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Supporting Evidence, Potential Adverse Effects, and known Drug Interactions of the Complementary Alternative Medicines which are Frequently used by Prostate Cancer Patients

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Abstract

A significant number of prostate cancer patients use complementary alternative medicines (CAMs) as an adjunct to their conventional treatment. Examples of CAMs that are frequently used by prostate cancer patients include green tea extract, lycopene, and pomegranate fruit extract. In many cases there is little if any clinical study-based evidence to support the efficacy of CAMs in this setting, and, importantly, some CAMs can cause serious adverse effects when taken a high doses and/or have significant drug interactions. The latter is an important consideration in this patient group as most patients are older and take multiple medications in addition to their anti-cancer drugs. This review summaries prostate cancer patient clinical trial data that is available for CAMs which are commonly used by prostate cancer patients, and provides dose, dose form, adverse effect, and drug interaction data. Providing evidence-based guidance regarding CAMs to prostate cancer patients can potentially improve patient outcomes, including the avoidance of adverse effects and drug interactions which impact drug efficacy.

Keywords

Prostate cancer, Complementary alternative medicines, Efficacy, Drug interactions, Adverse effects

Introduction

Prostate cancer (PC) is the second most frequently diagnosed cancer in men [1]. The median age at diagnosis is 66 and major risk factors include age, family his-tory, and race (it is more common in African American men) [1]. In 2015, there were approximately 1,735,350 new cases diagnosed and it is estimated that 11.6% of men will be diagnosed with PC at some point during their lifetime [2]. Advances in early detection and treatment have contributed to improved patient outcomes; in 1980 the 5-year survival rate was ~70.2%, the most recent statistics estimate 5-year survival at 99.0% [2,3]. These advances have resulted in there being a huge number of men in the US living with PC. Many of these patients (estimated at between 9 - 64% by various studies), as well as men at high risk of developing PC, use complementary alternative medicines (CAMs) as an adjunct to their treatment, and the majority of patients (estimated at 75%) will do so without informing their doctor [4-7]. Questionnaire-based studies indicate that PC patients take CAMs for a variety of reasons, including to ameliorate treatment-associated side effects, to reduce the risk of disease progression, and to increase their sense of having control over their disease and its treatment [8]. A major issue is that typically patients assume, often incorrectly, that CAMs are completely harmless and will not cause any adverse effects. This review names and describes several CAMs that are frequently used by men with PC and/or men at high risk of PC; green tea, modified citrus pectin (MCP), pomegran-

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ate fruit extract (PFE), lycopene, soy, vitamin D, sulphoraphane, selenium, vitamin E, and saw palmetto. Data from peer-reviewed questionnaire studies which report the frequency of CAM usage by PC patients is available for some of these; selenium (4.1-26.6%; 11 studies, total n = 7,109 patients), vitamin E (5-53.3%; 8 studies, total n = 3,261), saw palmetto (1.9-24.5%; 11 studies, total n = 6,525 patients), green tea (51%; 1 study, n = 451 patients), lycopene (31%; 1 study, n = 451 patients) [5,9]. The other CAMs reviewed here are frequently discussed in online PC patient discussion boards and have been the focus of multiple clinical, epidemiological, and *in vitro* studies indicating that they are also relevant to the PC community. This review provides information regarding the clinical evidence supporting usage of these

CAMs as well as information regarding dosage forms, dosing, potential side effects and potential drug interactions. While none of the CAMs discussed have a validated drug interaction with PC standard of care therapies, PC patients often have comorbidities (e.g. hypertension (~42% of patients), diabetes (~11% of patients), and congestive heart failure (CHF)/valvular disease (~5% of patients) [10], and an interaction with a drug used to treat these co-morbidities could thereby indirectly impact their PC treatment and outcomes. For example, green tea, PFE, soy, vitamin D, vitamin E, and lycopene all have validated drug interactions with drugs commonly used to treat hypertension (Table 1). A summary of the dose forms available for each CAM as well as potential side effects and potential drug interactions are provided in

Table 1: Potential benefits, dose forms available, and potential side effect/drug interaction data for CAMs used by prostate cancer patients as part of their treatment regimen (note that the potential drug interaction list does not include drugs which are used to treat prostate cancer, however, many of these drugs are used to treat co-morbidities that prostate cancer patients frequently experience and may therefore meaning these CAMs may indirectly interfere with their prostate cancer treatment). A drug interaction is defined as an interaction between the CAM and the drug which may either increase treatment-associated toxicity and/or decrease drug efficacy.

