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Clinical trials of natural products as chemopreventive agents for prostate cancer

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Epidemiological research on prostate cancer risk in men throughout the world has identified significant correlations between dietary habits and prostate cancer occurrence. These studies served as a catalyst for exploration into the potential of dietary substances to act as chemopreventive agents against this disease, and include green tea catechins, lycopene, soy isoflavones, pomegranate phenolics, selenium, vitamins E and D, curcumin and resveratrol. Before these agents (in the dietary or purified forms) can be recommended as useful chemopreventive strategies for patients, their activity must be confirmed in rigorously designed clinical trials. This review discusses the preclinical and clinical data available for these dietary agents and describes relevant clinical trials currently being conducted.

Keywords: chemoprevention, clinical trials, green tea catechins, isoflavones, lycopene, pomegranate phenolics, prostate cancer, selenium, vitamin D, vitamin E, Zyflamend®

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1. Introduction

One of the most striking epidemiological aspects of prostate cancer is the disparate rate of occurrence and mortality observed between Eastern and Western cultures [1-3] and even between more proximal regions such as the Mediterranean area and Northern Europe [4,5]. This discrepancy has led to a search for those environmental and/or lifestyle factors that are associated with populations of men with low prostate cancer rates. There are increasing reasons to suspect that dietary habits of men in these regions contribute significantly to this observation. Among the most often cited dietary factors thought to play a role in protection against prostate cancer are green tea catechins, lycopene, soy isoflavones, pomegranate phenolics, selenium, vitamins E and D, curcumin and resveratrol. Indeed, epidemiological and laboratory data suggest that dietary modifications that enrich one's intake of these substances may have chemopreventive effects against prostate cancer. Chemoprevention – defined as pharmacological intervention with naturally occurring or synthetic agents to prevent, arrest or reverse carcinogenesis [6] – could be a prudent course of action for those men in regions with a high risk of developing prostate cancer. In addition, because this disease typically occurs in older men (generally after the age of 50 years), there is a reasonable amount of time for interventions with chemopreventive strategies involving dietary modification and nutritional supplementation.

In recognition of the extensive amount of epidemiological and laboratory research that is identifying dietary substances as effectors of prostate cancer risk, there are numerous ongoing clinical studies attempting to define the clinical benefits of specific natural products in preventing the occurrence of this disease. Observational analyses of human patients (case-controlled and cohort studies) are extremely beneficial in identifying important correlations between diet and prostate cancer

risk. These studies are further driven by the demand for evidence-based medical practice even in the realm of natural products and nutritional supplements. Data generated from these types of studies are critical for the development of meaningful randomised, double-blinded, placebo-controlled clinical trials that are ultimately needed to elucidate the chemopreventive potential of these agents. Although this field is still in its infancy and only limited clinical data are available, a few initial studies have been conducted and several others are currently ongoing and/or nearing completion. This review discusses the current research findings and clinical data available concerning the potential chemopreventive actions of natural products that have been tested in both preclinical and clinical settings so far.

2. Dietary substances with preclinical and clinical evidence for prostate cancer chemoprevention

2.1 Green tea and green tea catechins

The low incidence of prostate cancer among Asian populations has been attributed (in part) to their generous consumption of green tea [7,8]. Laboratory evidence collected from both *in vitro* and *in vivo* model systems further supports the anticancer activities of green tea catechins, particularly (-)-epigallocatechin-3-gallate (EGCG) against prostate cancer. In prostate cancer cell lines, EGCG has been demonstrated to induce apoptosis [9-11], induce a G0/G1 cell-cycle arrest [12], inhibit 5-α-reductase [13,14] and downregulate androgen receptor (AR) protein expression [15]. Furthermore, studies in the transgenic adenocarcinoma mouse prostate (TRAMP) model have shown that green tea catechins can significantly reduce or prevent the progression of prostate cancer in this model [16,17]. Interestingly, a synergistic relationship between green tea catechins has been observed when compared with EGCG alone in human colon cancer cells [18]. These data offer insight into the potential mechanisms of action through which green tea consumption may reduce prostate cancer risk.

