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Review

Facts and Fiction of Phytotherapy for Prostate Cancer: A Critical Assessment of Preclinical and Clinical Data

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Abstract. *The objective of this work was to substantially review all preclinical and clinical data on phytochemicals, such as genistein, lycopene, curcumin, epigallocatechin-gallate, and resveratrol, in terms of their effects as a potential treatment of prostate cancer. It is known, that prostate cancer patients increasingly use complementary and alternative medicines in the hope of preventing or curing cancer. The preclinical data for the phytochemicals presented in this review show a remarkable efficacy against prostate cancer cells in vitro, with molecular targets ranging from cell cycle regulation to induction of apoptosis. In addition, well-conducted animal experiments support the belief that these substances might have a clinical activity on human cancer. However, it is impossible to make definite statements or conclusions on the clinical efficacy in cancer patients because of the great variability and differences of the study designs, small patient numbers, short treatment duration and lack of a standardised drug formulation. Although some results from these clinical studies seem encouraging, reliable or long-term data on tumor recurrence, disease progression and survival are unknown. At present, there is no convincing clinical proof or evidence that the cited phythochemicals might be used in an attempt to cure cancer of the prostate.*

Abbreviations: AR, androgen receptor; CAM, complementary and alternative medicine; EGCG, epigallocatechin-3-gallate; EGF, epidermal growth factor; EPIC, European Prospective Investigation into Cancer and Nutrition; PCa, prostate cancer; MMP, metalloproteinase; NF-κB, nuclear factor-kappa beta; PSA, prostate-specific antigen, TRAMP, transgenic adenocarcinoma of the mouse prostate.

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In Europe, cancer of the prostate (PCa) is the most frequent cancer among men. About 190,000 new cases occur each year (15% of all cancers in men) (1). In most European countries, the incidence has increased more than any other cancer over the past two decades by about 10% every five years (2). About 80% of patients with prostate cancer are over 65 years of age. There are about 80,000 deaths a year from prostate cancer in Europe (1, 3). The five-year relative survival varies with the stage at diagnosis, from 80% or more when malignancy is confined to the prostate to about 25% where distant metastases are present (4).

PCa patients increasingly use complementary and alternative medicines for several reasons. First, in the hope of supporting the body's own functions (*i.e.* to improve the immune system) to fight the cancer, in addition to conventional treatment. Second, in the hope of minimizing morbidity associated with conventional treatment and third in the fear of suffering and dying from PCa when conventional treatment failes (5). Complementary and alternative medicine (CAM) is a widely used term comprising techniques, methods, herbal medicines and nutritional supplements used in addition to conventional care for symptom management and improving the quality of life. Many of these alternative therapies comprise unproven methods promoted as treatment or cure with questionable benefit, however, there is increasing evidence in the scientific literature of an effective activity of phytochemicals in modulating cancer cell growth. Phytochemicals differ from what are traditionally termed nutrients because they are not a necessity for normal metabolism nor will their absence result in a deficiency disease. The phytochemicals of plants, *i.e.* vegetables and fruits can act as chemo-preventive agents in cancer (6). Many studies using PCa cells and animal studies of chemical carcinogenesis have shown that a wide range of dietary compounds have cancer chemopreventive potential. Additionally, a growing body of epidemiological and other studies has revealed that populations with diets rich in fruits and vegetables, soy intake and many others of a large variety of nutrients may

significantly lower the incidence of PCa (6-39). In spite of this, some epidemiological studies are balanced between promising and disappointing results and they are always difficult to interpretate because of the many confounding factors present when assessing the effect of diet on cancer risk. These difficulties are evident in a large study on food consumption and cancer incidence in Europe, the European Prospective Investigation into Cancer and Nutrition (EPIC), where no association was observed between vegetables and fruit intake and the risk of PCa (22, 24).

This paper critically reviews the preclinical and clinical data on phytosubstances, the flavonoids (genistein, daidzein, quercetin and glycetin), the carotenoid lycopene, the polyphenols curcumin and epigallocatechin-gallate (green tea), resveratrol and mistletoe, when used for the treatment of prostate cancer.

Phytotherapeutic Agents

Phytoestrogens (Genistein, Quercetin). Phytoestrogens are naturally occuring phenolic plant compounds classified as flavones, isoflavones, coumestans and lignans. They are highly concentrated in soy products (beans and tofu) and plant lignans are found in legumes, whole grain, various seeds and vegetables (40, 41). Biochemically, phytoestrogens are heterocyclic phenols with a structural similarity to estrogenic steroids (mammalian endogenous estrogens) and therefore, these compounds display estrogen-like activity or weak anti-estrogen-like properties (40, 42). The beneficial effects of a soy diet have been attributed to isoflavones. Genistein, the predominant isoflavone in human nutrition is derived mainly from soybeans but also from other legumes, including peas, lentils or beans. Quercetin is the main representative of the flavonol class and a polyphenolic antioxidant found in a variety of fruits and vegetables. It is highly concentrated in onions, broccoli, apples, grapes (red wine), and in soybeans. Among the differences between Eastern and Western diets is the greater intake of soy in the eastern cultures. This might be one factor contributing to a lower incidence of PCa in Asian men (26, 28, 43).