Name and proposed mechanisms of action (MOA)	Dose form(s)	Potential side effects	Potential drug interactions[1]
Green tea and green tea constituents (e.g. EGCG) Proposed MOAs include; anti-oxidant, inhibits PC cell proliferation and metastasis, promotes PC cell apoptosis	Liquid (brewed tea, some energy drinks), powder, capsules, tablets	May cause acute liver injury, nausea, insomnia, and/or abdominal pain at EGCG doses of 30 - 90 mg/kg/day mg/kg per day [12,13]	Bortezomib and other proteasome inhibitors, dipyridamole, disulfiram, ephedrine, estrogens, fluconazole, fluvoxamine, hepatotoxic drugs, lithium, mexiletine, midazolam, MAOIs, nadolol, nicardipine, nicotine, pentobarbital, phenylpropanolamine, riluzole, stimulants, theophylline, verapamil, warfarin
Modified citrus pectin (MCP) Proposed MOAs include; inhibits metastasis, promotes PC cell apoptosis	Capsules, powder	May cause abdominal cramping and/or diarrhea at doses of > 14 g per day [18]	Oral medications, digoxin, lovastatin, tetracyclines
Pomegranate fruit extract (PFE) Proposed MOAs include; anti-oxidant, inhibits PC cell proliferation, promotes PC cell apoptosis	Capsules, powder	May cause diarrhea at doses of > 3 g per day [30]	Ace inhibitors, antihypertensives, carbamazepine, CYP 2D6 substrates, warfarin, rosuvastatin, tolbutamide
Soy Proposed MOAs include; inhibits metastasis and PC cell proliferation, promotes PC cell apoptosis	Capsules, tablets, powder	No side effects observed in clinical trials (1 - 16 mg/kg per day) [66]	Antibiotics, antidiabetic, antihypertensives, CYP 2C9 substrates, diuretics, estrogens, levothyroxine, MAOIs, progestrones, tamoxifen, warfarin
Selenium Proposed MOAs include; Anti-oxidant, improves immune system function, inhibits PC cell proliferation, promotes PC cell apoptosis	Capsules, liquid concentrate	At high levels may cause GI disturbances, teeth decay, hair loss, neurological disturbances ([2]upper tolerable dose for adults is 400 ug per day)	Anticoagulants, antiplatelets, barbiturates, contraceptives, gold salts, statins, immunosuppressants, niacin, warfarin
Saw palmetto Proposed MOAs include; inhibits PC cell proliferation	Capsules and softgels	Minimal to no toxicity has been reported at doses as high as 960 mg per day [79]	Anticoagulants, antiplatelets, contraceptives, estrogens
Vitamin D Proposed MOAs include; improves immune function, decreases inflammation, inhibits PC cell proliferation and metastasis	Tablets, softgels	Constipation, nausea, vomiting ([2]upper tolerable dose is 400 ug per day)	Aluminum, atorvastatin, calcipotriene, cimetidine, CYP 3A4 substrates, digoxin, diltiazem, heparin LMWH, thiazides, verapamil

Vitamin E Proposed MOA; anti-oxidant	Capsules, tablets, liquid concentrate	May cause nausea and upset stomach ([2]upper tolerable dose is 1,000 mg per day)	Anticoagulants, antiplatelets, cyclosporine, CYP 3A4 substrates, statins, niacin, warfarin
Lycopene Proposed MOA; anti-oxidant	Capsules, tablets, liquid concentrate	May cause nausea, headache, diarrhea, and upset stomach at ~ 120 mg per day [54]	No known drug-drug interactions
Sulforaphane Proposed MOA; histone deacetylase (HDAC) inhibitor, inhibits cell proliferation	Capsules	May cause bloating at 60 mg per day [94]	Clozapine, cyclobenzaprine, fluvoxamine, haloperidol, imipramine, mexiletine, olanzapine, pentazocine, propranolol, tacrine, theophylline, zileuton, zolmitriptan

[1]data was obtained from https://naturalmedicines.therapeuticresearch.com;

[2]https://ods.od.nih.gov/factsheets.