A literature search on PubMed [101] using the search terms 'green tea prostate cancer' and 'epigallocatechin gallate prostate cancer' with the search constraints set to include only clinical trials resulted in the identification of three studies; the chemoprevention trial and two chemotherapeutic trials. The chemoprevention study [19] was a double-blind, placebo-controlled trial conducted in patients with high-grade prostatic intraepithelial neoplasia (HG-PIN) who were administered 600 mg/day of mixed green tea catechins. The first-year follow up of the 5-year study reported the conversion rate from HG-PIN to prostate cancer was ~ 3% in the experimental group and 30% in the control group; however, no significant change was observed in total prostate-specific antigen (PSA) between the 2 arms. These promising findings were the first to be reported for the chemopreventive actions of green tea catechins in human patients.

However, data obtained from the two chemotherapeutic studies are less suggestive of a benefit of green tea catechins for prostate cancer treatment. The first study [20] was a Phase II trial that showed very limited clinical benefit for patients with asymptomatic prostate cancer with biopsy-proven malignancy and clinical evidence of androgen-independent disease (n = 42) [20]. Following a dosing schedule of green tea powder 6 g/day for 6 months, only 1 patient (2%) demonstrated a decline in serum PSA. No reductions in tumour mass were noted by either radiographic assessment or physical examination. The authors of this study concluded that the green tea powder did not demonstrate promising antineoplastic activity in the patient population studied. The last study [21] was a prospective single-arm clinical trial that considered the toxicity and clinical response rate of a green tea extract (250 mg b.i.d.) against hormone-refractory prostate cancer in 19 patients. The end point of the study was defined as either a relative PSA rise of > 25% over baseline within a 2-month period or radiological progression. Only one patient demonstrated a modest decrease in the rate of PSA elevation and went on to develop progressive nodal disease. A total of 6 out of 15 patients who took the green tea extract for ≥ 2 months experienced slight delay in disease progression from 2 months to 3 – 5 months following the onset of therapy. Based on the data, the authors stated that the green tea extract did not modulate the course of disease progression in patients with hormone-refractory prostate cancer; however, they observed a doubling in time to disease progression from 2 months to 3 – 5 months that should not be overlooked. From the data available, green tea catechins appear to be most useful in the realm of chemoprevention. More data obtained from rigorously designed randomised, double-blinded, placebo-controlled trials with large sample sizes are needed to fully ascertain the potential clinical benefit of green tea catechins.

2.2 Tomatoes and lycopene

Lycopene is one of the main carotenoids in the regional Mediterranean diet and can account for ~ 50% of the carotenoids in human serum [22]. Lycopene, the red pigment in tomatoes, is also found in smaller quantities in grapefruit, guava and watermelon. Its bioavailability from these food sources is drastically increased by regional processing techniques that involve the use of oil because of its lipophilic nature [23,24]. Epidemiological studies have demonstrated a link between elevated consumption of tomato products and lycopene with reduced risk of prostate cancer [25,26].

Physiological concentrations of lycopene (1 μM) have been shown to inhibit growth of cultured androgen-sensitive prostate cancer cells [27,28]; however, others have only observed this effect at supraphysiological concentrations (20 μM) [29]. Growth of human prostate cancer cells xenografted into immunosuppressed mice was significantly suppressed when the diets of the mice were supplemented with lycopene 100 and 300 mg/kg [30]. As with other carotenoids, lycopene is a known antioxidant that prevents lipid oxidation in cells [31-33],

but it is not clear whether this action is critical for its effects on prostate cancer cells.

Several prospective clinical studies have been conducted to further probe the potential of lycopene in both the food and supplement form to mitigate prostate cancer disease progression. At least three patient trials have reported that lycopene reduces PSA values. In 1 study, 32 patients were given tomato sauce entrees (lycopene 30 mg/day) for 3 weeks prior to surgery and had their PSA levels monitored and prostatectomy tissue analysed. PSA levels were observed to decrease by 20% following this intervention and prostate tissue oxidative DNA damage was significantly less in the intervention group compared with randomly selected patients [34]. PSA levels were found to decline by 18% in another study [35] in which lycopene 15 mg b.i.d. was administered in the supplement form for 3 weeks prior to radical prostatectomy. In addition, occurrence of HG-PIN was also significantly lower in the lycopene-treated group (67%; n = 15) compared with the control (100%; n = 11). Another trial [36] involving 3-month supplementation with lycopene 10 mg/day was conducted on patients who had already undergone hormone therapy and had clinical and biochemical evidence of disease progression. Only 15% of the patients demonstrated disease progression with lycopene supplementation, whereas 85% had either complete response (5%), partial response (30%) or remained stable (50%) as defined by PSA values and other signs of disease (Eastern Cooperative Oncology Group performance status [ECOG PS] score and presence of bone pain).