In vitro effects of phytoestrogens. Physiological concentrations of the soy-derived isoflavone genistein have been shown to down-regulate the androgen receptor of PCa cells via the estrogen receptor beta, resulting in a modified response to hormonal stimuli (44). They also inhibited several steroid metabolizing enzymes such as 5-alpha-reductase or aromatase (17, 45). It has been postulated that these activities may be protective for PCa by creating a more favorable hormonal milieu. Isoflavones have been well analysed in human prostate tumor cells over the past years. Genistein inhibited the growth and induced apoptosis in LNCaP, DU-145 and PC3 PCa cells at a concentration ≤20 μM (46-54). Genistein blocked the cell-cycle progression at G1, inhibited PSA expression and modulated cell cycle gene regulation (49, 50, 52, 55). The expression of hTERT (telomerase reverse transcriptase), c-myc mRNA and the MDM2 oncogene were down-regulated by genistein, whereas p21 mRNA increased in response to genistein in the PCa cells DU-145 and LNCap (54, 56). In another study, genistein inhibited endothelial cell proliferation and *in vitro* angiogenesis associated with cancer progression at concentrations of 5 and 150 μM (57). Further, it has been demonstrated that genistein interfered with apoptosis signal transduction by down-regulating Bcl-XL expression (58). Genistein inhibited the nuclear factor-kappa beta (NF-κB) activation via the AKT signaling pathway and induced apoptosis in the androgen-sensitive PCa cell line LNCaP and the androgen-insensitive cell line PC3 at a concentration of 50 μM, whereas no apoptosis was seen in the nontumorigenic CRL-2221 human prostate epithelial cells under genistein treatment (53, 59). The AKT signaling pathway is an important survival pathway in cellular transduction activated by various growth factors such as the epidermal growth factor (EGF). NF-κB activity was completely abrogated in cells pretreated with genistein (53, 55, 59, 60). Furthermore, the effects of genistein on PC3 cancer cells and experimental PC3 bone tumors were evaluated by injecting these cells into human bone fragments previously implanted in immunodeficient (SCID) mice. Genistein significantly inhibited PC3 bone tumor growth by regulating the expression of multiple genes involved in the control of cell growth, apoptosis, and metastasis both *in vitro* and *in vivo*. For example, the expression of various metalloproteinases (MMPs) in PC3 bone tumors was inhibited by genistein treatment, whereas osteoprotegerin was upregulated. MMP immunostaining and transfection experiments have demonstrated inhibition of MMP-9 expression in PC3 cells *in vitro* and PC3 bone tumors *in vivo* after genistein treatment (61).

In vivo effects of phytoestrogens. The dorsolateral lobe of rat prostates is an embryologic homologue of the human prostate. Hence, Lobund-Wistar rats have been used in several studies investigating the expression of mitogenic receptors and the prevention of spontaneous prostatic tumors. One study with Lobund-Wistar rats that received a high-isoflavone diet showed a significant reduction of prostate tumor growth compared with the control group receiving a low-isoflavone diet (62). A study with TRAMP (transgenic adenocarcinoma of the mouse prostate) mice fed on a genistein-rich diet also found reduction of tumor incidence (63). Additionally, genistein lowered androgen and estrogen-receptor expression in the rat prostate, shown when a diet of 250 to 1000 mg genistein/kg was fed to male Sprague-Dawley rats (64, 65). These and other trials with animal models have provided promising data for the

treatment of prostate cancer with isoflavonoids (66-69). A compilation of preclinical *in vitro* and *in vivo* data is shown in Table I.

Clinical data on genistein. Although there are plenty of experimental data available, large epidemiologic trials to underline the antitumoral effect of isoflavones are rare. The first prospective cohort study was conducted in 1994 and showed that flavonoid intake was not associated with mortality from cancer (35). This was confirmed in a cross-national study of seven countries with 16 cohorts. A positive effect on coronary heart disease may be attributed to flavonoid intake but not cancer mortality (36). However, another cross-national study from 42 countries found that soy products were significantly protective against PCa mortality ($p=0.0001$) with an effect per kilocalorie at least four times as large as that of any other dietary factor (34). A substantial review of epidemiologic studies on phytoestrogens and prostate cancer risk by Ganry in 2005 showed that the positive trends of experimental data cannot be supported by positive effects on PCa risk reduction (32). However, there are some Phase I and II trials evaluating efficacy and safety of genistein in patients with PCa. In a nonrandomized, nonblinded trial of 38 patients (20 with clinically significant PCa and 18 controls), a daily intake of 160 mg isoflavones extract until radical prostatectomy led to significantly higher apoptosis of tumor cells ($p=0.0018$). No adverse events were reported, the median treatment time was 20 days (70). With the objective of assessing the potential genotoxicity of a purified unconjucated isoflavone mix, Miltyk *et al.* observed 20 PCa patients treated with 300 mg genistein/d for 28 days and with 600 mg/d for 56 days but could not find any significant genetic damage (71). A study by De Vere White *et al.* attempted to determine whether supplemental amounts of soy isoflavone (genistein-rich extract) would lower PSA (prostate-specific antigen) levels more than 50% in patients with prostate cancer. A total of 62 men with histologically proven PCa who had two consecutive elevated PSA readings were accrued into an open-label pilot study. Patients took capsules containing the genistein-rich extract three times daily by mouth. The subjects were in one of five groups: after radical retropubic prostatectomy (n=9), after radiotherapy (n=17), after both radical retropubic prostatectomy and radiotherapy (n=6), off-cycle during hormonal therapy (intermittent hormones, n=14), or active surveillance (n=16). The primary endpoint for the trial was a 50% reduction in the PSA level at six months compared with before treatment. Fifty-two patients were available for evaluation at six months. One out of the 52 patients had a more than 50% reduction in the PSA level, an additional seven patients had PSA reductions that were less than 50%. All eight patients with lower PSA levels at six months were in the active surveillance (watchful waiting) treatment subgroup. Repeated measure regression models allowing for correlation between initial levels and change also indicated a decline in PSA in this group compared with the other groups: 0 out of 52 had a complete response, nine (17%) had a partial response, eight (15%) had stable disease and 35 (67%) had disease progression. Taken together, genistein may hold some promise in PCa treatment but more study is warranted (72). A summary of clinical trails with genistein is depicted in Table II.

