

Complementary and Alternative Medicines in Prostate Cancer: From Bench to Bedside?

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ABSTRACT

Complementary and alternative medicine (CAM) use is common among adults, and recent reports suggest that 25%–50% of prostate cancer (PCa) patients use at least one CAM modality. The most common CAM modalities used by PCa patients are vitamin and herbal preparations with purported antitumor effects despite only modest underlying preclinical or clinical evidence of efficacy. In this review we provide a brief overview of the basic scientific and clinical studies underlying the most common herbal and vitamin preparations including common antioxidants, pomegranate extract, green tea, turmeric, resveratrol, silibinin, and herbal combination

preparations. When available, prostate cancer clinical trial data are reviewed. Importantly, we have compared the concentration of these agents used in in vitro experiments to that likely to be achievable in humans. From the available data we conclude that there is insufficient evidence to support the use of CAMs for the treatment of prostate cancer patients outside of a clinical trial. The purpose of this review is to more rigorously evaluate CAM therapy in prostate cancer and educate oncologists and patients. This review focuses on examples from the general classes of agents in common use. *The Oncologist* 2012;17:830–837

INTRODUCTION

Complementary and alternative medicine (CAM) use is common among adults with some reports demonstrating 25%–50% of prostate cancer (PCa) patients use at least one CAM modality [1–4]. Adults in the U.S. spent \$33.9 billion on CAM products and visits to CAM practitioners in 2007; and prostate cancer patients are among the largest users of these preparations [5]. Despite their common use, there have been few controlled clinical trials involving CAM therapies, and treatment is often undertaken without proven clinical efficacy. Moreover, although in many cases CAMs may be derived from natural substances, there is still the possibility of untoward effects. For example, the recently published update of the SELECT trial showed an increased risk of PCa in men randomized to vitamin E, even after subjects stopped this vitamin [6]. This finding alone should call into question the role of CAMs

that are untested with respect to either treatment or chemoprevention for prostate cancer and other malignancies.

What is problematic to the CAM field is that although there are often multiple cell-based and even animal models demonstrating efficacy, there is a paucity of clinical trial data. Making trials more difficult to accomplish are a reliable source of the CAM, lot-to-lot variability, a lack of reliable biomarkers, and a paucity of pharmacokinetic data to base decisions regarding schedule or dose. Lastly, there is little incentive for manufacturers to participate in or sponsor these trials, given that the market, especially the Internet market, is already so large for their products, and FDA approval is not necessary. Despite the lack of rigorous clinical studies, oncologists are frequently approached with questions and for advice regarding CAM therapies from prostate cancer patients.

In this review we describe potential scientific and molecu-

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lar mechanisms for some of the more commonly used herbal and supplemental substances used in prostate cancer. We focus on agents that have been tested, even nominally, in the clinical setting. We have also tried to compare the drug concentrations needed to produce an effect in vitro with published concentrations achieved in humans. In some cases, the scientific basis for the CAM's effectiveness and the potential to achieve active in vivo levels of the CAM might make further evaluation reasonable. In other cases there may be less data to support further clinical experimentation. In either case an understanding of the possible mechanisms of action and achievable drug concentrations in patients may make this difficult field more tractable for patients and clinicians alike.

MATERIALS AND METHODS

Data reviewed are from experiments involving human prostate cancer cell lines, prostate cancer animal models, and human clinical trials. We have focused primarily on preclinical and clinical data that relates to treatment, rather than the prevention, of prostate cancer. The findings in all referenced articles have been confirmed in at least one other publication available through PubMed. When possible, drug doses have been converted to micromolar (μM) units or microgram per milliliter ($\mu\text{g}/\text{mL}$) concentrations to better compare CAM drug levels between cell lines, xenograft, and human data. There are no unpublished data or personal communications included in the preparation of this review.

SELENIUM, VITAMIN E, AND OTHER ANTIOXIDANTS

The concept that antioxidants can prevent malignant transformation or treat established malignancy has been reported for many years and previously reviewed [7–9]. Briefly, this concept is based on the idea that free radicals (molecules with incomplete electron shells) are able to induce DNA damage that may ultimately lead to mutations that predispose cells to malignant transformation [7, 8]. In humans, the most common free radical is the hydroxyl radical ($\cdot\text{OH}$) and the term reactive oxygen species is commonly used to encompass all oxygen-containing free radicals.

