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Cancer Chemoprevention by Pomegranate: Laboratory and Clinical Evidence

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Abstract

Pomegranate fruit from the tree *Punica granatum* has been dubbed as the "nature's power fruit." Dating back to Biblical times, the tree itself is attributed to possess extraordinary medicinal properties. The geographical distribution of the tree, being native to the Middle East and some Asian countries, is generally attributed to a lack of interest in its medicinal properties by many western scientists. However, the unique biochemical composition of the pomegranate fruit being rich in antioxidant tannins and flavonoids has recently drawn attention of many investigators to study its exceptional healing qualities. Recent research has shown that pomegranate extracts selectively inhibit the growth of breast, prostate, colon and lung cancer cells in culture. In preclinical animal studies, oral consumption of pomegranate extract inhibited growth of lung, skin, colon and prostate tumors. An initial phase II clinical trial of pomegranate juice in patients with prostate cancer reported significant prolongation of prostate specific antigen doubling time. This review focuses on recent investigations into the effects of pomegranate fruit on cancer.

INTRODUCTION

The fruit of the tree *Punica granatum*, grown mainly in the Mediterranean region, has been shown to possess many medicinal properties such as being antioxidant and anti-inflammatory (1). The antioxidant activity of flavonoids obtained from pomegranate juice (PJ) was observed to be close to that of butylated hydroxyanisole, green tea, and significantly greater than red wine (2,3). Commercially available pomegranate juices tested for their antioxidant activity by the Trolox Equivalent Antioxidant Capacity (TEAC) assay showed antioxidant activity of ~18 to 20 TEAC that was three times higher than those of red wine and green tea (6–8 TEAC). Interestingly, the antioxidant activity was higher in commercial juices that were extracted from whole pomegranates than in experimental juices that were obtained from the arils only (4). Antioxidant activities of freeze-dried preparations of pomegranate and its 3 major anthocyanidins (delphinidin, cyanidin, and pelargonidin) were evaluated by Noda et al. (3) by the method of electron spin resonance technique and spin trapping. Pomegranate extract exhibited scavenging activity against OH and O_2^-. The anthocyanidins were found to inhibit a Fenton reagent $^-$OH generating system possibly by chelating with ferrous ion. Also, anthocyanidins scavenged O_2^- in a dose-dependent manner, and ID_{50} values of delphinidin, cyanidin, and pelargonidin were 2.4, 22, and 456 μM, respectively. Anthocyanidins inhibited H_2O_2-induced lipid peroxidation in the rat brain homogenates and ID_{50} values of delphinidin, cyanidin, and pelargonidin were 0.7, 3.5, and 85 μM, respectively (3). Pomegranates have only

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recently been studied for their anticancer effects (Table 1). The following sections will summarize the studies on the effects of pomegranate against various cancers.

POMEGRANATE AND BREAST CANCER

Polyphenolic fractions from pomegranate fruit were assessed in vitro for their possible chemopreventive activity or as adjuvant in a therapeutic setting against human breast cancer cells (5). Polyphenols obtained from fermented juice at concentrations ranging from 100 to 1,000 μg/ml inhibited aromatase and 17-β-hydroxysteroid dehydrogenase type 1 activity by 60–80%. Human breast cancer cell lines MCF-7 and MB-MDA-231 cells were treated with fermented pomegranate juice and fresh pomegranate juice. Polyphenols from fermented juice showed about twice the antiproliferative effect as compared to polyphenols from fresh pomegranate juice. Pomegranate seed oil (PGO; 100 μg/ml of medium) resulted in 90% inhibition of proliferation of MCF-7 cells. Invasion of MCF-7 cells across a Matrigel membrane was inhibited by 75% at 10 μg/ml of PGO. PGO (50 μg/ml) also induced 54% apoptosis in MDA-MB-435 estrogen receptor negative metastatic human breast cancer cells. Fermented juice polyphenols resulted in 47% inhibition of cancerous lesion formation induced by the carcinogen 7,12-dimethylbenz[a]anthracene (DMBA) in a murine mammary gland organ culture (MMOC). Mehta and Lansky (6) further explored and compared the chemopreventive efficacy of a purified chromatographic peak of pomegranate fermented juice and also of whole PGO. MMOC cultures were treated with pomegranate fermented juice polyphenols, a high-performance liquid chromatographic (HPLC) peak separated from fermented juice or PGO, and on Day 3 exposed to the carcinogen DMBA and for 10 days treated with the putative pomegranate preparations. Fermented pomegranate juice resulted in 42% reduction in the number of lesions compared with control, whereas the peak separated from the fermented juice and the PGO each resulted in 87% reduction in number of tumorigenic lesions. The results suggested enhanced potential for the purified compound as well as PGO, both greater than pomegranate fermented juice polyphenols.

