav, B., Bhoola, K. D. (2003) Natural products for cancer prevention: a global perspective. *Pharmacol. Ther*. **99**: 1–13

Roehrborn, C. (2006) Insights into the relationships between prostatic disorders and their potential impact on future urologic practice. *Eur. Urol. Suppl.* **5**: 698–703

Saleem, M., Adhami, V. M., Siddiqui, I. A., Mukhtar, H. (2003) Tea beverage in chemoprevention of prostate cancer: a mini-review. *Nutr. Cancer* **47:** 13–23

Schaid, D. J. (2004) The complex genetic epidemiology of prostate cancer. *Hum. Mol. Genet.* **13**: R103–R121

Schubert, S. Y., Lansky, E. P. Neeman, I. (1999) Antioxidant and eicosanoid enzyme inhibition properties of pomegranate seed oil and fermented juice flavonoids. *J. Ethnopharmacol.* **66**: 11–17

Seeram, N. P., Heber, D. (2004) Bioavailability of ellagic acid in human plasma after consumption of ellagitannins from pomegranate juice. *Clin. Chem. Acta* **348**: 63–68

Seeram, N. P., Adams, L. S., Henning, S. M., Niu, Y., Zhang, Y., Nair, M. G., Heber, D. (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**: 360–367

Sestilli, P., Fraternale, D., Martinelli, C., Giamperi, L., Bucchini, A., Stocchi, V., Ricci, D. (2006) Antioxidant activity of pomegranate (*Punica granatum* L.) extracts in cell-free and cell culture systems. *Phytother. Res.* **20**: 322–332

Sigurdsson, S., Thorlacius, S., Tomasson, J., Tryggvadottir, L., Benediktsdottir, K., Eyfjord, J. E., Jonsson, E. (1997) BRCA-2 mutation in Icelandic prostate cancer patients. *J. Mol. Med*. **75**: 758–761

Smith, J. R., Freije, D., Carpten, J. D., Gronberg, H., Xu, J. F., Isaacs, S. D., Brownstein, M. J., Bova, G. S., Guo, H., Bujnovszky, P., Nusskern, D. R., Damber, J. E., Bergh, A., Emanuelsson, M., Kallioniemi, O. P., Walker Daniels, J., Bailey Wilson, J. E., Beaty, T. H., Meyers, D. A., Walsh, P. C., Collins, F. S., Trent, J. M., Isaacs, W. B. (1996) Major susceptibility locus for prostate cancer on chromosome 1 suggested by a genome-wide search. *Science* **274**: 1371–1374

Spitz, M. R., Currier, R. D., Fueger, J. J., Babaian, R. J., Newell, G. R. (1991) Familial patterns of prostate cancer: a case control analysis. *J. Urol*. **146**: 1305–1307

Teillac, P., Scarpa, R. M. (2006) Economic issues in the treatment of BPH. *Eur. Urol. Suppl.* **5**: 1018–1024

Whittemore, A. S., Wu, A. H., Kolonel, L. N., John, E. M., Gallagher, R. P., Howe, G. R., West, D. W., Heh, C. Z., Stamey, T. (1995) Family history and prostate cancer risk in black, white and asian men in the U.S and Canada. *Am. J. Epidemiol*. **141**: 732–740

Wynder, E. L., Rose, D. P. Cohen, L. A. (1994) Nutrition and prostate cancer—a proposal for dietary intervention. *Nutr. Cancer Int. J*. **22**: 1–10

Yu, Y. M., Chang, W. C., Wu, C. H., Chiang, S. Y. (2005) Reduction of oxidative stress in hyperlipidemic rabbits by ellagic acid. *J. Nutr. Biochem*. **16**: 675–681