Table 2: Summary of prostate cancer-related clinical trial data (primary and secondary prevention studies) that is available for frequently used complementary alternative medicines (CAMs).

CAM	Number of clinical studies, level of evidence, number of patients enrolled (n), and primary clinical outcome measure that was assessed	Outcome
Green tea	Two clinical studies; Clinical study 1: level 1 evidence, n = 97, primary outcome measure was progression of HGPIN to PC [16]. Clinical study 2: level 3 evidence, n = 42, primary outcome measure was 50% reduction in baseline PSA level [17].	None of these studies showed efficacy
Modified citrus pectin (MCP)	Two clinical studies; Clinical study 1: level 3 evidence, n = 13, primary outcome measure was increase in PSADT [18]. Clinical study 2: level 3 evidence, n = 49, outcome was tumor response per RESIST criteria [24].	Only study 1 showed efficacy
Pomegranate fruit extract (PFE)	Four clinical studies; Clinical study 1: level 3 evidence, n = 46, outcome measure was reduction in PSA levels [27]. Clinical study 2: level 3 evidence, n = 104, outcome measure was increase in PSADT [30]. Clinical study 3: level 1 evidence, n = 70, outcome measure was a reduction in oxidative stress markers in patient tumors [31]. Clinical study 4: level 1 evidence, n = 102, outcome measure was increase in PSADT [32].	Only studies 1 and 2 showed efficacy
Selenium	Four clinical studies: Clinical study 1: level 1 evidence, n = 35,533, outcome measure was PC incidence [39]. Clinical study 2: level 1 evidence, n = 423, outcome measure was PC incidence [38]. Clinical study 3: level 1 evidence, n = 699, outcome measure was PC incidence [38]. Clinical study 4: level 1 evidence, n = 1,561, outcome measure was PC incidence [38].	None of these studies showed efficacy
Vitamin E	Two clinical studies: Clinical study 1: level 1 evidence, n = 35,533, outcome measure was PC incidence [39]. Clinical study 2: level 1 evidence, n = 14,641, outcome measure was PC incidence [45].	None of these studies showed efficacy
Lycopene	Three clinical studies: Clinical study 1: level 1ii evidence, n = 41, outcome measure was decrease in PSA levels [52]. Clinical study 2: level 1ii evidence, n = 36, outcome measure was decrease in PSA levels [53]. Clinical study 3: level 1ii evidence, n = 71, outcome measure was decrease in PSA levels [54].	Only study 3 showed efficacy

Soy	Eight clinical studies; Clinical study 1: level 1 evidence, n = 66, outcome measure was decrease in PSA level [67]. Clinical study 2: level 1 evidence, n = 53, outcome measure was decrease in sex hormone-binding globulin [68]. Clinical study 3: level 1 evidence, n = 45, outcome measure was decrease in sex hormone-binding globulin [69]. Clinical study 4: level 1 evidence, n = 47, outcome measure was decrease in PSA levels [70]. Clinical study 5: level 1 evidence, n = 158, outcome measure was decrease in PSA levels [71]. Clinical study 6: level 1 evidence, n = 29, outcome measure was decrease in PSA levels [72]. Clinical study 7: level 1 evidence, n = 66, outcome measure was decrease in circulating androgen levels [73]. Clinical study 8: level 1 evidence, n = 76, outcome measure was decrease in PSA levels [74].	Only studies 4, 6, and 7 showed efficacy. Meta-analysis of all 8 studies was inconclusive
Saw palmetto extract	One clinical study: level 1 evidence, n = 369, outcome measures were AUA symptom score and PSA levels [77].	Did not show efficacy
Vitamin D	Three clinical studies; Clinical study 1: level 3 evidence, n = 21, outcome measure was decrease in PSA levels [85]. Clinical study 2: level 3 evidence, n = 18, outcome measure was decrease in PSA levels [86]. Clinical study 3: level 1 evidence, n = 52, outcome measures were decrease in PSA levels and Gleason score [85].	Studies 1 and 3 showed efficacy
Sulforaphane	Two clinical studies; Clinical study 1: level 3 evidence, n = 20, outcome measure was PSADT [93]. Clinical study 2: level 1 evidence, n = 78, outcome measure was decreased PSA level [94].	Study 1 showed efficacy

HGPIN: High Grade Prostatic Intraepithelial Neoplasia; PC: Prostate Cancer; PSADT: PSA Doubling Time.