Toi et al. (7) evaluated the antiangiogenic potential of pomegranate polyphenols by measuring vascular endothelial growth factor (VEGF), interleukin-4 (IL-4) and migration inhibitory factor (MIF) in the conditioned media of MCF-7 or MDA-MB-231 human breast cancer cells or immortalized normal human breast epithelial cells (MCF-10A). VEGF was strongly downregulated in MCF-10A and MCF-7, and MIF was upregulated in MDA-MB-231, overall showing significant potential for downregulation of angiogenesis by pomegranate fractions. These fractions further inhibited proliferation of human umbilical vein endothelial cells (HUVEC), and angiogenic cells in myometrial and amniotic fluid fibroblasts. A significant decrease in new blood vessel formation using the chicken chorioallantoic membrane (CAM) model was also observed. These findings demonstrate an anti-angiogenic potential of pomegranate fractions. The effect of pomegranate extracts in combination with genistein was investigated on the growth rate and apoptosis induction in human breast cancer cells MCF-7 (8). Both pomegranate extracts and genistein had significant dose- and time-dependent cytotoxic effects on MCF-7 cells. The inhibition and apoptosis induction were significantly higher in the combination treatments than in the single treatments with either agent.

POMEGRANATE AND PROSTATE CANCER

The effects of pomegranate on prostate cancer (PCa) have been investigated in the cell culture system, animal models, and in a phase II clinical trial in humans. Various preparations of pomegranate, in the form of oils, fermented juice polyphenols, and pericarp polyphenols, were tested on human PCa cell growth both in vitro and in vivo (9–18). Each preparation inhibited growth of human PCa LNCaP, PC-3, and DU 145 cells, whereas normal prostate epithelial cells were significantly less affected (9). These effects were observed to be mediated by

changes in cell cycle distribution and induction of apoptosis. Androgen-independent DU145 cells were treated with pomegranate cold pressed oil (35 μg/ml) and found to accumulate in the G2/M phase of the cell cycle that was associated with a significant upregulation of the cyclin-dependent kinase inhibitor (cki) p21 and downregulation of c-myc (9). In contrast, cell proliferation was inhibited predominantly by induction of apoptosis in PC-3 cells through a caspasc 3-mediated pathway (9). All forms of pomegranate preparations were found to inhibit PC-3 cell invasion through Matrigel and also inhibited the growth of PC-3 xenograft in athymic nude mice (9,10). These findings have suggested an overall significant antiproliferative and antitumor action of pomegranate-derived fractions against human PCa. Components from pomegranate fruit each belonging to different representative chemical classes and showing known anticancer activities have been tested as potential inhibitors of in vitro invasion of human PCa cells in an assay employing Matrigel artificial membranes (11–13). All compounds significantly inhibited invasion when employed individually at 4 μg/ml and when equally combined at the same dose showed a supra-additive inhibition of invasion (14).

Antiproliferative and proapoptotic properties of pomegranate fruit extract (PFE) against human PCa cells were demonstrated by the authors (15,16) both in the cell culture system and in a xenograft mouse model. Human PCa PC-3 cells treated with PFE (10–100 μg/tml) for 48 h resulted in a dose-dependent inhibition of cell growth and induction of apoptosis (16). The induction of apoptosis and cell cycle arrest was associated with upregulation of proapoptotic Bax and Bak, downregulation of anti-apoptotic Bcl-XL and Bcl-2, induction of WAF1/p21 and KIP1/p27, a decrease in cyclins D1, D2, and E; and a decrease in the protein expression of cyclin-dependent Kinase-2, -4 and -6(16). To demonstrate the efficacy of PFE in an in vivo setting, athymic nude mice were implanted with androgen-responsive CWR22Rv1 cells and given 0.1% and 0.2% (wt/vol) PFE in drinking water starting simultaneously after cell implantation (16). The selection of doses, 0.1% and 0.2%, was based on the assumption that a typical healthy individual (~70 kg) may be persuaded to drink 250 or 500 ml of pomegranate juice extracted from one or two fruits, respectively. Oral infusion of PFE to mice resulted in a significant inhibition in tumor growth as observed by prolongation of tumor appearance. Tumor volumes were consistently lower in mice that received PFE, with effects being dose-dependent and the maximum inhibitory effect observed in the 0.2% PFE-fed group. Tumor growth inhibition was accompanied with a concomitant decrease in serum prostate-specific antigen and serum PSA levels were 70–85% lower in PFE-fed mice as compared to water-fed mice (16). The reduction in prostate tumor growth with concomitant reduction in PSA levels observed in the xenograft model suggested that PFE may have clinical relevance.