Carotenoids (Lycopene)

Lycopene is one of the most common carotenoids found in the human diet supplied mostly by tomatoes and tomato-based products. Pink grapefruit, watermelon and guave contain similar amounts of lycopene. Lycopene is an acyclic isomer of β-carotene and a highly unsaturated hydrocarbon that also shows antioxidant activity (73). As a non-provitamin A carotenoid, lycopene was found to be one of the most potent antioxidants with a singlet-oxygen-generating ability twice as high as that of β-carotene and ten times higher than that of α-tocopherol (74). Of all the carotenoids, lycopene is the most predominant and highly concentrated in low-density and very-low-density lipoprotein due to its lipophilic nature. Lycopene levels occur in organs with hormonally regulated tissues such as the prostate, where the highest concentration of lycopene can be observed (75, 76). Lycopene uptake, absorption and bioavailability in humans has appeared to depend on its preparation, being better from processed and heat-treated tomatoes than from unprocessed or raw tomatoes (77-80).

In vitro effects of lycopene. Lycopene at concentrations up to 5 mM significantly reduced the growth of LNCaP and normal human prostate epithelial (PrEC) cells (81). Androgen-independent DU-145 and PC-3 cells were more potently inhibited by lycopene (at concentrations of 26.6 μM) than androgen-dependent LNCaP cells (at concentrations of 40.3 μM) (82). Hwang *et al.* have found cell growth inhibition of 55% at low concentrations (1 μM) of lycopene and of 33% by tomato paste extract on 48 h incubated LNCaP cell lines. At low concentrations, reduction of lipid peroxidation was seen, whereas DNA damage increased at high concentrations (>5 μM) of lycopene. At this concentration, lycopene increased the number of cells in the G_2/M-phase from 13% to 28% and decreased S-phase cells from 45% to 29% (83-85).

In physiological concentrations of 0.3-3.0 μM, lycopene decreased the mitochondrial function significantly and induced apoptosis in LNCaP cells (86). A study in Japan tested 15 kinds of carotenoids on the viability of human PCa cells PC-3, DU-145 and LNCaP and found that lycopene at a 20 μM concentration reduced cell viability significantly after 72 h (87).

Table I. *Summary of molecular targets affected by phytochemicals in vitro and in vivo in androgen-insensitive (PC-3, DU145) and androgen-sensitive (LNCaP, PNT-1, PNT-2, VeCaP, 267B-1, BRFF-41T and SKRC-1) prostatic cell lines.*

Substance	Target	Cell culture system / Animals (Ref.)
Genistein	Inhibition of tumor cell growth	LNCaP (48, 51, 66), PC-3 (47, 48), DU-145,
in vitro		PNT-1, PNT-2 (47), LNCaP in SCID mice (66, 67)
	Induction of apoptosis	LNCaP (50, 51), PC-3 (50), LNCaP, PC-3, DU-145 in SCID mice (66)
	Inhibition of PSA expression	LNCaP (49, 51, 142), VeCaP (142)
	Suppression of DNA synthesis	LNCaP (51)
	Down-regulating of cyclin-B	LNCaP, PC-3 (50)
	Up-regulating of p21 WAF1 protein	LNCaP (49, 50), PC-3 (50)
	Up-regulating of p27KIP1 protein	LNCaP (49)
	Inhibition of NF-κB activation	LNCaP, PC-3 (59), PC-3 (53)
	Modulation of AKT signaling pathway	PC-3 (53)
	Induction of G1 cell cycle block	LNCaP (49)
	Induction of G2/M cell-cycle arrest	LNCaP, PC-3 (48)
	Inhibition of mitogenic signaling pathways	DU-145 (69)
	Reduction of CYP27B1 and CYP24 protein levels	DU-145 (30)
Genistein	Induction of DNA fragmentation, reduction of	LNCaP, PC-3, DU-145 in SCID mice (66)
in vivo	tumor vessel density, reduction of serum IGF-level	
	Inhibition of tumor growth, apoptosis	Nude mice / LNCaP (68)
	Suppression of tumor growth	Lobund-Wistar rats (62)
	Development and function of the rat dorsolateral prostate	Sprague-Dawley rats (65)
	Androgen and estrogen receptor expression	Sprague-Dawley rats (64)
Lycopene	Inhibition of tumor cell growth	LNCaP (82, 87, 143, 144), DU-145 (82, 87), PC-3 (82, 87)
in vitro	Induction of apoptosis	LNCaP (85, 86)
	Inhibition of PSA expression	LNCaP (144)
	Induction of G2/M-phase, reduction of S-phase cells	LNCaP (84, 85)
	Induction of plasminogen urokinase activator expression	PC-3 – MM2 cells (145)
	Reduction of lipid peroxidation at low concentrations	LNCaP (83)
	Reduction of mitochondrial transmembrane potential	LNCaP (86)
Lycopene		
in vivo	Inhibition of spontaneous mutagenesis in the prostate	(BaP)-treated LacZ mouse (146)
	Inhibition of tumor cell growth, induction of apoptosis	DU-145 in BALB/c mice (82)
	No reproducibility of *in vitro* tumor cell growth-inhibition	Fischer 344 rats (88)
	Reduction of carcinogenesis	(NMU)-treated Wistar rats (89)
Curcumin	Down-regulating of EGF-R protein, inhibiton of EGF-R	LNCaP, PC-3 (116, 117, 123-126)
in vitro	tyrosine kinase, inhibiton of ligand-induced activation of EGF-R, down-regulating of AR gene expression, inhibition of AP-1, inhibition of NF-κB activation, down-regulating of CBP, inhibition of AKT activation	
	Induction of apoptosis, inhibition of NF-κB activation, down-regulating of Bcl-2, Bcl-xL gene expression	LNCaP, DU-145 (114)
	Inhibition of EGF-R phosphorylation, inhibition of NF-κB activation	Metastatic C4-2B cells (126)
Curcumin	Inhibiton of tumor cell growth, induction of apoptosis,	LNCaP in nude mice (125)
in vivo	inhibition of angiogenesis	
EGCG	Induction of apoptosis	LNCaP (48, 128), PC-3 (48, 128), DU-145 (128, 131)
in vitro	Induction of PKC-α, suppression of TrkE, induction of p53	LNCaP (128, 132)
	Arrest of cell cycle in S-phase, inhibition of proteasome activity	LNCaP, PC-3 (48, 147)
	Induction of G0/G1 cell-cycle arrest, induction of WAF1/p21	LNCaP, DU-145 (128)
	Up-regulation of protein expression WAF1/p21, KIP1/p27, INK4a/p16, INK4c/p18, down-regulation of protein expression cyclin D1, cyclin E, cdk2, cdk4, cdk6, inhibition of PI3K/PKB and phosphorylation of AKT	LNCaP, DU-145 (130, 148)
	Inhibition of COX-2 expression	LNCaP, PC-3 (133)