Not all of the patient trials have demonstrated a benefit of tomato and/or lycopene supplementation for prostate cancer patients. In fact, a recently published prospective study of 1338 patients diagnosed with prostate cancer in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial determined that lycopene intake was not associated with prostate cancer risk [37]. The authors found a reduction in prostate cancer risk in patients with a family history of prostate cancer in relation to increased intake of lycopene and certain tomato-based foods but they noted that these data were based on small numbers of patients and could have been due to chance. Another cohort (prospective) study [38,39] that did not demonstrate an inverse relationship between lycopene intake and prostate cancer risk was conducted on Japanese Americans living in Hawaii; however, their serum lycopene concentrations were found to be almost three times less than the average serum lycopene concentrations in studies that identified an inverse relationship.

More rigorously designed clinical trials are needed to clarify the potential benefit of lycopene and/or tomato products for prostate cancer patients. Additional information is expected to be available within the next few years as the NCI is currently sponsoring two randomised, placebo-controlled clinical trials that are considering oral tomato/lycopene supplementation for potential use as a chemopreventive agent against prostate cancer [40]. The first trial [102] is an intervention trial in healthy participants (n = 150) to determine if a 3-week oral tomato/lycopene supplementation period modulates free and bound PSA levels. Secondary objectives are to determine if lycopene can reduce oxidative stress in the participants and if lycopene, PSA and lipid peroxidation products are returned to baseline levels after a 21-day washout period. The other NCI-sponsored trial [103] is also a randomised, intervention trial that is comparing the effectiveness of lycopene to isoflavones as chemopreventive agents in patients with stage I or II prostate cancer. Patients will receive either a multivitamin alone (control; group 1); a multivitamin in addition to 1 or 3 doses of isoflavones (groups 2 and 3) or a multivitamin plus 1 or 3 doses of lycopene orally twice daily (groups 4 and 5). The primary objectives of this study will compare the effects of lycopene and isoflavones on changes in markers of disease progression (serum PSA) and intermediate biomarkers in tumour tissue (i.e., proliferation and apoptosis indices). In addition, tissue and plasma levels of these nutritional supplements and their effects on serum steroid hormones will be measured. When available, results from these studies will help to determine if lycopene supplementation is warranted and to what patient population is most appropriate.

2.3 Isoflavones

Isoflavones are nonsteroidal diphenolic compounds that are found in leguminous plants (such as soy) and are known to have estrogenic (estrogen receptor-β agonists) and anti-estrogenic activities, in addition to antiproliferative activities that appear to be independent of the estrogen receptor [41]. Observational studies have suggested that a diet rich in soy isoflavones (such as the typical Asian diet) is one of the most significant contributing factors for the lower observed incidence and mortality of prostate cancers in Asia [42-45]. The potential relationship between isoflavones and prostate cancer does not appear to be resultant only on genetic susceptibility because an inverse relationship between soy intake and prostate cancer was also noted in a study conducted on Seventh-day Adventist Caucasian men [46] and not just in Asian men. Although a variety of case-controlled and cohort studies demonstrate a statistically significant reduction of prostate cancer risk as high as 70% associated with soy isoflavone consumption, a clear relationship between isoflavone intake and prostate cancer cannot yet be determined due to methodological concerns with these studies, such as recall bias with food-frequency questionnaires [42,43,46].