There are multiple preclinical models in prostate and other malignancies to suggest that antioxidants (also known as free-radical scavengers) can prevent malignant transformation and/or delay progression [8–12]. Antioxidants such as selenium and vitamin E have long been touted, and until quite recently, commonly used by PCa patients with both preventive and therapeutic intent.

In 2009 the SELECT prevention trial reported the results of a randomized trial of vitamin E, selenium, or both for the prevention of prostate cancer in men over 50 [13]. Although the SELECT trial was a prevention trial, the nature of prostate cancer is such that it is likely that many of the participants had prostate cancer at the time of randomization, especially since prostate biopsies were not required for entry. Therefore, an effect on existing cancers during the course of the 7-year study might have been reflected by a reduced frequency of cancer in patients receiving active treatment (selenium, vitamin E, or both) compared with placebo [13]. However, with longer fol-

low-up, a significant and lasting increase in prostate cancer emerged in patients treated with vitamin E (hazard ratio 1.17) and no effect on prostate cancer incidence in patients treated with selenium [6, 13]. The finding that even two fairly robust antioxidant agents in combination were not effective, and potentially harmful, further highlights the potential harm of treatment with untested CAM supplements and the need for their rigorous study before their widespread use [6, 13].

Although the SELECT trial and Physicians' Health Study (PHS II) have shed doubt on the role of selenium and vitamin E in the prevention of prostate cancer, there continue to be ongoing National Cancer Institute-sponsored (NCI-sponsored) treatment trials (see NCT00736645 and NCT01155791 for references) based on preclinical evidence. The preclinical data for selenium and vitamin E has been previously well reviewed and will not be further discussed in this review [14–17]. Further antioxidant studies are complicated by clinically applicable methods and ranges of antioxidant action on which to base assessment of efficacy and harm. Although the degree of antioxidant capacity can be readily quantified under controlled experimental conditions, there are no reliable clinical correlates. On the basis of phase III data from the SELECT trial, it is likely that continued research into antioxidants, including lycopene, as PCa treatment will wane.

POMEGRANATE EXTRACT

Pomegranate (*Punica granatum*) has been used in medicine for over 3,000 years, with applications ranging from hypertension to malignancy [18]. Prior studies have shown the ability of pomegranate to inhibit several human cancer cell lines [19]. The most active and abundant anti-neoplastic ingredients are the polyphenol punicalagins and specifically the ellagitannin polyphenol punicalagin, commonly measured as ellagic acid (EA) in bioavailability studies [20]. Punicalagins are isomers of 2,3-(S)-hexahydroxydiphenoyl-4,6-(S,S)-gallagyl-D-glucose and exist as both alpha and beta forms in pomegranate. Both forms are abundant and typically constitute 2 g/L of juice [21].

Pomegranate polyphenols have robust antioxidant properties with a reactive oxygen species capacity higher than either red wine or green tea [22]. However, as discussed, it is not at all certain that any degree of antioxidant capacity accounts for an anticancer effect in prostate cancer. Beyond their pure antioxidant capabilities, the punicalagins have been shown to have multiple effects on signal transduction. The PCa cell line PC3 cells, exposed to pomegranate extract (PE) at high concentrations ranging from 10 to 100 $\mu\text{g}/\text{mL}$, showed dose-dependent apoptosis through induction of p21/WAF1 and p27/KIP1, a decrease in B-cell lymphoma 2 (Bcl-2), and an increase in Bcl-2-associated X protein (Bax) (favoring apoptosis) [23]. These results were confirmed in vivo with CWR22Rv1 prostate cancer xenografts in nude mice fed pomegranate extract. However, the concentrations needed to achieve these effects in vitro and in nude mice are likely to be far greater than that which can be achieved in patients.

It has previously been shown that inflammation and prostate cancer may be linked, perhaps through constitutive activation of the nuclear factor- κB (NF- κB) pathway [24, 25].

