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ORIGINAL PAPER

Anti-Oxidants from Green Tea and Pomegranate for Chemoprevention of Prostate Cancer

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Abstract Among males, prostate cancer has become the second leading cause of cancer-related deaths in North America, with similar trends in many Western and developing countries. One way to control prostate cancer is through chemoprevention, which refers to the administration of synthetic or naturally occurring agents to block, reverse, or delay the process of carcinogenesis. For a variety of reasons, the most important of which is human acceptance, for chemopreventive intervention, naturally occurring diet-based agents are preferred. Prostate cancer is an ideal candidate disease for chemopreventive intervention, because it grows very slowly, likely for decades, before symptoms arise and a diagnosis is finally established, it has a long latency period, and it is typically diagnosed in men >50 years of age. Most chemopreventive agents are antioxidant in nature. We have been defining the usefulness of dietary anti-oxidants for chemoprevention of prostate and other cancers. It is increasingly appreciated that some of these dietary anti-oxidants are nature's gift molecules endowed with cancer preventive and therapeutic properties. This review will focus on prostate cancer chemopreventive effects of polyphenolic anti-oxidants derived from green tea and pomegranate. It is a challenge to custom-tailor these gift molecules as cocktails in concentrations that can easily be consumed by humans for delaying prostate and other cancers.

Keywords Green tea · Pomegranate · Polyphenols · Prostate cancer · Chemoprevention

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Introduction

Recent data suggest that one-third of the 559,650 cancer deaths expected to occur in the year 2007 will be related to nutrition, obesity, and lack of physical activity, and therefore can be prevented [1]. One approach to decreasing the incidence of cancer is chemoprevention, a means of cancer control in which the occurrence of the disease can be entirely prevented, slowed, or reversed by the administration of one or more naturally occurring and/or synthetic compounds [2–5]. Chemoprevention also encompasses treatment of precancerous lesions [3] and includes such chemopreventive compounds that ideally have (a) little or no toxic effects, (b) high efficacy in multiple sites, (c) capability of oral consumption, (d) a known mechanism of action, (e) low cost, and above all (f) human acceptance.

Of all cancers, prostate cancer (PCa) is considered an ideal disease for chemoprevention, because it is usually diagnosed in men over the age of 50 and has a high-latency period; therefore, even a modest delay in the progression of this disease by chemopreventive intervention could result in a considerable reduction in its incidence and, more importantly, improve the overall quality of life of the patients [5, 6]. The identification of agents and their molecular targets for PCa chemoprevention is guided by data derived from a variety of sources including epidemiological, clinical, and laboratory studies. The fact that PCa is manifested by aberrations in different molecular events, blocking or inhibiting only one event may not be adequate to prevent the onset of the disease, and therefore, efforts are ongoing for a better understanding of the disease and for the development of novel approaches for its prevention and treatment.

Geographic and epidemiological data suggest that environmental factors and diet play important roles in the

development of PCa, and an increase in the incidence of PCa has been found in Asian populations migrating to the west, possibly as a result of adoption of a western lifestyle [7, 8]. There is epidemiological evidence suggesting lower PCa risk in populations with higher consumption of selenium, vitamin E, green tea, fruits, and tomatoes [9]. These observations have kindled an interest in the use of natural agents for the prevention of PCa and, at present, several natural agents are being studied for their cancer chemopreventive potential. The beverage tea has been studied extensively and has emerged as an agent having antimutagenic and anti-cancer effects in animal tumor models [4]. Recently, interest has been generated in understanding the PCa chemopreventive properties of pomegranate, a polyphenol-rich fruit grown in the Mediterranean [10].

Prostate Cancer Prevention by Green Tea Polyphenols

Tea, a popular beverage made from the leaves of *Camellia sinensis*, is a rich source of catechins, which account for 30–42% of its dry weight. The major catechins in green tea are epicatechin (EC), epicatechin-3-gallate (ECG), epigallocatechin (EGC), and epigallocatechin-3-gallate (EGCG). EGCG constitutes up to 50% of the total polyphenols and is considered the most active catechin in tea [11]. Laboratory studies from around the world have demonstrated cancer chemopreventive properties of tea, and green tea consumption has been shown to protect against all stages of carcinogenesis in several animal tumor bioassay systems including PCa [4, 5].

In vitro Studies with Green Tea

In the prostate, androgens are considered to the major stimuli for inducing neoplastic transformation, and therefore, androgens constitute potential targets for PCa prevention [12]. EGCG and ECG inhibit 5-α reductase, the enzyme that converts testosterone to its active metabolite 5-α-dihydroxytestosterone [13]. EGCG was found to inhibit growth of androgen-responsive LNCaP cells and the expression of androgen-regulated PSA and hK2 genes. An Sp1 binding site in the androgen receptor gene promoter was identified as the target for the tea polyphenols because treatments of EGCG decreased the expression, DNA binding activity, and transactivation of Sp1 protein [14]. Production of PSA was significantly decreased in a dose- as well as time-dependent manner when human PCa LNCaP cells were treated with EGCG [15]. Activity of ornithine decarboxylase (ODC), an androgen-regulated molecule that is upregulated in PCa, was significantly inhibited when LNCaP cells were treated with GTP [16]. GTP also inhibited testosterone-induced colony formation in LNCaP cells in a dose-dependent manner [17].