Genistein, a major isoflavone present in soy, has been reported to exert prohibitive effects on prostate cancer cells *in vitro* through a variety of mechanisms including the inhibition of several receptor tyrosine kinase pathways, inhibition of topoisomerase II, downregulation of mouse double minute 2 (Mdm2), scavenging of free radicals, induction of cell-cycle block at G2/M, suppression of angiogenesis and inhibition of cell invasion [47-52]. Genistein has also been demonstrated to induce cell-cycle arrest at physiological concentrations (≤ 20 μM) and apoptosis in human prostate cancer cell

lines [53,54] and in animal models of prostate cancer [56-58]. Other soy isoflavones (such as daidzein and glycitein) also have anticancer activities in human prostate cancer cell lines and in prostate cancer patients [46,55]. Deglycosylation of isoflavones by fermentation increases bioavailability and some soy fermentation products, such as Genistein Combined Polysaccharide (GCP™), show enhanced activity against prostate cancer cells both *in vitro* and *in vivo* compared with the purified aglycone isoflavone, genistein [55].

At this time, only a few randomised clinical trials considering the chemopreventive benefits of isoflavones have been conducted. A total of two studies were identified in PubMed using the keywords 'isoflavone prostate cancer' and restricting the search to 'clinical trials'. There was one study that observed a statistically significant decrease in serum PSA concentrations in the group of patients ingesting 4 slices of a specially manufactured bread that incorporated soy grits 50 g/slice (n = 8) compared with the control group that ingested a similar wheat bread without the soy supplementation (n = 8) and another experimental group that ate a soy- and linseed-supplemented bread (n = 10) [56]. However, an important concern with this study is the small sample size. In another study [57], 76 patients were randomised into 2 groups: a placebo control (n = 37) and experimental group (n = 39) that received a dietary supplement of soy isoflavones 60 mg/day for 12 weeks and a nonsignificant decreasing trend in PSA concentration was observed.

More insight into the potential clinical benefits of isoflavones for prostate cancer patients is expected to be available within the next few years as the NCI is currently sponsoring four randomised, placebo-controlled interventional trials to consider this possibility. One of the studies [104] involves consumption of a soy isoflavone supplement for 2 – 4 weeks prior to surgery for prostate cancer. This is a Phase II study in which endogenous hormone production and PSA levels will be monitored, and prostate specimens will be analysed for expression of estrogen receptors and cell cycle-regulatory molecules. Another Phase II study [105] is considering the effect of isoflavone supplementation in combination with radiation therapy in patients with prostate cancer. This study will last for 6 months: patients will be randomised into an arm in which they will consume the isoflavone supplement twice daily or the placebo arm. The effect of this treatment on modulation of biomarkers, potential toxicity and quality of life of the patient will all be analysed. The next trial [106] has been designed to determine the potential of a soy isoflavone preparation fermented with Reishi mushroom mycelia, GCP™, to reduce serum PSA levels in men with prostate cancer currently undergoing active surveillance. A previously published cohort study [58] identified this preparation to be of potential clinical benefit for patients undergoing 'watchful waiting' as it either stabilised PSA levels or decreased the rate of PSA increase in these patients. Finally, a Phase II trial is being conducted on patients with a negative biopsy for prostate cancer and will determine if the consumption of a soy protein supplement for 1 year will decrease serum PSA levels or reduce the occurrence of HG-PIN [107]. At the time of preparation of this manuscript, the first three studies [104-106] were still recruiting patients and the fourth study [107] recently completed enrolment.

2.4 Selenium or selenium–vitamin E combinations

Although the roles in prostate cancer chemoprevention for green tea catechins, soy isoflavones and lycopene were driven by epidemiological studies of dietary components associated with populations at low or high risk for prostate cancer, a serious interest in selenium and vitamin E as prostate cancer chemopreventatives arose subsequent to clinical dietary intervention studies that were focused on other tumour systems. These dietary intervention studies were initially designed to analyse the effects of selenium supplementation on skin cancer and the effects of vitamin E (α-tocopherol) and β-carotene supplementation on lung cancer. However, secondary analyses of the outcomes of both studies identified the likelihood that these agents diminished the occurrence of prostate cancer in the treated groups [59-62].

A recently published meta-analysis of 16 published studies (11 cohort and 5 case-control studies) also concluded that selenium intake may reduce the risk of prostate cancer, and this conclusion reached statistical significance for the cohort studies [63]. Further evidence for the ability of α-tocopherol to reduce prostate cancer risk was found in the results of the CARET (β-Carotene and Retinol Efficacy Trial) in which lower serum levels of α-tocopherol were associated with a higher risk of prostate cancer [64].