Table I. *continued*

Table I. *continued*

Substance	Target	Cell culture system / Animals (Ref.)
Resve-	Inhibition of tumor cell growth	LNCaP (149, 150), DU-145 (149-151), PC-3 (149, 150)
ratrol	Induction of apoptosis	LNCaP (48, 152), DU-145 (152, 153), PC-3 (48)
in vitro	Reduction of PSA expression and AR expression	LNCaP (137, 154)
	Inhibition of AR expression and function, induction of S-phase, inhibition of DNA synthesis, induction of G_1- and S-phase cells	LNCaP (136-138)
	Induction of p53, induction of p21, inhibition of cdk-4 expression, arrest of cell cycle in S-phase	DU-145 (151)
	Reduction of NO production, modulation of phosphoglycerate mutase B	LNCaP, DU-145, PC-3 (149, 150)

AR, androgen receptor; AP-1, activator protein; CBP, cAMP-binding protein; Cdk, cyclin-dependent kinase; COX, cyclooxygenase; EGF-R, epidermal growth factor-receptor; LDH, lactate dehydrogenase; NO, nitric oxide; PacP, prostatic acid phosphatase; PI3K, phosphatidylinositol-3-kinase; PKB, protein kinase B; PKC, protein kinase C; PSA, prostate-specific antigen.

In vivo effects of lycopene. A study from Japan with male F344 rats over 60 weeks found no chemopreventive effect of lycopene on prostate carcinogenesis (88). Another study group fed lycopene or tomato powder to NMU (N-methyl-nitrosourea)-testosterone treated rats and found that the tomato powder but not the lycopene alone inhibited prostate carcinogenesis (89). A recent study has hypothesized a "stage specific" effect of lycopene on prostate cancer and demonstrated an inhibition of tumor cell growth in a dose-depending manner. The growth of DU-145 PCa cell xenografts in BALB/c nude mice was inhibited by 56 to 76% at a concentration of 100 or 300 mg/kg lycopene administered five days/week for eight weeks (82).

Clinical data on lycopene. Up to now, there have been several clinical studies to emphasize the findings of experimental data on lycopene and its effects on PCa. A recent epidemiological meta-analysis summarized the results of 23 studies presenting data on raw or cooked tomato, pure lycopene intake and serum lycopene with an overall "not overwhelming evidence" of the benefit of lycopene in PCa prevention. Only some serum- or plasma-based studies have supported a 25-30% reduction in the risk of prostate cancer (9, 31). Other studies, mostly dietary case-control studies, have not been as supportive of this hypothesis because the concentration and bioavailability of lycopene vary greatly across the various food items. Dietary questionnaires vary markedly in their usefulness for estimating the true variation in tissue lycopene concentrations across individuals. On the other hand, clinical phase I and II trials have demonstrated effects of lycopene against PCa by showing decreasing serum PSA- and IGF-levels and increasing tumor cell apoptosis. However, these studies have in common the small number of patients, short periods of treatment and lack of standardized drug dose (Table III) (90-94).

Polyphenols (Curcumin, Epigallocatechin-gallate, Resveratrol)

Dietary polyphenols with biological activity comprise several substances, which are very popular among CAM users and have recently presented interesting experimental data. Curcumin (diferuloylmethane) is a yellow pigment of turmeric (curcuma longa) and is traditionally used in the Indian Southeast Asian cuisine as a seasoning spice to give specific flavor and yellow color to the Asian food. The dietary ingredient is also used as a natural anti-inflammatory agent in these countries and several epidemiological studies suggest that it has anticarcinogenic potential against human prostate cancer (95-101).

Green tea is an aqueous infusion of dried nonoxidized, unfermented leaves of *Camellia sinensis* (family Theaceae) and a popular beverage worldwide with most frequent consumption in Asian countries. Green tea contains a variety of polyphenolic compounds, such as epicatechin, epicatechin gallate, epigallocatechin and epigallocatechin-3-gallate (EGCG), which is the most prevalent polyphenol of green tea. The cancer preventive effects of green tea were mostly seen in Asian countries, where large amounts of green tea are consumed each day (23, 95, 102-105).

