Abstract. Prostate cancer continues to be one of the most commonly diagnosed diseases and the second leading cause of cancer-related deaths among men in the United States. Options exist to treat localized disease, including surgery, radiation therapy, and hormonal therapy, but clinical management of advanced prostate cancer is challenging. In the past few decades, chemoprevention involving naturally-occurring compounds has emerged as a promising and cost-effective approach to reduce incidence and morbidity of prostate cancer by inhibiting the precancerous events before the occurrence of clinical disease. The present review focuses on summarizing the recent advances in studies of major dietary phytochemicals and their role in prostate cancer development.

Prostate cancer (PCa) is one of the most commonly diagnosed diseases and is the second leading cause of cancer-related deaths among men in the United States (1). It is typically diagnosed in the sixth and seventh decades of life, and hence a modest delay in disease progression could have a significant impact on disease-related morbidity, mortality and quality of life. Molecular mechanisms underlying onset and progression of PCa are not fully understood, but the factors implicated in pathogenesis of this disease include age, race, diet, androgen secretion and metabolism, and activated oncogenes (2-4). Several options exist to treat localized disease including surgery, radiation therapy, and hormonal therapy, but clinical management of advanced PCa is challenging (5). Androgen ablation is one of the most frequently suggested treatment options for PCa, but this treatment selection is palliative and has a limited scope for hormone-refractory cancer (6). In addition, chemotherapy and radiation therapy are largely ineffective against advanced PCa (5).

A continuous increase in incidence and failure of conventional therapies against advanced PCa warrants development of novel agents to treat and prevent this malignancy. In the past few decades, chemoprevention involving naturally occurring compounds has emerged as a promising and cost-effective approach to reduce incidence and morbidity of PCa by inhibiting the precancerous events even before the occurrence of clinical disease (7). PCa provides a large window of opportunity for intervention to prevent or slow its progression and in many ways remains an ideal candidate for chemoprevention because of its high incidence and long latency. Therefore, development of agents which offer significant protection against the development of this disease is highly desirable. Such chemopreventive agents could have a significant impact on disease-related costs, morbidity, and mortality for a large segment of the population (8-13). The identification of agents and their molecular targets for PCa chemoprevention is guided by data derived from a variety of sources including epidemiological, clinical, and pre-clinical studies (9). As with other types of cancer, PCa is thought to develop via modifications in different molecular events, and hence blocking or inhibiting only one event may not be sufficient to prevent or delay the disease onset. Therefore, ongoing research to better understand the disease and to develop novel approaches for its prevention and treatment is critical. Epidemiological evidence suggests lower PCa risk in populations with higher consumption of major phytochemical-containing diets (14). These observations have generated enough curiosity among the scientific world to explore the utility of natural agents for the prevention of PCa. Several naturally occurring agents are currently being studied for their chemopreventive potential. This...
review summarizes the recent advances on four major phytochemicals, namely lycopene, resveratrol, capsaicin, and curcumin and their potential role in PCa prevention and or treatment, including details of clinical trials.

**Lycopene**

Lycopene (Figure 1) is a member of the carotenoid family and is commonly synthesized in plants. Lycopene occurs in many plant foods including but not limited to watermelon, tomatoes, papaya, and apricots. It is the substance that gives these fruit and vegetables their characteristic red color (15-17). In the United States and other western countries, dietary lycopene comes from the consumption of tomatoes and tomato-based products, including tomato sauce, tomato juice and pizza sauce. Lycopene metabolites circulate in serum and accumulate in tissues at concentrations equivalent to those of bioactive retinoids (18). Studies from around the world have demonstrated cancer chemopreventive properties of lycopene and other carotenoids specifically against PCa. Lycopene has been noted for its protective effects against PCa, acting as an antioxidant and inhibiting cell proliferation (19).