Apoptosis, a form of programmed cell death, is essential for maintaining tissue homeostasis. Induction of apoptosis of cancerous cells has, however, emerged as a therapeutic modality against cancer by naturally derived bioactive agents from diet [18]. EGCG treatment resulted in an induction of apoptosis in several human cancer cells, including human PCa cells DU145, LNCaP, and PC-3, regardless of their androgen or p53 status [19, 20]. In subsequent experiments, we observed that EGCG-mediated cell cycle dysregulation and apoptosis is mediated through modulation of cyclin kinase inhibitor (cki)-cyclin-cyclin-dependent kinase (cdk) pathway and via a concurrent effect on two important transcription factors, p53 and NF-kappa B, causing a change in the ratio of Bax/Bcl-2 in a manner that favors apoptosis [21–23]. Further studies showed that EGCG activates growth arrest and apoptosis primarily via a p53-dependent pathway that involves the function of both p21 and Bax such that downregulation of either molecule confers a growth advantage to the cells [23, 24]. The ubiquitin-proteasome system plays a vital role in degradation of cellular proteins and hence allows tumor cell survival, while proteasome inhibitors induce tumor growth arrest [25]. EGCG was found to inhibit the chymotrypsin-like activity of the proteasome in vitro in several tumor and transformed cell lines, resulting in the accumulation of p27/Kip1 and IkB-α, an inhibitor of transcription factor NF-κB, and leading to cell cycle arrest [26, 27]. These studies suggested the proteasome as a cancer-related molecular target of tea polyphenols and partly explained the cancer-preventive effects of tea. Employing cDNA microarray, we identified a total of 25 genes in LNCaP cells that showed a significant response to EGCG (12 μM, for 12 h). Expression of 16 genes was significantly increased and nine genes were found to be significantly repressed by EGCG treatment [28]. Among these genes, the repression of PKC-α was most prominent, suggesting that inhibition of PKC-α gene expression could inhibit cancer cell proliferation [29, 30]. The cDNA microarray also identified induction of the expression of receptor-type protein tyrosine phosphatase-γ gene, a tumor suppressor gene candidate frequently deleted in some human cancers [28].

In vivo Studies with Green Tea

EGCG (daily 1 mg/mouse, i.p.) treatment to athymic nude mice implanted with androgen-insensitive PC-3 and androgen-sensitive LNCaP 104-R cells resulted in reduction in the initial tumor growth of both cell types by 20–30% [31]. Similar findings were observed when nude mice with xenografts were fed with a nutrient mixture containing

green tea extract [32]. Employing androgen-responsive CWR22R*v*l PCa tumor xenografts implanted in athymic nude mice, we demonstrated that treatment with GTP and EGCG not only resulted in significant inhibition of growth of implanted tumors, but also a reduction in the serum PSA levels [33]. Furthermore, GTP (0.01 or 0.05% w/v) given after establishment of CWR22R*v*1 tumors caused a significant regression of tumors, suggesting therapeutic effects of GTP at concentrations achievable in humans. Using the transgenic adenocarcinoma of the mouse prostate (TRAMP), a model in which progressive forms of human disease occur spontaneously [34], we showed that oral infusion of GTP at a human-achievable dose significantly inhibits PCa development and increases overall survival in these mice [35]. In a follow-up study, we demonstrated that continuous GTP infusion to these mice for 24 weeks resulted in substantial reduction in the levels of IGF-I and significant increase in the levels of IGFBP-3, suggesting that the IGF-I/IGFBP-3 signaling pathway is a prime pathway for GTP-mediated inhibition of PCa [36]. These effects of green tea on the development of PCa in TRAMP were subsequently corroborated by Caporali et al. [37], who demonstrated progressive accumulation of clusterin mRNA and protein in the prostate gland, suggesting a possible role for clusterin as a novel tumor-suppressor gene in the prostate.

Epidemiologic and Clinical Studies

Epidemiologic evidence suggests that regular use of green tea in the Asian population in general is inversely associated with the risk of several types of human cancers including PCa compared to that in Western societies [38, 39]. These observations are further supported by facts that suggest that Asian men migrating to the United States and their subsequent US-born generations acquire a higher clinical incidence of PCa [40]. Several epidemiologic studies show beneficial effects of tea consumption [41]. A recent case–control study conducted in Hangzhou, southeast China suggested that PCa risk declined with increasing frequency, duration, and quantity of green tea consumption [41]. Two clinical studies reported that green tea carries limited anti-neoplastic activity against hormone refractory PCa; however, these studies were conducted in patients with advanced disease, and therefore, did not meet the criteria required for chemopreventive studies [42, 43]. An ideal chemopreventive study, in principle, should include a population at a high risk for PCa development. A recent proof-of-principle clinical trial in volunteers with high-grade prostatic intraepithelial neoplasia showed that green tea is safe and very effective for treating pre-malignant lesions before PCa develops [44].