The transhydroxystilbene resveratrol is a naturally occurring phenolic phytoalexin mostly found in the skin of grapes, in peanuts and many types of berries. It has been reported to have anticarcinogenic, antioxidative, cardioprotective and phytoestrogenic activities and might therefore be a potent chemopreventive agent not only for prostate cancer (106-111). In grape juice or wine, resveratrol is particularly highly concentrated (1.5 to 3.0 mg and 50 to 100 mg, respectively) (107, 108) and it has

Table II. *Compilation of recent clinical studies on soy-isoflavones (genistein, daidzein) for prostate cancer.*

Substance / Preparation / Scheduling	Patient characteristics	Efficacy / Response	Toxicity	Clinical phase	Ref.
Normal "Western" diet	63 pts with BPH 31 pts with PCa	Genistein plasma levels were greater in group A (small prostate) than in group B (large prostate) (p=0.023) and in group C (PCa) similar to the entire BPH group (p=0.34); PSA level in group C was greater than in BPH groups (p=0.004); BPH volumes were greater in groups A+B than in C (p=0.037)	Not noted.	Phase I	(41)
Soy beverages twice daily for a 6 week period ISP+ (42 mg genistein plus 27 mg daidzein) ISP– (2.1 mg genistein and 1.3 mg daidzein)	34 elderly men with elevated PSA	ISP+ and ISP– increased serum concentrations and urinary output of the isoflavones and their metabolites, IPS+ decreased serum cholesterol, no effect on serum PSA or p105erB-2 proto-oncogene	No systemic or local toxicity noted.	Phase I	(155)
Genistein preparation (43% genistein, 21% daidzein, 3% glycitein) 300 mg/d for 28 d and then 600 mg/d for another 56 d	20 pts with PCa 6 controls	A single elevated micronucleus frequency (MF) was found. No genistein-induced rearrangements of the MLL gene were detected. Total genistein never exceeded a peak concentration of 27.1 μmol/L, unconjugated genistein never exceeded a peak concentration of 0.32 μmol/L.	No systemic or local toxicity noted.	Phase I	(71)
Soy Formulation 300 or 600 mg genistein and 150 or 300 mg daidzein for 84 days	20 pts with PCa 84 days	Serum DHT decreased by 31.7% (p=0.0004), genistein and daidzein were rapidly cleared from plasma and excreated in urine.	Mild estrogenic effects like breast changes, frequency of hot flushes.	Phase I	(156)
Purified soy-isoflavones A (90% genistein, 10% daidzein, 1% glycitein) B (43% genistein, 21% daidzein, 2% glycitein	30 healthy men 5 dose groups – each with 6 subjects	Pharmacokinetic analyses in the 24h after single-dose administration of mean elimination half lives for free genistein was 3.2 h and 4.2 h for free daidzein with both formulations.	Well tolerated, no physical changes, elevation of lipoprotein lipase and hypophosphatemia.	Phase I	(157)
Unconjugated soy isoflavones PTI G-2535 (43% genistein, 21% daidzein, 3% glycitein) PTI-G4660 (90% genistein, 9% daidzein, 1%glycitein) Cohorts of four patients received single doses of 2, 4, or 8 mg/kg orally, each dose was separated by 1 week.	11 pts with PCa, 2 pts with Colon-Ca	Maximal plasma concentrations (C_{max} ranged between 4.3 and 16.3 μM for total genistein and 0.066 and 0.17 μM for free genistein). For PTI G-2535 and PTI G-4660, half-life was 15.03 and 22.41 h, respectively, and volume of distribution was 189.9 and 653.8 l, respectively, there was a trend toward higher AUC for PTI G-2535 (p=0.07 at the 8 mg/kg dose). Treatment-related increases in tyrosine phosphorylation were observed in PBMC. Plasma concentrations of genistein are achieved that have been associated with antimetastatic activity *in vitro*.	One of 13 patients treated developed a treatment-related rash. No other toxicities were observed.	Phase I	(158)

Table II. *continued*

Table II. *continued*

Substance / Preparation / Scheduling	Patient characteristics	Efficacy / Response	Toxicity	Clinical Phase	Ref.
Diet rich in soy and linseed soy group (high phytoestrogen) soy and linseed group (high phytoestrogen) wheat group (low phytoestrogen)	28 pts with PCa soy group (n=8), soy and linseed group (n=10), wheat group (n=8)	Statistically significant differences were detected between the soy group and the wheat group for the % change in total PSA (–12.7% *vs.* 40%, $p=0.02$) and the percentage of change in free/total PSA ratio (27.4% *vs.* 15.6%, $p=0.01$) and between the soy group and the soy/linseed group for the % of change in free androgen index (16.4% *vs.* 15.5%, $p=0.04$) and the % change in free/total PSA ratio (27.4% *vs.* 10%, $p=0.007$).	No systemic or local toxicity noted.	Phase I/II	(159)
Dietary isoflavones 160 mg/d containing genistein, daidzein, formononetin, biochanin A for 6 weeks	38 pts before therapy for PCa 18 controls	Apoptosis in radical prostatectomy specimens from treated patients was significantly higher than in control subjects ($p=0.0018$), specifically in regions of low to moderate-grade cancer (Gleason grade 1-3).	No systemic toxicity noted.	Phase II	(70)
Isoflavones 2 x 100 mg soy/d for 3 to 6 months	41 pts in 3 groups – Group I: watchful waiting with rising PSA (n=4); group II: increasing PSA with local therapy (n=18); group III: with hormone therapy (n=19)	Median follow-up was 5.5 months; 39 pts were analysed, no CR or PR, SD (PSA) was 83% in group II and 35% in group III, no changes in serum levels of testosterone, IGF-1, IGFBP-3 or 5-OHmdU.	No systemic toxicity noted.	Phase II	(160)
Genistein-rich extract capsules 3 cps for 6 month	62 pts with PCa who had two consecutive elevated PSA	CR was 0%, 9 pts (17%) had a PR, 8 (15%) had SD, and 35 (67%) had disease progression. The total testosterone level was lowered in 1 of the patients responding, but it was higher in five others.	3 pts discontinued because of adverse events (diarrhea) and 7 because of personal choice.	Phase II	(72)
Soy isoflavone (60 mg/d) or placebo for 12 weeks	76 pts with PCa	59 pts completed 12 weeks, serum free testosterone was reduced or unchanged at 61% in the isoflavone group *vs.* 31% in the placebo group, serum total PSA decreased or remained unchanged in 69% of the isoflavone group *vs.* 55% in the placebo group ($p=0.07$)	No systemic or local toxicity noted.	Phase II	(38)

AUC, area under the concentration curve; BPH, benign prostatic hyperplasia; CR, complete response; PBMC, peripheral blood mononuclear cells; PCa, prostate cancer; PD, progressive disease; PR, partial response; pts, patients; SD, stable disease.

been proposed that it is responsible for the beneficial effects of a moderate red wine consumption. Resveratrol has been found to inhibit platelet aggregation, increase high-density lipoprotein and to have vasorelaxing effects on the aortal endothelium in several experimental investigations (110-113).