Lycopene has demonstrated potential anticancer properties in multiple human cancer cell lines. Cell lines treated with lycopene (1-5 μM) for 48 and 96 h were analyzed by various techniques for apoptotic cells [by flow cytometry, Terminal Deoxynucleotidyl Transferase-Mediated DuTP Nick Labeling (TUNEL) and 4', 6-diamidino-2-phenylindole (DAPI assay)]. There was a significant decrease in the number of viable cells after a 48-h treatment with lycopene along with changes in the fraction of cells retained in different phases of the cell-cycle. After 96 h, lycopene-promoted cell cycle arrest was followed by a decrease in cell viability in the majority of cell lines tested. Additionally, there was an increase in apoptosis compared to the controls. A rate-limiting step in the cell cycle that is often seen with the used anticancer agents is inhibition of the progression of cells through the first gap (G1) phase. In a recent study, it was shown that lycopene induces cell-cycle arrest at the G1 phase and thus has chemopreventive properties (20).

Lycopene has also shown its antitumor properties through changes in the mevalonate pathway and in rat sarcoma (RAS) activation of PCa cells. Incubation of RAS-activated prostatic carcinoma LNCaP cells with 24-h lycopene treatment (2.5-10 μM) reduced intracellular total cholesterol in a dose-dependent manner. Lycopene inhibited 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA reductase), consequently, inactivating RAS and reducing the RAS-dependent activation of nuclear factor-kappaB (NF-κB). PCa cells have abnormal cholesterol biosynthetic pathways that are resistant to down-regulation by cholesterol. Thus, by inhibiting this key step in cholesterol synthesis (HMG-CoA reductase), lycopene may control tumor cell growth (21).

The modulation of the nuclear factor erythroid 2-related factor 2 (NRF2)-mediated oxidative stress response signaling pathway may be an important mechanism involved in chemoprevention (22). NRF2 is a transcription factor that is commonly activated by increased reactive oxygen species (ROS) and often induces the transcription of several antioxidant and detoxification enzymes, including several classes of glutathione S-Transferases (GSTs) (22). Antioxidants function by neutralizing free radicals and reducing oxidative stress, both of which cause significant damage to DNA on generation of ROS (23). This damage can lead to the formation of cancer in various tissues (23). PCa tissues, in particular, have high levels of oxidative damage (23). The risk of prostate damage has been reported to be lower in patients who regularly consume higher levels of lycopene (23). Patients with localized prostate adenocarcinoma who consumed tomato sauce-based dishes for three weeks (30 mg of lycopene per day) exhibited a statistically significant decrease in oxidative DNA damage in the prostate tissues (23). This was concluded through observations of serum prostate-specific antigen (PSA) levels as well as DNA oxidative damage to DNA in leukocytes. Compared with ratios from leukocytes isolated before the intervention, the average leukocyte DNA [8-OHdG/105 dG] ratio of 31 patients with PCa decreased by 21.3% from 0.61 to 0.48 after the tomato sauce intervention, a statistically significant difference (23). In a randomized trial of transgenic adenoma of mouse prostate (TRAMP) mice, equivalent doses of lycopene from a tomato paste product and from a lycopene beadlet were given to mice; after 20 weeks of administration, prostate histopathology was compared with mice on a control diet. The lycopene beadlet group had a significant reduction in the incidence of PCa relative to the control group (60% vs.
The difference in PCa incidence between the tomato paste and control group, however, was not statistically significant (80% vs. 95%, p=0.34). One speculative explanation for these results is that the tomato paste used in the study did not contain the skin and seeds of the tomato. There may be anticarcinogenic properties associated with the skin and seeds, therefore explaining the variation in results (24). In another study using the MatLyLu orthotopic Dunning tumor model, a rat model for aggressive PCa, rats were grouped and fed a diet supplemented with 200 ppm lycopene or 540 ppm vitamin E for four weeks. Both compounds accumulated in tumor tissue and the levels achieved were comparable with those of humans. After four weeks of feeding, a highly aggressive and metastatic cell line, MatLyLu, was injected into the ventral lobes of the prostate and the prostate tumors were monitored for necrosis by magnetic resonance imaging (MRI). There were no differences in tumor volume among all groups. However, a significant increase in the necrotic area of tumor was reported in both lycopene- and vitamin E-supplemented groups compared to the control. Moreover, mechanistic details revealed that lycopene interfered with local testosterone activation by down-regulating 5-α-reductase and consequently reduced steroid target gene expression (25). In a nude mouse model, orally-gavaged lycopene alone (5 or 50 mg/kg body weight) did not affect androgen-independent human PC-346C PCa xenograft growth, however, combination of low-dose lycopene and vitamin E significantly reduced tumor growth (26). In a different study, it was shown that consumption of tomato powder and not lycopene is associated with reduced prostate carcinogenesis. Male rats (n=194) treated with the carcinogen N-methyl-N-nitrosourea and testosterone to induce PCa were fed diets containing whole tomato powder (13 mg lycopene/kg diet), lycopene beadlets (161 mg lycopene/kg diet), or control beadlets (27). The authors concluded that consumption of tomato phytochemicals and diet restriction may independently act to reduce the risk of PCa development (27). As noted, there are varying degrees of evidence that show that tomato products containing lycopene reduce oxidative damage and tumor growth through multiple mechanisms.