Table 1, data from both primary and secondary prevention clinical studies is summarized in Table 2.

Green Tea (Camellia sinensis, synonyms Camellia thea, Camellia theifera, Thea bohea, Thea sinensis, Thea viridis. Family: Theaceae)

Green tea contains several flavonoid polyphenols, the most important of which is thought to be epigallo-catechin-3-gallate (EGCG), as well as caffeine. The content of each of these can vary widely between products. Typically, an 8 fl. oz cup of brewed green tea contains 200 - 300 mg flavonoids, 300 - 400 mg polyphenols (8 - 12% of which is EGCG), and 25 mg caffeine. There have been multiple reports of EGCG-related toxicity. The usual range of EGCG-related toxicity is 30 - 90 mg/kg daily in humans, and multiple studies have reported hepatotoxicity in patients consuming EGCG-containing products [11,12]. It is noteworthy that the authors state that some of these cases may have resulted from drug interactions (please refer to Table 1 for a list of drugs that are commonly taken by PC patients to treat comorbidities and which have drug interactions with green tea and/or other CAMs). Flavonoids and polyphenols have anti-oxidant properties which may help reduce cancer risk by neutralizing free radical-induced damage. Multiple cell line, animal model, and epidemiological studies have shown a link between free radical activity/levels and in-cidence and progression of PC [13,14], and indicate constituents of green tea can inhibit cell proliferation and metastasis, promote apoptosis and inhibit 5-alpha reductase activity (the enzyme that catalyzes conversion of testosterone to dihydrotestosterone (DHT)).

Epidemiological and clinical data

While several epidemiological studies have shown a link between green tea consumption and reduced incidence of PC, others have shown no benefit. A meta-analysis of studies in which participants consumed > 3 cups of green tea per day showed no benefit in terms of PC risk reduction [15]. There have 2 clinical trials. The first study, a randomized, placebo-controlled, double-blind trial of EGCG (400 mg/day) of men at high risk of developing PC (97 patients, total, level 1 evidence), showed no difference in the number of PC cases between the treatment and placebo group after 1 year [16] and there was no difference in adverse event rate between the 2 groups. In a phase two clinical trial of 42 patients with advanced PC (non-controlled, level 3 evidence), green tea failed to show antineoplastic activity [17]; only 1 patient experienced a 50% decrease in PSA (note the median time on study was only 1 month). Sixty-nine percent of patients who participated in this study experienced a grade 1 or 2 toxicity that manifested as nausea, emesis, insomnia, fatigue, diarrhea, abdominal pain, or confusion, and this is likely due to the high dosage of green

tea that participants received; 6 grams of green tea per day orally in 6 divided doses.

Modified Citrus Pectin (MCP) (Pectin)

Citrus pectin is a naturally occurring indigestible complex polysaccharide that is found in the peel and pulp of citrus fruits [18]. Exposure of citrus pectin to high pH and high temperature produces modified citrus pectin (MCP) and, unlike regular citrus pectin, this is readily absorbed into the gastrointestinal tract [11]. Several cell line and animal studies have demonstrated MCP can delay or prevent PC cell movement and metastasis via antagonizing beta-galactoside binding protein galectin-3 (Gal-3), a molecule that is present on endothelial cells which line blood vessels [19-23]. These studies indicate MCP prevents cancer cells from adhering to blood vessel walls and metastasizing. Cell line studies have shown MCP can also promote apoptosis of PC cells by causing activation of caspase 3 [23]. *Epidemiological and clinical data:* Two non-controlled phase II clinical studies have been performed in PC patients, and one of these showed efficacy (note that both studies enrolled a limited number of patients and had a relatively short follow-up period, level 3 evidence). Grade 1 and 2 toxicities were observed in both studies. Guess, et al. conducted a phase II pilot study to evaluate MCP use in PC patients who had failed local curative therapy (total of 13 patients) [18]. Patients were asked to take six 800 mg capsules 3 times per day (total of 14.4 g of MCP per day) for a 12-month period. Three patients withdrew early due to side effects, noted mostly as either abdominal cramps and/or diarrhea. Seven out of the 10 patients remaining patients had a statistically significant decrease in PSA doubling time (PSADT, the primary endpoint of the study). There was no long-term follow-up of these patients to determine whether or not they developed metastases. A pilot study which included 10 PC patients (and an additional 39 patients with other solid tumor types) found that one PC patient experienced a 50% decrease in PSA levels 16 weeks after initiating treatment [24]. Patients were treated with 5 g MCP 3 times per day (15 g per day, total) over a 24-week period. No differences in PSA levels were observed in the other 9 PC patients over the 24-week period. Out of the 49 patients enrolled in this study, 11 patients experience grade 1 or 2 adverse events which manifested as dyspepsia, pruritus, nausea, constipation, and weight loss. One patient experienced a grade 3 adverse event; pruritus.