Table 1. Comparison of CAM concentrations used in cell line/xenograft and human studies

CAM substance	Targets	Cell line concentration(s)	Achievable human plasma concentration	Human clinical trials	Barriers to clinical translation	References
Pomegranate extract (Punicalagin)	NF- κ B, p21, p27	10–100 μ g/mL	0.06 μ mol/L (~0.06 μ g/mL)	Yes, phase III in PSA-only recurrence	High cell line concentration, bioavailability	[21, 22]
Green tea (EGCG)	AR signaling, NF- κ B, Bcl-2	10–100 μ M	0.4–0.8 μ M (0.9–3.3 μ g/mL)	Yes, phase II neoadjuvant, PSA-only recurrent disease	Variable metabolism, absence of biomarkers, side effects at required doses	[34, 39–42]
Curcumin	NF- κ B, MDM2, PI3K/Akt/mTOR	25–100 μ M	0.5–0.75 nM (0.19–0.28 μ g/mL)	Yes, phase II pancreatic, neoadjuvant rectal with capecitabine	High cell line concentrations needed, low bioavailability	[65, 66]
Resveratrol	AR signaling, SIRT1, FOXO genes, Akt	50–150 μ M	2 μ M (0.5 μ g/mL)	Yes, multiple bioavailability studies	Low bioavailability	[94, 95]
Muscadine	Akt, proteasome, DJ-1	10–20 μ g/mL (0.01 μ M)	N/A	Yes, phase I-II in PSA-only recurrence	Low bioavailability	[100]
Silibinin	IGF-1, IGFBP-3, VEGF	50–100 μ g/mL	4.0–19.7 μ M (1.9–9.4 μ g/mL)	None	Low bioavailability	[111, 112]
Combination therapy	Multiple	N/A	N/A	Yes	Drug-CAM interactions	[118–124]

Data for several common CAM therapies used by prostate cancer patients have been converted to micromolar (μ M) units and microgram per milliliter (μ g/mL) concentrations. Achievable human concentrations are shown as μ M and μ g/mL to facilitate comparison.

Abbreviations: AR, androgen receptor; Bcl-2, B-cell lymphoma 2; CAM, complementary and alternative medicine; EGCG, epigallocatechin 3-gallate; FOXO, forkhead box O; IGF, insulin-like growth factor; mTOR, mammalian target of rapamycin; NF, nuclear factor; PI3K, phosphoinositol-3-kinase; PSA, prostate-specific antigen; VEGF, vascular endothelial growth factor.

Increased levels of NF- κ B in primary prostate cancer specimens have been shown to be an independent risk factor for recurrence after definitive therapy [26, 27]. PE inhibited NF- κ B expression in the androgen-independent DU145 prostate cancer cell line, in a dose-dependent fashion, but at doses estimated to be more than 10 times greater than what could be achieved in patients [28]. PE also delayed the appearance of androgen-independent tumors in LAPC4 xenografts, an effect at least partially dependent on the NF- κ B inhibitory effects of PE [28].

Although it was not certain that adequate levels of PE could be achieved in vivo, the preclinical data showing growth inhibition and apoptosis induction led to initiation of human trials with pomegranate juice. Pantuck et al. demonstrate the remarkable initial clinical observation that 8 ounces of pomegranate juice per day prolonged the prostate-specific antigen (PSA) doubling time from a baseline of 15 months to 54 months post-PE treatment in hormone-naïve non-metastatic patients with rising PSA after surgery or radiotherapy [29]. Importantly, this is one of the few studies to show a clinical benefit from a CAM in prostate cancer. This study potentially addresses a large unmet need for those prostate cancer patients who have biochemical (PSA only) recurrence after primary therapy. Patients and providers are motivated to delay or prevent the side effects of androgen-deprivation therapy for PSA-only recurrence. There are currently 11 prospective cancer trials registered with www.clinicaltrials.gov evaluating the impact of pomegranate supplementation (see NCT01100866, NCT00719030, NCT00336934, NCT00413530, and NCT01220817 for reference).

In trying to understand the mechanism of PE, it is helpful to first assess what levels can be reliably achieved in patients. Investigators found that the 8 ounces per day of pomegranate juice (POM Wonderful, Los Angeles) used in the Pantuck study standardized to 570 mg of total polyphenol gallic acid equivalents per day achieved serum ellagic acid (EA) concen-

trations of $0.14 \pm 0.05 \mu$ M/L [21, 29] (Table 1). However, in a separate study EA concentrations achieved were only 0.06 μ M/L 1 hour after consuming 180 mL (approximately 6 ounces) of pomegranate juice) [22]. The effect of possible polymorphisms in metabolic enzymes such as catechol-*o*-methyltransferase and uridine 5'-diphospho-glucuronosyltransferases, as well as whether or not EA is the optimal metabolite to measure, remains to be determined [21]. Post-treatment tissue samples from prostatectomy specimens with measurement of EA concentrations at the tissue level from planned neoadjuvant trials, as is planned by Carducci and colleagues (NCT00719030), will also be informative.