Epidemiological evidence suggests that increased consumption of tomatoes or its major carotenoid lycopene is associated with a decreased risk for PCa (28). Tomato products and lycopene have been shown to reduce the proliferation of cancer cells, induce apoptosis, enhance gap junction communication between cells, alter normal cell-cycle progression, and modulate androgen signaling pathways (19, 28). It has been noted that a reduction in testosterone levels is a key goal when treating PCa. In mouse models, it was shown that the expression of key testosterone metabolism genes or receptors is significantly reduced in response to a diet containing 248 nmol lycopene per gram of diet. This decrease in the expression of these genes suggests a reduction in androgen signaling in prostate. Out of the four phytochemicals reviewed here, lycopene has been studied in the largest number of human trials which are either completed or in progress. These trials highlight the chemopreventive and therapeutic properties of lycopene as well as its effects on cancer development. A web search using the terms “lycopene” and “cancer” on the accredited site clinicaltrials.gov revealed 21 studies out of which 18 are related to the role of lycopene in PCa prevention and treatment, either alone or in combination with other therapeutic regimens. According to several clinical trials, varying degrees of evidence exist in the ability of dietary lycopene and tomato products to reduce the risk of PCa. This evidence is measured clinically by the observation of increasing apoptotic cell proteins and also observations of various biological markers such as the level of PSA. In patients diagnosed with PCa who were given tomato sauce pasta entrees (30 mg lycopene/day) for three weeks, an increase in apoptotic cell death in comparison to placebo showed that tomato sauce consumption may suppress the progression of PCa. Apoptotic cell death and associated B-cell lymphoma-2 (BCL-2) and BCL2-associated X protein (BAX) proteins were markers in this case and showed a comparable increase (29). The inverse relationship between lycopene/tomato intake and the risk of PCa has been noted through observation of PSA response. This response is an outcome that is associated with risk of PCa and overall disease progression. The majority of clinical trials with a small number of enrolled patients have found an improved PSA response with intake of lycopene or tomato consumption indicating that consumption of lycopene and or tomato products can reduce the burden of PCa (26). However, a large multicenter trial, termed the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial, examined the relationship between tomato or lycopene intake and PCa risk among participants and concluded that greater lycopene/tomato product consumption does not protect from PCa development (30). Similar results were observed in a recent PCa prevention trial examining whether serum lycopene concentration was associated with PCa risk (31, 32). The results of several pre-clinical and clinical trials reveal tomato products and lycopene may have a role in prostate cancer prevention and treatment, however, further studies are warranted to specify the beneficial properties of lycopene and tomato products and their role in disease prevention and treatment.

Resveratrol

Resveratrol (3, 5, 4′-trihydroxystilbene; Figure 2), a naturally-occurring phytoalexin, is produced in plants by the enzyme stilbene in response to infection or other stress conditions. It is found in various dietary sources, including
red grapes, red wine, peanuts, and mulberries. Two isoforms of resveratrol have been isolated, trans- and cis-resveratrol (33). Numerous studies have demonstrated the ability of resveratrol to function as an antioxidant and a cardioprotective agent but recent research has focused on its potential to function as a chemopreventive agent after it was demonstrated to inhibit the carcinogenic process at multiple stages (34). These properties may play an important role in preventing or delaying the progression of PCa.