In vitro and in vivo effects of polyphenols

Curcumin. The treatment of both androgen-dependent and independent PCa cell lines LNCaP, PC-3 and DU 145 with curcumin and its analogues has shown significant effects on cell growth, activation of signal transduction and transforming activities. Curcumin suppressed NF-κB

Table III. *Compilation of recent clinical studies on lycopene for prostate cancer.*

Substance / Preparation / Scheduling	Patient characteristics	Efficacy / Response	Toxicity	Clinical phase	Ref.
Tomato sauce and oleoresin for 1 week	19 healthy volunteers	Significant increase in serum lycopene levels, tendency of lower protein and DNA oxidation was observed.	No systemic or local toxicity noted.	Phase I	(78)
Regular diet	12 pts with PCa 12 aged matched controls	Lower serum ($p=0.04$) and tissue ($p=0.05$) lycopene levels in PCa pts *vs.* controls, no difference in serum lipid peroxidation ($p=0.76$), serum protein thiol levels were lower in cancer patients ($p=0.026$) *vs.* controls.	No systemic or local toxicity noted.	Phase I	(161)
Tomato sauce based pasta dishes 30 mg lycopene/d	32 pts with PCa for 3 weeks before RPE	Mean serum PSA concentrations decreased by 17.5% ($p<0.002$) and leukocyte 8OHdG decreased by 21.3% ($p<0.005$) after tomato sauce consumption. Resected tissues from tomato sauce-supplemented patients had 28.3% lower prostate 8OHdG compared with the nonstudy control group ($p<0.03$). Cancer cell 8OHdG staining of Gleason Score-matched resected prostate sections was reduced by 40.5% in mean nuclear density ($p<0.005$) and by 36.4% in mean area ($p<0.018$) compared with the presupplementation biopsy. Apoptotic index was higher in hyperplastic and neoplastic cells in the resected tissue after supplementation.	Not evaluated.	Phase I	(92)
Tomato oleoresin extract 2 x 15 mg/d *vs.* no lycopene for 6 weeks	26 pts with PCa 11 controls before RPE	PSA decreased in 18% *vs.* 14% in controls, surgical margins involved and/or extra-prostatic tissues in 73% *vs.* 18% in controls, tumor <4 ml in 80% *vs.* 45% in controls, high grade PIN in 67% *vs.* 100% in controls.	No systemic or local toxicity noted.	Phase II	(94)
Lycopene (2 x 2 mg/d) plus orchidectomy (OL) *vs.* orchidectomy alone	54 pts confirmed metastatic PCa (27 pts in each group)	After 2 years there was a significant reduction in PSA level (mean 3.01 and 9.02 ng/mL; $p<0.001$). Eleven (40%) patients in orchidectomy and 21 (78%) in the OL group had a complete PSA response ($p<0.05$), with a PR in 9 (33%) and 4 (15%), and progression in 7 (25%) and 2 (7%), respectively ($p<0.05$). Bone scans showed that in the orchidectomy arm only 4 (15%) patients had a complete response, *vs.* 8 (30%) in the OL group ($p<0.02$), with a PR in 19 (70%) and 17 (63%), and progression in 4 (15%) and 2 (7%), respectively ($2 < 0.02$). Of the 54 pts, 19 (35%) died, 12 (22%) in orchidectomy and seven (13%) in OL group ($p<0.001$).	Well tolerated.	Phase II	(90)
Lycopene 10 mg/d for 3 months	20 pts with hormone-refractory PCa	CR was 5% (1/20), PR 30% (6/20), SD: 50% (10/20), overall duration of response 8 m, survival: 14 m.	No systemic or local toxicity noted.	Phase II	(91)

80HDG, 8-Hydroxydeoxyguanosine; CR, complete response; PCa, prostate cancer; PD, progressive disease; PIN, prostatic intraepithelial neoplasia; PR, partial response; pts, patients; RPE, radical prostatectomy; SD, stable disease.

activation and activator Protein-1 (AP-1) and induced apoptosis, correlating with the down-regulation of Bcl-2 and Bcl-xL expression and the activation of procaspase-3 and procaspase-8 (114). In addition, suppression of cyclin D1 by curcumin led to the inhibition of CDK4-mediated phosphorylation of the retinoblastoma protein. Curcumin also down-regulated mRNA expression and inhibited the activity of the cyclin D1 promoter-dependent reporter gene expression, suggesting transcriptional regulation (115). Additionally, curcumin down-regulated transactivation and expression of AR (androgen rezeptor) and CREB (cAMP response element-binding protein) contributing to the antiproliferative effects against PCa growth (116). Curcumin also targets the activated cell signaling pathway threonine kinase AKT by reducing the level of activated (phosphorylated) AKT thereby inhibiting the AKT kinase

activity (117, 118). Deeb *et al.* have shown that curcumin interferes with TRAIL (tumor necrosis (TNF)-related apoptosis-inducing ligand) -induced signal transduction and increases the sensitivity of LNCaP cells to apoptosis (119-121). Curcumin in combination with radiation has shown inhibition of TNF-α-mediated NF-κB activity resulting in Bcl-2 protein down-regulation (122). Durai *et al.* have shown that curcumin inhibited the intrinsic EGF-R tyrosine kinase (the ligand-induced activation of the EGF-R) and down-regulated the EGF-R protein in LNCaP, PC-3 and highly metastatic C4-2B PCa cells. LNCaP cell xenografts in nude mice have shown a significant decrease in the microvessel density with curcumin treatment (123-126).