GREEN TEA

Tea (*Camellia sinensis*) is one of the most widely consumed beverages in the world and epidemiologic studies have suggested varying effects on cancer incidence [30–34]. By far most of the attention for anticancer treatment and prevention has focused on green tea, and other tea preparations are not reviewed here.

Polyphenols account for up to 30% of green tea dry weight [35, 36]. The monomer flavan-3-ols are called catechins and account for the bitter taste of green tea as well as most of the biologic properties [37]. In green tea the most abundant catechin is epigallocatechin 3-gallate (EGCG), which may account for up to 50%–80% of the total catechin content [35, 36, 38]. One cup (7 ounces) of green tea contains roughly 142 mg of EGCG, and the equivalent of 8–16 cups per day is needed to achieve plasma free ECGC concentrations of 0.4–0.8 μ M [34, 36, 39–42] (Table 1). However, variations in steeping will result in highly variable levels of serum and tissue polyphenols. Therefore, there are now standardized preparations such as polyphenon-E (poly-E) capsules (standardized for 400, 800, or 1200 mg of EGCG), which have been shown to achieve plasma free EGCG concentration of 1.5 μ g/mL after single dosing

(800 mg of EGCG) in human patients on an empty stomach [43]. These preparations may result in peak concentrations of up to 5 μM at best, although these levels, often reached with the 1200 mg poly-E capsules are commonly associated with gastrointestinal upset [43]. Plasma free EGCG concentrations have been highly variable in phase I trials possibly related to the green tea extract formulation, the presence or absence of recent food intake, metabolic polymorphisms, and/or the methodology used to measure plasma free EGCG concentrations [44].

In prostate cancer there has been intense investigation of the effects of EGCG on androgen receptor (AR) signaling in both cell line and xenograft experiments [45–50]. Siddiqui et al. demonstrated that EGCG is a direct antagonist of androgen action and physically interacts with the ligand binding domain of the androgen receptor [50]. EGCG at 40 and 60 μM doses both inhibited growth of hormone refractory C4-2 prostate cancer cells and decreased AR protein expression in EGCG-treated mice bearing a CWR22Rv1 xenograft [50]. In this context it is well to remember that serum levels achieved are likely to be an order of magnitude less than 40 μM .

Nonhormonal effects have also been shown for EGCG [51, 52]. EGCG demonstrated a dose-responsive effect for increasing p53 expression and stabilization via serine phosphorylation in LNCaP cells [51]. EGCG has been shown to downregulate transcriptional activity of NF- κB , which creates a proapoptotic environment, and to increase the sensitivity of LNCaP cells to tumor necrosis factor [48, 51]. Overall, the data supports EGCG-mediated anticancer effects via multiple mechanisms with multiple targets, but the concentrations used in cell line and xenograft experiments range from 10–200 μM [51–56]. These levels are significantly higher than the 5 μM concentration that can be achieved in patients. There is also preclinical data for EGCG (at somewhat lower concentrations) used to sensitize cells for treatment in combination with taxanes in prostate and breast cancer cell lines, as well as combinations with doxorubicin (ovarian sarcoma) [57, 58].

In a small study of patients with the potential prostate cancer precursor lesion, high-grade prostatic intraepithelial neoplasia (HG-PIN) patients were randomized into a control and an EGCG-treated group. Patients had routine prostate biopsies every 3–6 months for 1 year. Patients treated with EGCG had a dramatic reduction in the detection of cancer on subsequent prostate biopsies (30% in the control arm to 3% in the EGCG-treated group) [59]. Potential anticancer effects of EGCG were also detected in a small phase II trial of 42 patients with castrate refractory PCa that demonstrated a low, but discernable, PSA response [60].

As with most anticancer herbal/vitamin preparations, there is difficulty translating cell line and xenograft data into disease-specific activity in patient studies. One method to overcome this problem is to ascertain levels and target effects of EGCG in prostate tissue. The current NCI-sponsored phase II trial of neoadjuvant green tea treatment in men treated prior to planned prostatectomy (NCT00685516) may be very informative if tissue levels can be adequately measured and equated with molecular or antitumor effects. There is also an ongoing

study of EGCG for men following biochemical recurrence (NCT00669656).