PCa initiates as an androgen regulated disease; however, advanced disease acquires androgen-independence. Overexpression of the androgen receptor promotes the development of androgen independence. Hong et al. (17) investigated the effects of pomegranate polyphenols, ellagitannin-rich extract, and whole juice extract on the expression of genes for key androgen-synthesizing enzymes and the androgen receptor. Genes HSD3B2 (3beta-hydroxysteroid dehydrogenase type 2), AKR1C3 (aldo-keto reductase family 1 member C3), and SRD5A1 (steroid 5alpha reductase type 1) were analyzed in LNCaP, LNCaP-AR, and DU-145 human PCa cells. Pomegranate polyphenols inhibited gene expression and AR most consistently in the LNCaP-AR cell line where androgen receptor was overexpressed (17). These studies have suggested that pomegranate polyphenols may be of particular importance in androgen-independent PCa cells and the subset of human prostate cancers where the androgen receptor is upregulated.

In a phase II clinical trial, Pantuck et al. (18) recruited patients with rising PSA and gave them 8 ounces of pomegranate juice daily until disease progression. PSA doubling time significantly increased with treatment from a mean of 15 mo at baseline to 54 mo posttreatment ($P < 0.001$). A major drawback of this study was the absence of a proper placebo control; however,

statistically significant prolongation of PSA doubling time suggested a potential of pomegranate for prevention of human PCa (18). This initial clinical trial bears evidence in support of PFE because it suggests that pomegranate consumption may retard PCa progression, which may prolong not only the survival but also improve the quality of life of patients.

POMEGRANATE AND LUNG CANCER

The effects of PFE on lung tumorigenesis were examined by authors both in vitro and in vivo (19–21). Normal human bronchial epithelial cells (NHBE) and human lung carcinoma A549 cells were treatment with PFE (50–150 μg/ml) for 72 h. Whereas PFE resulted in a significant decrease in the viability of A549 cells, only minimal effects were observed on NHBE cells (19). PFE treatment of A549 cells resulted in dose-dependent arrest of cells in G0/G1 phase of the cell cycle, which was associated with induction of WAF1/p21 and KIP1/p27 and accompanied by decrease in the expression of downstream cell cycle regulatory proteins. PFE treatment also resulted in inhibition of several signaling pathways, including MAPK PI3K)/Akt, and NF-κB. The effect of PFE was tested in mice implanted with A549 cells (19). The appearance of tumors was observed in animals receiving water as early as 15 days post cell inoculation. This latency period was prolonged to 19 days in animals receiving PFE in drinking fluid. In mice that received water, the average tumor volume of 1,200 mm^3 was reached in 55 ± 2 days after tumor cell inoculation. At this time point, the average tumor volumes in the 0.1 and 0.2% PFE-fed groups were 621 and 540 mm^3, respectively (19). The average tumor volume of 1,200 mm^3 was achieved in 67 ± 4 days after tumor cell inoculation in the 0.1% PFE-fed group, and the 0.2% PFE-fed group showed the most effective tumor growth inhibitory response in which the targeted average tumor volume of 1,200 mm^3 was reached at 79 ± 3 days after tumor cell inoculation. These observations indicated that PFE could be a useful chemopreventive/chemotherapeutic agent against human lung cancer.