Pomegranate Fruit Extract (PFE) (Punica granatum. Family: Lythraceae or Punicaceae)

Pomegranate fruit and pomegranate fruit extract (PFE) are rich in flavonoids and polyphenols as well as important minerals such as potassium and magnesium. The part of the pomegranate fruit that is usually consumed, the red seeds, may be eaten raw or made into juice/juice concentrate. PFE is made from the entire pomegranate including the peel. This is important because punicalagin,

a polyphenol that is thought to be the primary component responsible for the anti-oxidant and anti-inflammatory properties of pomegranate fruit, is found primarily in the pomegranate peel. It should be noted that there can be significant variation in the punicalagin content of pomegranates fruits depending on their ripeness, growing region, and storage amongst other things. A study of pomegranate fruit juice and PFE capsules determined that pomegranate fruit juice typically contains between 9 - 310 mg/L punicalagins, while fruit juice concentrates contain between 1400 - 29900 mg/L and PFE capsules contain between 38400 - 103000 mg/kg [25]. Consumption of > 3000 mg/day of PFE has been associated with diarrhea, but otherwise no serious side effects have been reported [25]. Cell line and animals studies have shown that PFE can reduce PC cell proliferation and induce PC cell death [26,27]. PFE has also been shown to reduce expression levels of androgen-synthesizing genes and NF-kappaB activity in PC cell lines [28,29].

Epidemiological and clinical data

A total of 4 clinical trials have been performed. The first 2 of these provided level 3 evidence demonstrating efficacy, however, 2 subsequent randomized, controlled, blinded studies (level 1 evidence) failed to show efficacy. Only a few patients experienced grade 1 or 2 toxicities in these studies. In the first study, a non-controlled phase II clinical trial in men with rising PSA after surgery or radiation therapy (level 3 evidence) in which patients were asked to consume 6 - 8 fl oz of pomegranate juice per day for a 2 year period, 16 of the 46 enrolled patients achieved a decrease in PSA levels (4 patients achieved a greater than 50% reduction) [27]. No serious adverse events were recorded, and the authors reported that the treatment was well tolerated. Another non-controlled phase II trial (level 3 evidence), conducted in 104 men with rising PSA levels without metastases over an 18 month period, showed that consumption of higher levels of PFE (1 versus 3 grams, daily) resulted in a significant increase in PSA doubling times regardless of the dose taken [30]. Diarrhea was seen in 1.9% of patients taking 1 g/day and in 13.5% of patients taking 3 g/day. A subsequent double-blind, randomized clinical study (level 1 evidence) of 70 men with PC who took PFE (2 grams/day) for 4 weeks prior to radical prostatectomy, observed no difference between groups [31]. Four of the patients in the treatment arm experienced diarrhea versus 2 in the placebo arm. Lastly, a double-blind, randomized phase IIb clinical trial of 102 PC patients (the majority of whom had castration resistant PC (68%), level 1 evidence) showed no difference in PSA kinetics between patients who consumed 500 ml/daily of pomegranate juice for 4 weeks versus those who consumed a placebo control [32]. One patient in the treatment group reported diarrhea.