CURCUMIN

Curcumin (isolated from *Curcuma longa*) is a major component of the popular spice turmeric, and curcuminoids are responsible for the yellow color of curry. The major component of curcumin is the lipophylic polyphenol curcumin I (diferuloylmethane) [61]. Curcumin has been used for treatment of many inflammatory conditions, and more recently for malignancies including prostate cancer [62]. The interest in the antineoplastic properties of curcumin grew out of epidemiologic studies correlating gastrointestinal and prostate cancer incidence and dietary turmeric intake [63, 64].

The safety of high doses of curcumin up to 8 grams per day is well described in humans [65]. Newer nanoparticle formulations of curcumin are able to achieve plasma curcumin concentrations in the range of 0.5–0.75 nM (189 and 275 ng/mL) for oral preparations of 150 and 210 mg, respectively [66] (Table 1). However, as has been the case with other CAMs, in vitro experiments with curcumin have typically been conducted at micromolar levels. For example, the levels used in DU145 prostate cell line to suppress NF- κB and AP-1 expression were 75 and 50 μM , respectively [67]. Curcumin has been shown to downregulate cyclin D1 in a dose-dependent manner in LNCaP cells as a result of activation of proteases involved in the ubiquitin-dependent proteasomal pathway [68]. Others have shown that curcumin at concentrations of 15 $\mu\text{mol/L}$ inhibits MDM2 expression independent of p53 status, possibly related to modulation of the erythroblastosis virus transcription factor 2 (ETS2), a transcription factor that can be activated as a result of the TMPRSS2-erg translocation in some prostate cancers [69]. Curcumin-mediated inhibition of the PI3K/Akt/mTOR pathway was demonstrated in PC-3 cells as a result of dephosphorylation of Akt and mTOR, but again at a high concentration (40 μM) [70, 71]. In C4-2 and LNCaP lines curcumin treatment has also been shown to downregulate the AR regulated TMPRSS2-ERG fusion transcript associated with prostate cancer progression at curcumin concentrations starting at 5 μM [72, 73].

Curcumin has been tested in combination with cytotoxic chemotherapies in prostate cancer cell lines. Synergism between 1–10 μM curcumin and 5-fluorouracil (5-FU) and paclitaxel in PC-3 cells has been observed [74]. The ability of curcumin to potentiate the cytotoxicity of chemotherapy agents has also been documented in other cell lines [75–79]. Curcumin-mediated MDM2 downregulation sensitized the PC3 prostate cancer cell line to both gemcitabine and radiation in cell line and mouse xenograft models [80].

The observed synergism of curcumin with cytotoxic therapies has prompted several combination trials currently ongoing. Curcumin is being investigated in combination with neoadjuvant capecitabine and radiation in rectal cancer (NCT00745134) and combined with FOLFOX in inoperable colon cancer (NCT01490996). There is also an ongoing study of curcumin monotherapy in advanced pancreatic cancer (NCT00094445).

Although it is apparent that curcumin can exert anticancer properties via multiple targets, the concentration needed to achieve these results may not be achievable in vivo. Therefore, there are several ongoing efforts evaluating newer nanoparticle curcumin formulations as well as combinations with piperine to improve bioavailability.

RESVERATROL AND OTHER GRAPE SKIN EXTRACTS

Resveratrol (RSV) is a phytoalexin found in high concentrations in grapes and has been shown to inhibit chemical carcinogenesis in several models [81]. Interest in RSV as a chemotherapeutic agent increased after the publication of a seminal 1997 paper by Jang et al. [81]. A recent review described the preclinical, animal model, and human studies across several malignancies [82].