Green tea (epigallocatechin-3-gallate [EGCG]). Adhami *et al.* have reviewed the numerous experimental data on EGCG from green tea, most of which have been collected by his own study group and suggested that there are multiple molecular targets for prostate cancer chemoprevention due to the polyphenolic fractions of green tea. In cell culture systems of DU-145, PC-3 and LNCaP PCa cells, the group showed in several studies that EGCG induced apoptosis, cell-growth inhibition and cell-cycle dysregulation (127). EGCG treatment of DU-145 and LNCaP cells induced apoptosis, G0/G1 cell cycle arrest and cyclin kinase inhibition of WAF1/p21, independent of the p53 status of the cells (128). Furthermore, it has been found that down-regulation of NF-κB activity by EGCG decreased the expression of proapoptotic protein Bcl-2 (129). EGCG treatment decreased the levels of phosphatidylinositol-3-kinase (P13K)/protein kinase B (PKB) and mitogen-activated protein kinase (MAPK) pathways in both DU-145 and LNCaP cells (128, 130). Ahmad *et al.* have investigated the effect of EGCG on apoptosis in different human cancer cells. Apoptosis in DU145 cells was assessed by evaluation of the formation of internucleosomal DNA fragments, confocal microscopy and flow cytometry (131). In LNCaP cells alone, an induction of protein kinase C-a and suppression of tyrosin kinase TrkE was seen (132). Hussain *et al.* have shown that EGCG selectively inhibited cyclooxygenase-2 expression (COX-2) in both androgen-sensitive LNCaP and androgen-insensitive PC-3 cells without affecting COX-1 expression and without severe toxic side effects like those of conventional anti-inflammatory drugs (NSAID) (133).

These effects could also be demonstrated in animal models that mimic progressive forms of human prostatic disease such as TRAMP and other rodent models. It has been shown that an oral infusion of green tea polyphenols (GTP) at a human achievable dose (equivalent to six cups of green tea/day) significantly inhibited PCa development and metastasis by modulating specific gene expression such as matrix metalloproteinases (MMP-2, MMP-9) and vascular endothelial growth factor (VEGF) that are related to the corresponding molecular pathways in prostate cancer (134). The continuous infusion of green tea for 24 weeks also resulted in the reduction of the IGF-levels and in the significant increase of the Insulin-like Growth Factor IGFBP-3 in the dorso-lateral prostate of TRAMP mice (135). Another study with Cpb:WU Wistar rats and C57BL/6 mice found a significant inhibition of testosterone-mediated induction of ornithine decarboxylase (ODC)-activity after oral feeding of 0.2% GTP (23).

Resveratrol. Interest has been shown in the phytoestrogenic activity of resveratrol, which is particularly of interest in hormone related cancers. *In vitro* studies of resveratrol have been performed with androgen dependent LNCaP PCa cells. Mitchell *et al.* have shown a dramatic decrease of PSA and hK2 protein gene expression, as well as a decline of the AR related ARA70 mRNA coactivator and cyclin-dependent kinase inhibitor p21 level, in the presence of 100 to 150 μM resveratrol. At a concentration of 200 μM, resveratrol induced massive apoptotic cell death. It has been demonstrated that the inhibition of androgen action by resveratrol is mediated via the reduced expression of important genes such as AR, ARA70 and p21 (136). A recent study with LNCaP cells has used DNA microarray analysis to show gene expression changes in over 1.600 transcripts after six hours treatment with resveratrol, including modulation of PSA and AR genes in the androgen pathway and accumulation of cells at the sub-G1 and S phase of the cell cycle (137). Kuwajerwala *et al.* have found that the inhibition of DNA synthesis in LNCaP, but not in the androgen independent DU-145 PCa cells, depended on the concentration and the duration of treatment. At concentrations ranging from 5 to 10 μM, resveratrol caused an increase of DNA synthesis, whereas at 15 μM it inhibited DNA synthesis (138). A compilation of preclinical *in vitro* and *in vivo* data on polyphenols Curcumin and resveratrol is depicted in Table I.

Clinical data on polyphenols. In a prospective cohort study in Japan in 1997, the association between green tea consumption and cancer incidence was studied, including the daily consumption of green tea of 8,552 individuals over 40 years of age. During the nine years of follow-up a total of 384 cases of cancer in all sites occured. The survey found a negative association between green tea consumption and cancer incidence, especially among females drinking more than ten cups a day even when stratified by smoking and adjusted for alcohol and dietary variables (37). In a phase I trial the maximum tolerated dose (MTD) of green tea was found to be 4.2 g/m^2. The side effects nervousness and reversible insomnia were related to the caffeine fraction (139). Two phase II trials in of green tea extract in PCa did

Table IV. *Compilation of recent clinical studies on green tea extract (GTE) for prostate cancer.*