Studies employing PCa cell culture models have focused on elucidating the poorly understood mechanisms by which resveratrol inhibits the development or progression of PCa. The focal points of these studies have included the compound’s effect on cellular signal transduction pathways, specifically intracellular regulatory proteins, cellular metabolism, and androgen receptors. In addition, induction of apoptosis and management of the cell cycle have also been investigated. Studies in different PCa cell lines revealed that resveratrol effectively inhibits cell growth in general, causes disruption of transition between G1/S in DU145 and PC-3 cell lines, and induces apoptosis in androgen-responsive LNCaP human PCa cells. Resveratrol caused cell-cycle arrest and increased apoptotic cell death in DU145 and PC-3 cells by sensitizing them to ionizing radiation (35-38). Moreover, resveratrol sensitized various human cancer cell lines, including PCa, to such chemotherapeutic agents as doxorubicin, cytarabine (AraC), actinomycin D, taxol, and methotrexate by down-regulating survivin expression and increasing apoptosis (39, 40). An additional study that demonstrated reduced proliferation rates and increased apoptosis in PCa cells in a dose-and time-dependent manner showed variability in cell cycle proteins in LNCaP and PC-3 cells. For example, expressions of cyclin-D1, -E, and cyclin-dependent kinase-4 (CDK4), as well as cyclin-D1/CDK4 kinase activity were reduced by resveratrol only in LNCaP cells. In contrast, cyclin-B and CDK1 expression and cyclin B/CDK1 kinase activity were decreased in both cell lines in the presence of resveratrol. Moreover, the induction of apoptosis in LNCaP and PC-3 cells was mediated by activation of caspases-3 and -9 and a change in the ratio of BAX/BCL2 (41).

The effect of resveratrol on the phosphatase and tensin homolog (PTEN)/Protein Kinase B (AKT) pathway, one of the most commonly dysregulated pathways in PCa, has been studied extensively. PTEN is a tumor suppressor protein and a negative regulator of the cell survival phosphoinositide 3-kinase [PI3K]/AKT pathway whose function is often lost in PCa and other types of cancer. It was shown that resveratrol stimulates PTEN in C4-2 cells, a sub-clone of LNCaP cells (42). Further investigation comparing PTEN-transfected C4-2 cells and DU145 cells resulted in activation of PTEN promoter constructs in the former but not in the latter (42). The direct effect of resveratrol on phosphorylation of AKT, a protein kinase involved in cellular proliferation and survival, was determined by Western blot analysis and the results demonstrated a reduction in phosphorylation. Resveratrol was also shown to inhibit the phosphorylation of mammalian target of rapamycin (mTOR) and forkhead box O (FOXO), downstream proteins in the PI3K/AKT pathway. Furthermore, dephosphorylation of FOXO results in its translocation to the nucleus and activation (43). These alterations serve as potential components of the compound’s overall mechanism of action within PCa cells. Resveratrol has demonstrated a high-affinity for quinone reductase-2 (NQO2), a phase II detoxification enzyme that may contribute to gene control in PCa cells. NQO2 was shown to reduce the stability of cyclin-D1, as compared to NQO2-knockdown cells, in the presence of cyclohexamide, indicating that NQO2 may play a crucial role in down-regulating the proliferation pathway. Additionally, it was demonstrated that 10 μM of resveratrol was sufficient to down-regulate cyclin-D1 in NQO2-containing cells, but 50 μM of resveratrol were required to achieve an equivalent reduction in NQO2-knockdown cells (44). The effects of resveratrol on cyclin-D1 levels are of particular interest due to the commonality of cyclin-D1 overexpression in malignant cells and the resulting dysregulation of the G1 to S phase transition.