Polyphenols from Pomegranate in the Prevention of Prostate Cancer

Pomegranate, recently described as nature's power fruit, is the fruit of a deciduous shrub (*Punica granatum*) widely cultivated in the Mediterranean region. In addition to its strong antioxidant and anti-inflammatory properties, recent studies have demonstrated its anti-cancer activity in several human cancers [45]. Flavonoids extracted from pomegranate showed strong anti-oxidant activity, close to that of green tea and significantly greater than that of red wine [46].

In vitro Studies with Pomegranate

Anti-cancer effects of polyphenols from pomegranate were tested in two human breast cancer cells, MCF-7 and MB-MDA-231. Fermented juice showed about twice the anti-proliferative effect as fresh pomegranate juice and inhibited aromatase activity by 60–80% and 17-β-hydroxysteroid dehydrogenase Type 1 activity by 79% [47]. Polyphenols from pomegranate strongly downregulated vascular endothelial growth factor and interleukin-4 in MCF-7 and MCF-10A cells and upregulated migration inhibitory factor in MDA-MB-231, showing an overall significant potential for inhibition of angiogenesis [48].

The effect pomegranate polyphenols on human PCa cell growth was tested both in vitro and in vivo [49, 50]. In vitro proliferation of LNCaP, PC-3, and DU 145 human PCa cells lines was significantly inhibited by changes in both cell cycle distribution and induction of apoptosis, whereas normal prostate epithelial cells were significantly less affected. While pomegranate preparations potently suppressed PC-3 invasion through Matrigel, overall, a significant anti-proliferative and anti-tumor activity of pomegranate-derived fractions against human PCa was observed [49, 50]. Components from pomegranate fruit inhibited in vitro invasion of human PC-3 prostate cancer cells in an assay employing Matrigel artificial membranes. Each component per se significantly inhibited invasion at 4 μg/ml and when combined at similar doses, showed supra-additive effect [51]. We recently demonstrated that pomegranate fruit extract (PFE) treatment (10–100 μg/ml for 48 h) of human PCa PC-3 cells resulted in a dose-dependent inhibition of cell growth/cell viability and induction of apoptosis [10]. These effects were accompanied with modulation of apoptotic and cell cycle regulatory molecules [10].

In vivo Studies with Pomegranate

To ascertain the in vivo relevance of pomegranate fruit, studies were conducted in xenograft models. Polyphenols

from pomegranate seed oil and pericarp potently inhibited growth of PC-3 xenografts in athymic mice [51]. Athymic nude mice that were implanted with androgen-responsive CWR22R*v*1 cells and received 0.1 and 0.2% (w/v) PFE in drinking water developed measurable tumors at 11–14 days compared to 8 days in the control mice. In control water-fed animals, targeted tumor volume of 1,200 mm^3 was reached in $\sim 31 \pm 3$ days after tumor cell inoculation, while tumor volumes at the same time point averaged 776 and 558 mm^3 in the 0.1 and 0.2% PFE-fed groups, respectively [10]. In PFE-fed animals, a significant inhibition of PSA secretion was observed at all time-points examined. The reduction in tumor growth with concomitant reduction in PSA levels observed in the xenograft model may have human clinical relevance.

Epidemiologic and Clinical Studies with Pomegranate

Epidemiologic, clinical, and case–control studies have not been undertaken with pomegranate; however, a recent phase II clinical trial in patients with rising PSA demonstrated beneficial effects of pomegranate juice in patients treated with 8 ounces daily (570 mg total polyphenol gallic acid equivalents) until disease progression. Mean PSA doubling time significantly increased with treatment from a mean of 15 months at baseline to 54 months post-treatment ($P < .001$). This study, although lacking a proper placebo control, suggested statistically significant prolongation of PSA doubling time and a potential of pomegranate for prevention of human PCa [52].

Conclusions

While considerable improvements in diagnosis and treatment have improved overall survival, PCa continues to remain a leading cause of death in men. Many non-toxic dietary ingredients are showing promise for PCa management, and it is increasingly appreciated that many such molecules are nature's gifts endowed with the power to prevent cancer in the human population. Based on many studies and as outlined in this review, there is an urgent need for more in-depth clinical studies to categorically identify and develop natural plant-based polyphenols. Due to the complex nature of the disease, it is advisable to conduct combination studies with agents with complementary mechanisms. While appropriate clinical trials have recently highlighted the importance of tea as a chemopreventive agent, there is a need to undertake similar studies with polyphenols from pomegranate fruit. Inconsistencies between epidemiologic, laboratory, and clinical studies require more extensive studies for obtaining conclusive evidence. It is hoped that one day, we may consume a cocktail of nature's gift molecules to effectively prevent prostate and other cancers.

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