To further explore the benefits of PFE against lung tumorigenesis, authors (20) examined the effect of oral consumption of a human achievable dose of PFE in two mouse lung tumor protocols. Benzo(a)pyrene [B(a)P] and N-nitroso-tris-chloroethylurea (NTCU) were used to induce lung tumors, and PFE was given in drinking water to A/J mice. Lung tumor yield was examined on the 84th day and 140 days after B(a)P dosing and 240 days after NTCU treatment. Mice treated with PFE and exposed to B(a)P and NTCU had statistically significant lower lung tumor multiplicities than mice treated with carcinogens only (20). Tumor reduction was 53.9% and 61.6% in the B(a)P + PFE group at 84 and 140 days, respectively, compared with the B (a)P group. The NTCU + PFE group had 65.9% tumor reduction compared with the NTCU group at 240 days (20). Tumors from these animals were examined for effects on cell proliferation and various signaling pathways. Tumors had low proliferative indexes as examined by ki-67 and PCNA staining. PFE treatment also resulted in inhibition of NF-κB, MAPK, and PI3K/Akt signaling. Since the mammalian target of rapamycin (mTOR) is downstream of both PI3K and Akt, it was determined whether phosphorylation of mTOR was a result of PI3K/Akt activation (20). Treatment with B(a)P and NTCU caused increased phosphorylation of mTOR at Ser^{2448}, whereas PFE administration resulted in inhibition of phosphorylation of mTOR. This observation was significant since the mTOR integrates mitogenic signals and intracellular nutrient levels to activate 4EBP1 and p70S6K that control protein translation and cell cycle progression. Phosphorylation of AMPKα, an upstream downregulator of mTOR, that was decreased in B(a)P and NTCU treated mice was restored in mice that received oral infusion of PFE (20).

POMEGRANATE AND COLON CANCER

The effect of PGO was studied in mice on the occurrence of colonic aberrant crypt foci induced by azoxymethane (AOM) (22–24). Colonic tumors were induced in 6-wk-old male F344 rats

by subcutaneous injections of AOM (20 mg/kg body weight) once, a week for 2 wk (22). At 1 wk before the AOM treatment, mice were started on a diet containing 0.01%, 0.1%, or 1% PGO for 32 wk. After 32 wk, the incidence of colon tumors was 81% with a tumor multiplicity of 1.88/mice. Administration of PGO in the diet significantly inhibited the incidence and multiplicity of colonic adenocarcinomas; however, a dose-response relationship was not observed (22). The inhibition of tumor incidence was associated with increased expression of peroxisome proliferator-activated receptor (PPAR) gamma protein in the nontumor mucosa (22). These findings suggest beneficial effects of pomegranate against the development of colonic tumors in mice.

Inflammation plays a key role in the development of colon cancer, and many anti-inflammatory agents have shown promise for prevention of colon cancer. Adams et al. (24) examined the effects of pomegranate juice (PJ) on inflammatory cell signaling proteins in HT-29 human colon cancer cell line. At a concentration of 50 mg/l, PJ significantly suppressed TNFα-induced (COX)-2 protein expression by 79% and also reduced phosphorylation of the NF-κB/p65 subunit and its binding to the NF-κB response element. PJ also abolished TNFα-induced AKT activation, needed for NF-κB activity (24). These data suggest that polyphenolic constituents in the pomegranate can play an important role in the modulation of inflammatory signals in colon cancer cells.

POMEGRANATE AND SKIN CANCER

PGO has been investigated for possible skin cancer chemopreventive efficacy in mice (25–29). Skin tumors were initiated in 5-wk-old, female, CD-1 mice with an initial topical application of DMBA followed by biweekly promotion using 12-O-tetradecanoylphorbol 13-acetate (TPA). Tumor incidence was 100% in control mice compared to 93% in mice pretreated with 5% PGO prior to each TPA application (25). The average number of tumors per mouse was 20.8 in control compared to 16.3 per mouse in PGO-treated groups (25). The effect of PGO on TPA-stimulated ornithine decarboxylase (ODC) activity, an important event in skin cancer promotion, showed a 17% reduction in ODC activity. These initial observations suggested that PGO is a safe and effective chemopreventive agent against skin cancer (25). We evaluated antitumor-promoting effects of PFE in a similar animal model of skin cancer development (26). Topical application of PFE (2 mg/mouse) 30 min prior to TPA (3.2 nmole/mouse) application on mouse skin afforded significant inhibition, in a time-dependent manner, against TPA-mediated increase in skin edema and hyperplasia, epidermal ODC activity, and protein expression of ODC and COX-2 (26). PFE treatment also resulted in inhibition of TPA-induced phosphorylation of ERK1/2, p38, and JNK1/2, as well as activation of NF-κB (26). The effect of skin application of PFE on TPA-induced skin tumor promotion in DMBA-initiated CD-1 mouse was also investigated. In TPA-treated group, 100% of the mice developed tumors at 16 wk on test; whereas at this time in the PFE-treated group, only 30% of mice exhibited tumors. Skin application of PFE prior to TPA application also resulted in a significant delay in latency period from 9 to 14 wk and afforded protection when tumor data were considered in terms of tumor incidence and tumor multiplicity. These observations provide clear evidence that PFE possesses anti-skin-tumor-promoting effects in CD-1 mouse by inhibiting conventional as well as novel biomarkers of TPA-induced tumor promotion.