Substance / Preparation / Scheduling	Patient characteristics	Efficacy / Response	Toxicity	Clinical phase	Ref.
Green tea extract 110, 200, 270 mg/d once or three times daily for 4 weeks	49 pts with solid cancers	No major responses occurred; 10 patients with SD completed 6 months of GTE. Pharmacokinetic analyses found accumulation of caffeine levels that were dose dependent, whereas epigallocatechin gallate levels did not accumulate nor appear dose related.	Mild to moderate toxicities at most dose levels promptly reversed on discontinuation of GTE. Dose-limiting toxicities were caffeine related and included neurologic and gastrointestinal effects. The MTD was 4.2 g/m^2 once daily or 1.0 g/m^2 three times daily.	Phase I	(139)
Green tea extract 6 g of green tea per day orally in 6 divided doses for 3 months	42 pts with androgen-independent PCa, continued use of LHRH agonist was permitted	Median follow-up 8 weeks, tumor response (def. as ≥50% decline of baseline PSA) was 2% (1/42 pts.)	Green tea toxicity, usually Grade 1 or 2, occurred in 69% of patients and included nausea, emesis, insomnia, fatigue, diarrhea, abdominal pain, confusion. Six episodes of Grade 3 toxicity and one episode of Grade 4 toxicity (severe confusion) occurred. No AE reported in 14 cases (39%).	Phase II	(140)
Green tea extract 250 mg twice daily for 2 months	19 pts with hormone-refractory PCa	Follow-up was 2-5 months, 15 patients completed at least 2 months of therapy. Disease progression was def. as >25% rise of baseline PSA or evidence of radiologic progression). CR 0% (0/19), PR 5% (1/19), SD 31% (6/19). Nine of these patients had progressive disease within 2 mth. of starting therapy. 6 patients developed progressive disease after additional 1 to 4 months of therapy.	The treatment was tolerated well. 12 patients reported at least one side effect; only two of these were of moderate or severe grade. Primary toxicity was related to gastrointestinal irritationor caffeine intake. 4 patients did notcomplete therapy because of intolerance (2 pts.), physician stoppage (1 pt.), death from cerebrovascular accident (1 pt.).	Phase II	(141)

AE, adverse events; CR, complete response; LHRH, luteinizing hormone-releasing hormone; mth, months; MTD, maximum-tolerated dose; PCa, prostate cancer; PD, progressive disease; PR, partial response; pts, patients; SD, stable disease.

not find relevant clinical activity. One trial evaluated 42 patients with asymptomatic prostate carcinoma, clinical evidence of androgen independent disease and progressive elevated PSA levels to explore whether green tea could decrease PSA levels ≥50% from the baseline in order to demonstrate tumor response. The patients had to take capsules of 6 g pulverized green tea per day, each dose containing 46 mg caffeine. The median time on the study was one month and the most common reason for dropping out before a 4-month assessment was disease progression (63%). After two months, only one patient had a 50% decrease of PSA from the baseline which is equivalent to a 2% response rate (140). The second study enrolled 19 patients with hormone refractory prostate cancer and an absolute PSA ≥10 ng/mL in a prospective single arm clinical trial to evaluate the toxicity and clinical response rate of commercially available green tea extracts. The patients took capsules of green tea extract at a dose of 250 mg twice daily. The extracts were decaffeinated, containing less than 2% caffeine and greater than 30% EGCG (75% polyphenols altogether). The primary endpoint of this study was disease progression by either PSA increase ≥25% over the baseline over a 2-months period, or radiological progression measured by CT or bone scan. 15 patients consumed green tea extract for at least 2 months; nine patients had progressive disease within two months of starting therapy and six patients within three to five months of starting therapy. A complete response rate defined as a PSA decline of ≥50% from the baseline was not seen in any of the patients at the end of the study (141). A summary of the clinical trials with green tea is shown in Table IV.

To date, clinical trials with curcumin, quercetin and resveratrol elucidating their effects on prostate cancer are not available.

Discussion

Prostate cancer represents an ideal target for chemoprevention, as it has a high incidence, a long latency, a specific tumor marker (PSA) and identifiable neoplastic lesions. If an agent can slow the growth of existing prostate cancer cells, it remains plausible that it may be effective on its own or as an adjunct to surgery, radiation, hormone or chemotherapy. Evidence-based data are needed in order to definitively prove the efficacy of phytomedicines for prostate cancer because of the growing interest in and use of herbal remedies as a persistent trend of our present-day health care. In order to evaluate phytomedicines in the prevention of prostate cancer, major prospective, randomized trials are underway that will assess the role of soy, vitamin E and selenium. Tantalizing prospects for effective chemoprevention of prostate cancer exist. Well-conducted randomized trials will allow us to answer many of these questions within the next years.

The summary of preclinical data presented in this review shows the remarkable efficacy of some of these agents against PCa cells *in vitro* with molecular targets ranging from cell cycle regulation to induction of apoptosis. In addition, animal experiments support the belief that phytomedicines will have a clinical activity in human cancer therapy. However, many protocols and endpoints chosen for the Phase I and II studies of prostate cancer therapies are of some concern and make interpretation of data quite difficult. Dose and concentrations of the drug/substance used in the studies have mostly been empirically derived and rarely tested systematically and the manufacturing and preparation has not been standardized. Some analyses have combined patients with androgen-dependent and androgen-independent tumors without stratification on this parameter, some have failed to consider the distinctiveness of PSA progress and tumor recurrence or have not had sufficient statistical power. It is difficult to make definite statements or conclusions because of the great variability and differences of the study results, small patient numbers, short treatment duration (six months) and lack of standardised drug formulations. A major problem remains the preparation of the compounds and standardization of the active molecules.

Although several agents have been evaluated in phase I and II studies and even though some results from these therapies seem encouraging, reliable or long-term data on tumor recurrence, disease progression and survival are unknown. Well performed, prospective, randomized, placebo-controlled studies should be undertaken to analyze the therapeutic effects and safety of phytochemicals on prostate cancer. Unfortunately, it is becoming increasingly difficult to conduct investigator initated clinical trials due to regulatory hurdles and the lack of interest by the pharmaceutical industry.

Up to now, there have been several clinical studies to confirm the findings of preclinical experimental data on lycopene and genistein and their effect on prostate cancer. The presented data allow the recommendation to patients of the use of tomatoes and tomato products, soy and green tea with the intention of a preventive approach against the development of prostate cancer. To date, epidemiological trial data exist only for vitamin E, calcium, beta-carotene and selenium. At this stage, there is not enough clinical proof by large randomized trials that the cited phythochemicals are reliable therapeutics capable of curing cancer of the prostate.

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