Although remarkably divergent in nature, selenium and vitamin E share antioxidant activity that may impart protective effects on the prostate epithelium. A double-blind, randomised, placebo-controlled trial [65] of the effects of selenium 247 μg/day in 36 healthy adult males determined that the selenium supplementation caused significant increase in blood glutathione (GSH) levels, a protector against oxidative stress, and a concomitant decrease in protein-bound GSH. Selenium (in the organic form) has been reported to inhibit cell growth of multiple prostate cancer cell lines [66], potentially through its effects on the expression of critical cell-cycle genes [67-69] and the AR protein that drives hormone-dependent prostate cancer cell growth [70]. The E vitamins are fat-soluble compounds that act as antioxidants in cell membranes and inhibit lipid peroxidation. The predominant form of vitamin E found in the human body is α-tocopherol. *In vitro* studies [68,71,72] of both α-tocopherol and α-tocopherol succinate (VES) have indicated that these compounds act as anti-prostate cancer agents through protection against DNA damage, induction of apoptosis, and inhibition of cell growth and AR signalling.

Currently, NIH is sponsoring three clinical trials involving selenium or selenium–vitamin E for prostate cancer treatment and prevention. The treatment study [108] is a Phase II randomised trial to compare the effects of selenium versus a

placebo on tissue biomarkers of prostate cancer in biopsy samples from patients before and after brachytherapy for stage I or II prostate cancer. The prevention trials [109] include a Phase III trial considering the effects of selenium in comparison with a placebo control on the incidence rate of prostate cancer in patients with HG-PIN over a 3-year period. Another significant ongoing NIH-supported prevention trial is the SELECT (Selenium and Vitamin E Cancer Prevention Trial) [210], which is a randomised Phase III trial considering the chemopreventive potential of selenium and vitamin E either alone or together against prostate cancer. This study has accrued > 35,000 men of ≥ 50 years of age who have been randomised into 4 different arms: 2 different placebos once daily; 1 selenium 200 µg and 1 placebo once daily; 1 vitamin E 400 IU and 1 placebo once daily; and 1 selenium 200 µg and 1 vitamin E 400 IU q.d. Supplementation will continue for 7 – 12 years and participants are followed annually. Results from this study are anticipated in 2013. Data obtained from randomised, double-blinded, placebo-controlled studies (such as the SELECT trial) are needed to determine if α-tocopherol indeed acts to reduce prostate cancer risk.

2.5 Vitamin D

A correlation between exposure to sunlight and reduced prostate cancer risk suggested a connection between vitamin D deficiency and prostate cancer as vitamin D synthesis in the skin is dependent on UV light [73]. Retrospective studies have supported this hypothesis as serum calcitriol levels (1,25-dihydroxycolecalciferol, the active form of vitamin D) were lower in patients who went on to develop prostate cancer in comparison with age-matched controls [74,75]. The potential impact of calcitriol on prostate cancer cells has been pursued in *in vitro* and *in vivo* studies and a substantial amount of evidence has been generated that has spurred interest in pursuing further clinical studies. The studies using *in vitro* models of prostate cancer have reported that calcitriol induces cell-cycle arrest in G0/G1 and apoptosis, stimulates differentiation and inhibits invasion of prostate cancer cells [76-78]. A number of mechanisms have been reported to mediate these effects of calcitriol and include elevation of p21 Waf/Cip1 and p27 Kip1 expression, increased expression of IGF-binding protein-3 (IGFBP-3), hyperphosphorylation of the retinoblastoma protein (pRb), downregulation of Bcl-2 and modulation of prostaglandin metabolism [79-82]. *In vivo* studies have also demonstrated antiprostate cancer effects of vitamin D [83,84].

However, the preclinical antineoplastic activities of calcitriol reported are typically observed at supraphysiological concentrations of > 1 nM, which cause hypocalcaemia and hypercalcuria if given to prostate cancer patients on a typical daily dosing schedule [85]. Because of this toxicity, weekly dosing schedules have been developed that combine calcitriol with other chemotherapeutics (i.e., docetaxel) and have shown promise as a beneficial therapeutic approach without the toxicity observed with daily calcitriol dosing [86,87]. Furthermore, much of the focus of this research has shifted towards synthetic analogues of calcitriol: the efficacy of several of these analogues have been and are currently being considered in the clinical trial setting [88,89,211]. As synthetics are beyond the scope of this article, these studies will not be discussed in further detail.