Excessive exposure of solar ultraviolet (UV) radiation, particularly its UV-B component, to humans causes many adverse effects that include erythema, hyperplasia, hyperpigmentation, immunosuppression, photoaging, and skin cancer. To investigate the effect of PFE for humans, authors (27) determined its effect in normal human epidermal keratinocytes (NHEK) exposed UV-B. PFE (10–40 μg/ml) for 24 h before UV-B (40 mJ/cm^2) exposure dose dependently inhibited UV-B-mediated phosphorylation of ERK1/2, JNK1/2, and p38 protein (27). PFE treatment of NHEK also resulted in a dose- and time-dependent inhibition of UV-B-activation

of NF-κB (27). These data demonstrated protective effects of PFE against UV-B radiation and provided a molecular basis for the observed effects. In a recent study, protective effects of pomegranate fruit extract against UVA- and UVB-induced damage were studied in SKU-1064 human skin fibroblast cells (28). Pomegranate extract (PE), in a range from 5 to 60 mg/l, was effective at protecting human skin fibroblasts from cell death following UV exposure, which were attributed to a reduced activation of the proinflammatory transcription factor NF-κB, downregulation of proapoptotic caspase-3, and an increased G0/G1 phase associated with DNA repair (28). However, higher polyphenolic concentrations (500–10,000 mg/l) were needed to achieve a significant reduction in UV-induced reactive oxygen species levels and increased intracellular antioxidant capacity (from 1.9 to 8.6 muM Trolox equivalents/ml) (28).

UV-A is the major portion of solar radiation reaching the earth's surface and has been shown to lead to formation of benign and malignant tumors. UVA exposure to NHEK led to an increase in phosphorylation of STAT3, AKT, and ERK1/2, which were inhibited when cells were pretreated with PFE (60–100 μg/ml) for 24 h (29). PFE pretreatment also resulted in a dose-dependent inhibition in the phosphorylation of mTOR and p70S6K (29). These observations suggest that PFE is an effective agent for ameliorating UVA-mediated damages by modulating cellular pathways. Overall results suggest protective effects of pomegranate against UVA- and UVB-induced cell damage and the potential use of pomegranate polyphenolics in topical applications.

CONCLUSIONS

Interest in the biological activity of pomegranate-derived products, especially their anticancer properties, is being investigated in earnest. This interest is largely attributed to initial experiments that have reported activity of PJ that was found to be greater than that of red wine or even green tea. Various dietary agents are being investigated for their potential beneficial effects against PCa. PJ has shown an initial promise in a phase II clinical trial against PCa. There is a need to undertake similar clinical studies in other cancers such as colon and breast. Although identifying individual active ingredients in the PJ would be ideal, it is interesting to note that many studies have observed the extract or the juice to be more beneficial compared to the individual or purified ingredient. This suggests the existence of a chemical synergy when using an extract. The use of an extract rather than a purified compound could explain the inhibition of multiple targets observed in many studies and thus greater likelihood for producing cancer chemopreventive effects in humans. This may account for the synergistic preventive and/or anti-cancer effects, and the approach can be explored in laboratory, animal, clinical, and epidemiological studies in the future. It is anticipated that in-depth research into the anticancer activities of naturally occurring compounds would enable one day to develop a cocktail of such molecules for effective prevention cancers.

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TABLE 1

Laboratory and clinical evidence for cancer chemoprevention by pomegranate fractions

Cancer Type	Pomegranate Fraction	Evidence (Reference No.)
Breast	Juice, seed-oil, fermented juice polyphenols, extract	5_8
Prostate	Seed-oil, fermented juice polyphenols, extract, juice	9,11_13 15–18[18] (phase II clinical trial)
Lung	Fruit extract	19,20
Colon	Seed-oil, juice	22,24
Skin	Seed-oil, fruit extract	25_29
Miscellaneous (Leukemia)	Fresh and fermented juice	30