Selenium (Selenium, Se, Atomic number 34)

Selenium is a naturally occurring trace mineral that

is present in both organic forms and inorganic forms in many food types as well as water [33,34]. According the World Health Organization (WHO), typical concentration ranges of selenium in water, meats/seafood and cereal are 0.06 - 400 ug/l, 0.3 - 0.5 mg/kg, and 0.1 - 10 mg/kg, respectively. Fruits/vegetables typically have < 0.01 mg/kg selenium. While selenium is essential for good health it is extremely toxic at higher concentrations. In animal studies the lethal dose is reported as 1.5 - 6 mg/kg body weight, and the lowest observed adverse effect level is 0.03 mg/kg body weight/day. The US Institute of Medicine has set 400 ug/day as the tolerable upper intake level for humans. High dietary intake in humans has been reported to cause gastrointestinal disturbances, skin discoloration, teeth decay, hair loss, brittle nails, and neurological disturbances. Multiple studies have focused on the role of selenium in cancer prevention, including PC prevention. Cell line and animal studies have shown that selenium can affect DNA stability, cell proliferation, and apoptotic cell death as well as regulate oxidative stress and immune system function [35].

Epidemiological and clinical data

A meta-analysis comparing 17 epidemiological studies that assessed the relationship between selenium intake and PC indicates that there is an association between selenium intake and decreased PC incidence (OR = 0.76, 95% CI 0.64, 0.91) [36], however, others have noted epidemiological studies of selenium should be interpreted with caution due to the difficulty of accurately estimating selenium levels in patients and/or estimating intake [37]. There have been a total of 5 clinical trials, including a controlled, randomized, double-blind phase III clinical trial (the Selenium and Vitamin E Cancer Prevention Trial (SELECT), level 1 evidence) and all of these trials determined that selenium did not decrease PC incidence [38]. The SELECT trial included 35,533 men greater than 50 years of age that were not at high risk for prostate cancer. The products were tested in 4 treatment arms: placebo, Vitamin E, selenium, and combination treatment. The trial was planned to last 11 years but was ended at 7 years since there was no observed benefit from any of the treatments [39]. It is noteworthy that a subsequent case-cohort study (level 3 evidence) determined that selenium supplementation in men with high baseline selenium levels increased the risk of high-grade PC [40].

Vitamin E

Vitamin E comprises of several fat soluble anti-oxidants molecules, including tocopherol isoforms and tocotrienol, which are found in fat-containing foods (e.g. vegetable oils and nuts) [41]. The majority of studies, including clinical studies, have focused on alpha-tocopherol (also known as APC-100) and it is the form found in most vitamin E supplements. Multiple cell line and animal studies shown that alpha-tocopherol has anti-oxidant activity which can decrease oxidative stress

and inhibit inflammatory processes associated with PC incidence and progression [41,42]. Recent studies demonstrate that other isoforms (primarily the gamma-tocopherol isoform but also alpha-tocopherol and tocopherol isoform mixtures) also have strong anti-oxidant activity and have anti-cancer activities in PC cell line and mouse models [43,44].

Epidemiological and clinical data

Level 1 evidence from two controlled, randomized, placebo-controlled clinical trials (level 1 evidence) shows that vitamin E does not affect PC incidence [38,45]. The Selenium and Vitamin E Cancer Prevention Trial (SELECT)) tested 4 treatment arms: placebo, vitamin E (400 IU/day), selenium, and combination treatment. A total of 35,533 men greater than 50 years of age that were not at high risk for prostate cancer participated in the study. The trial was planned to last 11 years but was ended at 7 years since there was no observed benefit from any of the treatment's selenium or vitamin E. The Physician's Health Study II tested 2 treatment arms: placebo and vitamin E (400 IU/day). A total of 14,641 men greater than 50 years old enrolled and were followed for 8 years. Again, no difference in PC incidence was observed between the groups. The recommended upper tolerable dose per day is 1000 mg [46].

Lycopene (All-Trans Lycopene)

Lycopene a carotenoid that is found in many fruits and vegetables including tomatoes. The average content in a ripe tomato is ~120 mg/kg although content can vary widely based on geographical location and species. It is noteworthy that processed tomato products such as juices and tomato paste allow for greater absorption and bioavailability of lycopene compared to raw tomatoes. Multiple cell line and animal studies have shown that lycopene is an anti-oxidant which can reduce oxidative stress in PC cells [47,48].