2.6 Pomegranate

Pomegranate juice is a rich source of polyphenolic compounds (including anthocyanins and hydrolysable tannins) and has been demonstrated to have greater antioxidant activity than green tea and red wine [90]. Although studies of the anticancer potential of pomegranate are still in their infancy, preclinical efforts have demonstrated that pomegranate fruit extract (PFE) can dose-dependently inhibit cell growth and induce apoptosis in the PC3 human prostate cancer cell line [91]. Effects on cell proliferation appear to be mediated through induction of WAF1/p21 and Kip1/p27, suppression of cyclins D1, D2 and E, and decrease in expression of cyclin-dependent kinase (CDK)-2, -4 and -6. In addition, oral administration of PFE to immunosuppressed nude mice carrying prostate cancer cell xenografts effectively reduced xenograft volume and serum PSA levels [91].

A NCI-sponsored open-label, single-arm Phase II study [92] was conducted over a 2-year period to consider the potential of pomegranate juice to decrease PSA levels in patients with rising PSA after either surgery or radiotherapy for prostate cancer. Patients enrolled had detectable levels of PSA (> 2 and < 5 ng/ml), a Gleason score of ≤ 7 and no evidence of metastatic disease. This study demonstrated that ingestion of 226.8 g/day of pomegranate juice for 18 months resulted in a statistically significant increase in PSA doubling time from 15 months at baseline to 54 months post treatment ($p < 0.001$). Further *in vitro* studies showed that patient serum collected post treatment elicited significant antiproliferative and pro-apoptotic effects, as well as reduced oxidative stress in cultured prostate cancer cells compared with serum collected from patients prior to the treatment.

2.7 Botanicals with anti-inflammatory activity to target prostate cancer

Although a direct correlation has yet to be proven between inflammation and prostate cancer, chronic or recurrent inflammation has been hypothesised to be the main predisposing factor for this disease [93]. Activation of an inflammatory response could contribute to the development of cancer via several mechanisms, including the induction of COX-2 in macrophages and epithelial cells, generation of mutagenic reactive oxygen species (ROS) and reactive nitrogen species by activated immune cells, and production of cytokines and growth factors that may favour cancer cell growth [94]. Prostate lesions defined as proliferative inflammatory atrophy (PIA) are thought to arise as a result of inflammatory injury to the prostate epithelium as they are

generally associated with inflammatory infiltrates, and they have been proposed to eventually give rise to prostate cancer [95]. Targeting inflammation early on in this process could prove to be an effective strategy in the chemoprevention of prostate cancer.

Numerous botanical extracts have been described to have anti-inflammatory activity. Among these include rosemary, turmeric, ginger, holy basil, green tea, hu zhang, Chinese goldthread, barberry, oregano and *Scutellaria baicalensis*. The authors of this review have been involved in the preclinical testing of a specific commercial agent named Zyflamend® that contains potency-assured extracts of each of these botanicals in an olive oil base designed to mitigate inflammation. In addition, some of the more prominent compounds present in these herbs (curcumin, EGCG, resveratrol and baicalein) have been individually identified to inhibit prostate and other cancers in a variety of *in vitro* and *in vivo* model systems.

The olive oil component of Zyflamend may also contribute significantly to the potential antiprostate cancer activities of this herbal preparation. A relatively high intake of olive oil is a main characteristic of the Mediterranean diet that has been correlated to the lower incidences of prostate, colorectal, breast and endometrial cancers in Mediterranean countries compared with Northern Europe and North America [5]. Olive oil has a high oleic acid content that has a lower oxidation potential than linoleic acid. Oleic acid may allow greater metabolism of 18:3ω-3 to longer-chain ω-3 fatty acids (such as the eicosapentaenoic acid and docosahexaenoic acid found in fish oils) and, therefore, could impart a similar suppressive effect on tumour growth as observed with these marine oils [96,97].