Specific interest for the treatment of prostate cancer was enhanced by a study in which resveratrol was shown to inhibit AR target genes due, at least in part, to androgen receptor transcriptional repression [83]. Other groups have shown resveratrol treatment leads to accelerated AR degradation, as well as modulating AR co-activator molecules such as SIRT1 at RSV concentrations of 50 μM [84–86]. In addition to resveratrol's influence on AR function, there is evidence for its nongenomic effects through the PI3K pathway in steroid hormone responsive tumor cell lines (estrogen receptor + breast and AR + prostate) [87–89]. High concentrations of 50–150 μM have been shown to result in significant inhibition of PKB/Akt phosphorylation in a concentration-dependent manner in both PC-3 and LNCaP cell lines [90]. The cellular effects of resveratrol-mediated PI3K inhibition may be partly mediated by inhibition of FOXO family tumor suppressor phosphorylation, thereby allowing upregulation of proapoptotic and antiproliferative FOXO targets such as Bim, TRAIL, DR5, DR4, and p27 [91]. Very recently, Park et al. elegantly demonstrated that resveratrol, at concentrations of 50 μM , directly inhibits cyclic-AMP dependent phosphodiesterases and ultimately leads to activation of SIRT1 and AMP kinase through the cyclic-AMP effector protein Epac1 [92].

Pharmacokinetic studies of resveratrol at doses up to 5 grams per day have demonstrated poor bioavailability due to extensive glucuronidation and sulfation as well as metabolism by gut bacterial enzymes [82, 93]. Estimates using liquid chromatography, mass spectrometry, and radiolabeled doses estimate oral bioavailability of 1% and peak plasma concentrations of 500 ng/mL (approximately 2 μM), which is well below the doses used in most cell line experiments [94, 95] (Table 1). However, low micromolar levels of 2.5–10 μM have been shown to sensitize prostate cancer cells to ionizing radiation without affecting normal prostate epithelial cells [96]. There is also data for the effect of RSV on inhibition of angiogenesis in lung, breast, and glioma xenograft models [97–99]. Interest in resveratrol as a therapeutic adjuvant to current therapy persists due to accumulating cell line data and ongoing efforts to improve oral bioavailability.

Other grape skin extracts such as muscadine grape (*Vitis rotundifolia*) skin extract, which does not contain resveratrol, have also been investigated in prostate cancer. Hudson and col-

leagues demonstrated 10–20 $\mu\text{g/mL}$ muscadine grape skin extract (approximately 10–100 nM) induced apoptosis in multiple prostate cell lines via decreased Akt signaling [100]. The Department of Defense Prostate Cancer Consortium has recently begun a phase I/II study of muscadine for men with biochemical recurrence of prostate cancer (NCT01317199).

SILIBININ

Silibinin is thought to be the major active ingredient in Milk Thistle extract (*Silybum marianum*), a supplement often used by prostate cancer patients and previously shown to be nontoxic in humans [101, 102]. Structurally, silibinin is a polyphenolic flavanoid and has historically been used in various liver tonic preparations on account of its antihepatotoxic effects [103, 104]. Silibinin may have a mechanism of action different from the previously reviewed CAMs in that it can modulate the insulin-like growth factor 1 (IGF-1) signaling pathway, known to be upregulated in prostate cancer [105, 106]. IGF ligand levels have been shown to be associated with prostate cancer risk, and IGF signaling can have downstream effects on the prosurvival and antiapoptotic Ras/Raf/MAPK and PI3K/Akt pathways [107, 108]. Mouse models have shown that oral silibinin increases insulin-like growth factor binding protein 3 (IGFBP-3) plasma concentrations, thereby possibly inhibiting IGF binding to IGF receptors [101, 105, 106, 108]. Silibinin has demonstrated synergy with doxorubicin and mitoxantrone in prostate cell lines at concentrations readily achievable in humans [109, 110].

Oral silibinin administration achieves measurable concentrations of between 0.3 and 4.0 $\mu\text{mol/L}$ depending on silibinin dose (range 360–1440 mg daily), which is roughly comparable to concentrations tested in mouse xenograft doses [111] (Table 1). In a small high-dose oral (13 grams per day) neoadjuvant trial for men with localized prostate cancer planned for radical prostatectomy, mean plasma silibinin levels of 19.7 μM were achieved, but silibinin was not detected in significant accumulation in prostate tissue [112]. Furthermore, there was no significant change in serum IGF or IGFBP-3 levels, although the treatment was of short duration (mean of 20 days) [112].

Silibinin has demonstrated interesting preventative and anticancer properties in prostate cancer animal models. It appears to be more bioavailable than some of the other CAMs, but there may be major differences in serum compared with tissue levels, making its future in clinical treatment uncertain.

COMBINATION CAM THERAPY

Although there is a strong preclinical rationale for the use of several CAMs, the concentrations needed to achieve an in vivo effect are not certain. One method to overcome this problem is to combine several CAMs with overlapping targets within the same preparation.