Cellular metabolism, frequently altered in cancer cells, may also serve as a target for induction of cell death by resveratrol. Glutamine expression is usually up-regulated in cancer cells to enhance production of citrate via α-ketoglutarate supplementation. The up-regulation of glutamine was demonstrated by treating C4-2 cells with U0126, a mitogen-activated protein kinase (MEK) 1 and 2 inhibitor, prior to treatment with resveratrol. Cells treated with U0126 were resistant to resveratrol-induced cell death. Additionally, U0126 demonstrated an ability to reduce mitochondrial membrane potential and ATP levels. Depletion of glutamine from the cell media provided a protective effect for the C4-2 cells for 60 h after the addition of resveratrol; cells observed in glutamine-free media did not display any morphological changes indicative of distress (45). These results demonstrate that the effects of resveratrol may, like
malignancies, depend on altering cellular metabolism to enhance or achieve cellular death. Androgens also play a critical role in prostatic carcinogenesis, and therefore the effects of resveratrol on the steroid hormones and their receptors are of interest. Resveratrol in the presence of an androgen receptor (AR) promoter induced a reduction in PSA mRNA levels and attenuation in AR transcription (46). Resveratrol also demonstrated an ability to inhibit the translocation of AR to the nucleus. By using wild-type AR and a ligand binding domain (LBD)-deleted mutant it was demonstrated that, unlike in estrogen receptors, the LBD binding site of AR does not play a role in the mechanism of action of resveratrol. Inhibition of AR transcriptional activity indicates that resveratrol impacts the receptor’s actions at a post-translational level (47).

Many studies employing in vivo models have attempted to reproduce the in vitro activities of resveratrol. The transgenic rat for adenocarcinoma of prostate (TRAP) model was used to assess the effects of resveratrol in vivo. Treatment with drinking water containing 50 μg/ml, 100 μg/ml, and 200 μg/ml of resveratrol, compared to normal drinking water resulted in a modest reduction in responses, including reduced prostatic neoplastic lesions in TRAP rats (48). While the in vitro reduction in AR protein expression was reproduced in TRAP rats, no significant difference in the incidence of adenocarcinoma or prostatic intraepithelial neoplasia (PIN) was demonstrated. The TRAP rat model revealed the translational effects of resveratrol from in vitro to in vivo; however, it failed to produce a clinically significant reduction in adenocarcinoma or PIN. In a PC-3M-MM2 xenografted severe combined immunodeficiency (SCID) mouse model of PCa, oral administration of resveratrol not only inhibited tumor growth but also reduced the incidence and number of metastatic lung lesions. The antitumor effects which were also observed in LNCaP and DU145 cells were attributed to reduced expression of miR-21 (only in xenograft tumors) and pAKT, and elevated programmed cell death protein 4 (PDCD4) (49). In a different study, Wang et al. reported that resveratrol exerts differential effects on in vitro and in vivo PCa models (50). It was shown that resveratrol exhibits growth-inhibitory effects on LNCaP cells through multiple mechanisms including steroid-dependent hormone pathways. However, in vivo studies employing LNCaP xenografts showed that resveratrol initially delayed tumor development, but further exposure resulted in the promotion of angiogenesis and inhibition of apoptosis (50). A recent study employing LAPC-4- and LNCaP-xenografted SCID mice which were on a diet supplemented with 50 mg/kg of resveratrol showed significantly worse survival of mice with LAPC-4 tumors, but unchanged survival for those with LNCaP tumors (51). In a different study which compared the chemopreventive effects of oral resveratrol and two of its analogs, trimethoxy-resveratrol (3M-Res) and piceatannol (PIC), in LNCaP-Luc-xenografts, it was found that two weeks of pre-treatment with the compounds diminished cell colonization, reduced tumor volume, and reduced tumor growth in the xenografts. The analogs 3M-Res and PIC demonstrated higher potency in inhibiting tumor progression compared to resveratrol alone (52).

Numerous clinical trials have demonstrated the safety of resveratrol in humans (53, 54). Although there are currently 17 human trials that have been completed or are in progress investigating the chemopreventive or therapeutic potential of resveratrol, no trial to date has examined specifically the effects of resveratrol on prostate cancer in humans.

**Capsaicin**

Capsaicin (Figure 3), a member of the vanilloid family is naturally present in a variety of foods of the human diet and is the element that is responsible for the hot burning sensation experienced upon physical contact with red and chili peppers (55, 56). Its structure is related to endogenous lipophillic agents such as N-arachidonoyl dopamine (NADA) (3). Capsaicin is known for its anti-inflammatory and analgesic effects and is a common ingredient in several creams and lotions used to treat arthritis and muscle pain (55, 56). Studies have found that capsaicin also has anti-proliferative and apoptotic effects on PCa cells. Its mechanism of action appears to be mediated via both transient receptor potential vanilloid-1 (TRPV-1) receptor-dependent and -independent means (56).