Epidemiological and clinical data

The majority of epidemiological studies have shown an association between lycopene intake and decreased PC incidence or progression [49-51]. A total of 3 phase II clinical trials of lycopene as a single agent have been conducted. Grainger, et al. enrolled 41 PC patients, 20 of whom were treated with lycopene (> 25 mg/day) and 21 with soy protein over a 2-month period (controlled, randomized, non-blinded; level 1ii evidence) [52]. 5 out of 20 patients in the lycopene arm experienced decreased PSA levels. Clark, et al. enrolled 36 PC patients. Six cohorts of 6 patients were treated with 15, 30, 45, 60, 90 or 120 mg/day for 1 year (controlled, randomized, non-blinded; level 1ii evidence). In this study efficacy was not shown and there was no PSA response, [53]. Vaishampayan, et al. enrolled 71 PC patients, 38 were treated with lycopene alone (15 mg/day) and 33 were treated with lycopene + soy isoflavones (controlled, randomized, non-blinded; level 1ii evidence) [54]. 95% of

the patients achieved PSA stabilization, however, partial response (50% reduction in PSA levels) and complete responses (< 4 ng/ml PSA) were not observed. The doses of lycopene administered in these clinical trials was well tolerated, a minimal number of patients experience GI upset or headache (reported as grade I toxicities).

Soy (Glycine max, Family: Fabaceae/Leguminosae)

Soy products are derived from the soybean, a legume that is native to East Asia but is now grown throughout the world. Soybeans and soybean products such as tofu, soy milk and fermented soybean (e.g. natto and tempeh) are a good source of protein, dietary fiber, vitamins (including B vitamins), and isoflavones. Isoflavones are thought to be the main component responsible for soy's anticancer properties, and of these genistein is the most well studied. Multiple observational studies, and a recent meta-analysis of observational studies (level 3 evidence), have demonstrated that consumption of soy products is associated with decreased risk of prostate cancer [55]. Cell line studies indicate that genistein can inhibit prostate cancer cell growth, cell survival, and metastasis [56-60] through multiple mechanisms including decreasing androgen receptor (AR) levels/activity, inhibition of the Akt and NFkappaB pathways, and decreasing VEGF and MMP production, respectively. Animal studies have produced less consistent results with some studies showing decreased tumorigenesis and other showing no impact or even promotion of tumorigenesis [61-64]. In regards to the latter, it has been suggested that genistein should be taken in combination with other soy isoflavones to counteract its tumorigenic effects [61]. It is noteworthy that soy does have weak estrogenic activity, however, the link between estrogen levels and PC remains controversial with some studies showing an association and showing no association [65].

Epidemiological and clinical data

Multiple small clinical studies have been conducted, including 8 randomized controlled trials (RCT, level 1 evidence) in which prostate cancer patients were treated with soy or soy isoflavones [66]. Primary clinical endpoints included decrease in PSA levels, alterations in sex hormone binding albumin, and alterations in circulating androgen levels ([67-74]. Three of the 8 studies showed efficacy, however, a meta-analysis of all 8 RCT was inconclusive in regard to efficacy (level 1 evidence); significance was not achieved. It should be noted that time on study was short (e.g. 3 - 6 weeks) for many of these studies. It is noteworthy that the meta-analysis did confirm that soy and soy isoflavones have a good safety profile in the study population [66].

Saw Palmetto Extract (Serenoa repens, Family: Arecaceae/Palmae)

Saw palmetto extract is obtained from berries of the saw palmetto tree (Serenoa repens). Saw palmet-

to is rich in a variety of plant sterols and several cell line studies have shown that some of these, including chalcanonol glycoside, beta-sitosterol and stigmasterol, have antiproliferative effects in prostate cancer cell lines [75,76]. Despite this, no benefit has been observed in epidemiological or clinical studies.