PC-SPEs, a previously patented blend of 8 herbs including baikal skullcap (*Scutellaria baicalensis* Georgi), chrysanthemum (*Dendranthema morifolium*), ganoderma (*Ganoderma lucidum*), isatis (*Isatis indigotica* fortune), licorice (*Glycyrrhiza glabra* licorice), Panax ginseng (*Panax pseudoginseng* var.), Hara (*Rabdosia rubescens*), and saw palmetto (*Serenoa repens*), was one of the early combination therapies in prostate

cancer [113]. In preclinical models PC-SPES demonstrated activity in androgen-dependent and androgen-independent in vitro and in vivo models [114–117]. Our group with others embarked on a randomized phase II trial of PC-SPES compared with diethylstilbestrol (DES) in patients with castrate refractory PCa. Over 40% of patients randomized to PC-SPES demonstrated a 50% decline in PSA and a median time to progression of 5.5 months compared with 2.9 months for DES [118]. However, concentrations up to 3.1% of DES were detected in PC-SPES formulations, which potentially confounded the trial and led to its early termination [118]. Subsequent analyses also detected low concentrations of warfarin and indomethacin contaminants in PC-SPES, and it was taken off even the Internet market in 2002.

A more recent herbal combination therapy common to many prostate cancer patients is Zyflamend (New Chapter, Brattleboro, Vermont), a proprietary blend of 10 standardized herbal extracts (turmeric, holy basil, green tea, hu zhang, ginger, Chinese goldthread, oregano, *Scutellaria baicalensis*, and barberry) [119]. In LNCAP cells Zyflamend has been shown to inhibit COX-1 and COX-2, induce cell cycle inhibitory proteins including p21, and suppress AR expression [120, 121]. Consistent with its anti-inflammatory actions, Zyflamend downregulates NF- κ B gene products and NF- κ B activation in lung cancer and leukemia cell lines at concentrations of 0.8 mg/mL [122]. Recently, Zyflamend demonstrated synergism with Bicalutamide in LNCaP cells and with gemcitabine in a mouse pancreatic cancer model [123, 124]. Combination preparations are currently in clinical trials in prostate cancer (NCT00669656). As with other CAMs discussed, the dosing and measurement of plasma concentrations in preformulated herbal combinations is complicated, and the potential interaction between constituents is often not well established.

SUMMARY

CAM use is common among prostate cancer patients and is expected to continue to increase over time. The preclinical anti-

cancer mechanistic data for many naturally occurring supplements can be impressive, but there is insufficient attention paid to meticulous establishment of meaningful biologic concentrations and whether these can be achieved in patients. Prior to mounting phase II-III clinical trials with these agents, rigorous phase I and pharmacokinetic data from standardized preparations will be needed to determine an appropriate dose and schedule for testing. Beyond this concern there are the issues of a more clear understanding of target-interactions, response biomarkers, and compound purity. Finally, there are likely to be issues about investigational new drug concerns for CAMs that are not controlled by established pharmaceutical companies. Most studies will of necessity be investigator-initiated, but without a funding source or even a reliable source of drug, these trials will continue to be problematic.

Here we have provided an overview of the preclinical data and proposed mechanisms for selected compounds in prostate cancer. It behooves the translational and practicing community oncologist to have a familiarity with CAMs because of their widespread use. On the basis of preclinical studies, there is a rationale for CAM use in prostate cancer, but it is difficult if not impossible for clinicians to sanction their use because of all the concerns above. For example, some preparations of Prostatol, a combination CAM widely used, may be associated with an increase in venous thrombosis, possibly because of estrogenic properties [125]. Nonetheless, for a well-studied, well-tolerated, and bioavailable CAM, studies in combination with established therapies such as docetaxel or as single agents aimed at slowing PSA progression in patients with biochemical recurrence are appropriate and much needed.

AUTHOR CONTRIBUTIONS

Conception/Design: Samuel J. Klempner, Glenn Bubley
Collection and/or assembly of data: Samuel J. Klempner, Glenn Bubley
Data analysis and interpretation: Samuel J. Klempner, Glenn Bubley
Manuscript writing: Samuel J. Klempner, Glenn Bubley
Final approval of manuscript: Samuel J. Klempner, Glenn Bubley

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