In addition to the high oleic acid content, olive oil provides a rich source of a variety of antioxidants including squalene, lignans and simple phenols (such as oleuropein, tyrosol, hydroxytyrosol, caffeic acid, apigenin and many others). It has been estimated that 10 – 20 mg of mixed phenols are provided daily by the olive oil component in a typical Mediterranean diet [98]. These phenolics and other antioxidants appear to contribute to the potential anticancer effects of olive oil due to their abilities to suppress oxidative DNA damage and mediate inflammation. Physiologically relevant concentrations of olive oil phenolics (10 – 50 μM) – particularly hydroxytyrosol – and oleic acid have been demonstrated to reduce DNA damage induced by H_2O_2 in prostate cells [99]. Oleic acid and olive oil phenolics were also reported to markedly reduce expression of 5-lipoxygenase (5-LOX) and its co-enzyme 5-LOX-activating protein (FLAP) in preclinical studies [96]. The production of pro-inflammatory prostaglandins was also found to be suppressed by hydroxytyrosol, tyrosol and caffeic acid.

In preclinical studies, the authors found that Zyflamend inhibited both COX-1 and COX-2 enzymatic activity, suppressed prostate cancer cell growth and induced apoptosis [100]; however, the antiproliferative and pro-apoptotic activities of Zyflamend appear to be mediated by COX-independent mechanisms as the addition of prostaglandin E_2 back to the cells following treatment with Zyflamend did not protect against Zyflamend-induced apoptosis. In addition, the LNCaP cells (in which these studies were conducted) were shown to not express COX-2. These COX-independent mechanisms responsible may involve enhanced expression of p21 and reduced expression of AR, phosphorylated STAT3 and phosphorylated protein kinase $C_{\alpha/\beta}$ [100].

The potential of Zyflamend to act as a chemopreventive agent is currently being considered as a secondary end point in a Phase I safety trial for patients diagnosed with PIN at Columbia University Medical Center, USA. This study is an 18-month study in which 48 patients will be randomly assigned to a cohort and placed on successive herbal supplement regimen starting with Zyflamend alone and individually adding on the following supplements in succession: probiotic complex, daily vitamin, green and white tea extracts, *Scutellaria baicalensis* extract and docosahexaenoic acid. The last regimen will be restricted to Zyflamend plus the probiotic complex only. Results from this study will help to determine if this multi-component herbal preparation warrants further assessment as a prostate cancer chemopreventive agent in a double-blinded, randomised, placebo-controlled clinical trial. It is important to mention that other commercially available herbal formulations are prescribed to have anti-inflammatory effects although the authors did not find any cases in which they were specifically tested for antiprostate cancer activity.

3. Conclusion

Enriching one's diet with naturally occurring bioactive compounds with anticancer activities may prove to be an effective strategy for prostate cancer chemoprevention and treatment. In this review, the authors discussed the chemopreventive and/or chemotherapeutic potential of several dietary substances and supplements as defined by the epidemiological, preclinical and clinical data available. Although many such substances appear to have promise in affecting the development and/or progression of prostate cancer, the data are not conclusive at this time. Currently, several randomised, double-blinded, placebo-controlled trials are being conducted that will most likely offer more information on the potential clinical benefit these agents may offer to patients.

4. Expert opinion

Although there may be a genetic predisposition that contributes to the occurrence of prostate cancer, epidemiological dietary studies strongly support the idea that regional diet and nutritional patterns play a significant role in the development of this disease. Scientists are now intensely analysing food-derived natural products that are present in regional diets from areas with low prostate cancer occurrence for

evidence of specific nutritional (natural) agents that can lower the risk for prostate cancer when supplemented to the diets of men from high-risk regions. At the current time, green tea catechins, soy isoflavones, lycopene, vitamins E and D, selenium, pomegranate polyphenols and other complex herbal extracts with anti-inflammatory activity (e.g., Zyflamend) have shown epidemiological and laboratory evidence to suggest that they may have a role in prostate cancer chemoprevention. As these natural agents are readily available in food and supplement forms, clinicians are in the process of conducting rigorously designed clinical trials that should provide the evidence to indicate whether any or all of these substances can protect men from the development and/or progression of prostate cancer. For those who have been convinced that natural products have a role in cancer prevention, this is an exciting period as the evidence that will support or refute these claims is awaited. In the meantime, ingesting a diet that incorporates a variety of these natural compounds appears to be a prudent course of action for maintaining one's health and potentially providing chemopreventive benefits.

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