Epidemiological and clinical data

An epidemiological study conducted by Bonnar-Pizzorno, et al. found no association between saw palmetto use and prostate cancer risk (in 35,171 men between ages 50-76) [77]. In a controlled, randomized, double-blind clinical study conducted by Andriole, et al. (CAMUS trial) which recruited 369 patients, dose escalation of saw palmetto did not affect AUA symptom scores or PSA levels more than placebo itself (controlled, randomized, double-blind; level 1 evidence) [78]. It is noteworthy that in an analysis of safety and toxicity on the CAMUS trial, Avins, et al. found no evidence of toxicity from saw palmetto use over 18 months, even at increased dosages [79].

Vitamin D (25-hydroxycholecalciferol, Calcipotriene, Calcitriol, Cholecalciferol, Ergocalciferol)

Vitamin D is a fat-soluble vitamin that is naturally produced by the body when exposed to sunlight and is essential for good health; it plays key roles in calcium absorption, maintenance of adequate calcium and phosphate levels, immune function, and reduction of inflammation. Cell line studies have demonstrated that vitamin D can inhibit PC cell proliferation and metastasis [80,81]. Animal study data have been conflicting, with some data showing that vitamin D can prevent metastasis and others showing the opposite [82,83].

Epidemiological and clinical data

While multiple epidemiological studies have reported an association between vitamin D and decreased prostate cancer risk, a recent meta-analysis showed that the collective data do not support this association [84]. A limited number of clinical intervention studies have been performed. One phase II trial with 21 prostate cancer patients on calcitriol (the active form of vitamin D3) and naproxen for progressive prostate cancer saw prolongation of PSA doubling time in 75% of the patients (non-controlled; level 3 evidence) [85]. Another phase II trial by Chadha, et al. (18 patients with castration resistant prostate cancer) showed no impact of calcitriol on PSA levels (non-controlled; level 3 evidence) [86]. Data from an ongoing randomized controlled trial by Hollis, et al. indicate that consumption of 4000 units/day of vitamin D3 or placebo in patients scheduled for elective prostatectomies (37 patients) may be able to keep low-grade prostate cancers from progressing (level 1 evidence) [87]. This is supported by a previous study that came to a similar conclusion with 24 out of 55 sub-

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jects showing an improvement with no adverse effects reported [88]. It is noteworthy that vitamin D3 can influence metal homeostasis, and a recent study showed that consumption of high doses (2000 IU) can cause lead accumulation in PC patients [89].

Sulphoraphane (Isothiocyanate present in many cruciferous vegetables)

Sulphoraphane is an organosulfur isothiocyanate which is found in cruciferous vegetables that belong to the gemmifera family (*Brassica oleracea*), e.g. broccoli, brussel sprouts, and cabbages. These vegetables typically contain ~1 uM/g of sulphoraphane [90]. It should be noted that cooking may decrease their sulphoraphane content [90]. Multiple *in vitro* studies have shown that sulforaphane can act as a histone deacetylase inhibitor (HDACi) and thereby cause decreased proliferation of PC cells [91]. Efficacy has also been observed in animal models [91].

Epidemiological and clinical data

A recent meta-analysis showed that consumption of cruciferous vegetables is associated with a reduction in PC risk [92]. It should be noted that these epidemiological studies were not limited to cruciferous vegetables which contain sulphoraphane. There have been two prospective studies of sulphoraphane in PC patients. A phase II study of 20 PC patients demonstrated that treatment with 200 uM of sulphoraphane per day mediated a significant lengthening in PSA doubling times (non-controlled; level 3 evidence) [93]. A subsequent controlled, randomized, double-blind phase III study (level 1 evidence) of 78 PC patients failed to reach statistical significance; treatment with 60 mg sulphoraphane per day did not cause a statistically significant decrease in PSA levels compared to a placebo group [94].

Conclusions

The level of evidence available to support the efficacy and effectiveness of these CAMs varies widely and conveying this information to PC patients may help guide their selection of a particular CAM. While many of the level 1 evidence studies failed to show efficacy, it should be noted that several of these had relatively short follow-up periods and so should be interpreted with caution. Importantly, some CAMs have significant toxicities if consumed at higher doses as well as drug interactions with medications that PC patients may be taking. Providing counseling to PC patients regarding CAM selection and usage could help prevent adverse events and help ensure the efficacy of anti-cancer therapies are not impacted.

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