Capsaicin demonstrated in vitro growth inhibition and induction of apoptosis of androgen-independent PCa cells, PC3 and DU-145, through many receptor-independent actions. A study found that capsaicin (≥10 μM) reduced proliferation of PC3 and DU-145 cells. It induced apoptosis.
by increasing production of ROS, dissipating the inner mitochondrial transmembrane potential, and activating caspase-3 (55). The increase induced in ROS is due to the inhibition of nicotinamide adenine dinucleotide hydrogen (NADH)-oxidoreductase, a key enzyme of the electron transport chain which interacts with caspase-3 during the S phase and possibly the G0/G1 phase of the cell cycle. Capsaicin may also be considered a coenzyme Q antagonist (56). All of these properties contribute to alterations in cell permeability, stability and viability. It is important to note that capsaicin specifically targets tumors due to their increased energy requirements and activity (56). Researchers have also found that capsaicin works by generating and accumulating ceramide from sphingomyelin hydrolysis. The molecular target involved for this specific action has not been determined yet but tNOX, a cancer specific cell surface NADH oxidase, is a candidate (57). In addition, capsaicin has been found to induce endoplasmic reticulum (ER) stress in PC3 cells by inducing eukaryotic initiation factor 2α (eIF-2α) phosphorylation, activating transcription factor 4 (ATF4) expression, and Growth arrest- and DNA damage-inducible gene 153 (GADD153)/C/EBP homologous protein (CHOP) expression (55, 58). Researchers completed a microarray analysis on different genes involved in stress and apoptosis. PC3 cells were treated with 20 μM capsaicin for 72 h and then total mRNA was extracted. It was found that capsaicin induces phosphorylation of eIF-2α, which then activates GADD153/CHOP, an ER stress-regulated gene. This triggers a signal transduction network to induce cellular apoptosis. Blockade of GADD153/CHOP activity significantly reduced capsaicin-induced anti-proliferative actions (58). Additional studies indicate that capsaicin also reduces transcription of the AR and impairs activation of the PSA promoter/enhancer. The same study also demonstrated that capsaicin inhibits the nuclear translocation and activation of NF-kB (59). Another study examined the effects of capsaicin on TRPV6, which is involved in the proliferation of LNCaP cells. They found that it is not involved in the apoptotic process but is also not regulated in advanced PCa cells (55). Its expression correlates with Gleason scores and metastasis, so this may be a marker to look at in more detail. Conversely, other studies found that capsaicin has a profound anti-proliferative effect on prostate cancer cells, inducing the apoptosis of both AR-positive (LNCaP) and -negative (PC-3, DU145) PCa cell lines associated with an increase of p53, p21, and BAX. Capsaicin reduced expression of PSA and AR, and activation of NF-κB (59). Another in vitro study examined the growth of LNCaP cells in monoculture and co-culture with osteoblasts and the response to tNOX inhibitors. They found that capsaicin preferentially inhibits growth and tNOX activity of a number of carcinoma cell lines. They also examined the effect of capsaicin on LNCaP cells when combined with a green tea mixture, Capsobiol T. Capsobiol T, at a concentration of 50 μM, was more potent at inhibiting the viability of LNCaP cells grown in co-culture with osteoblasts compared to LNCaP cells grown in monoculture. This suggests that the combination of tea catechins with capsaicin has the potential to inhibit the growth of PCa cells in the bone environment, making it appropriate for further study in this particularly common metastatic site (62).

Studies have also demonstrated the in vivo effect of capsaicin on PC-3 xenografts in nude mice. Oral administration of capsaicin (5 mg/kg) three days a week resulted in tumors which were significantly smaller in size and volume compared to the control group (63). In a different study, capsaicin at 10 mM concentration was used to induce prostatitis in a rat model (64). This difference in concentration of capsaicin used suggests that there is a clinical therapeutic window which must be determined to achieve beneficial effects (65).

A literature search yielded only one epidemiological study, thus far, with capsaicin. Chili peppers are native to Nigeria and sub-Saharan Africa where the incidence of PCa
is very prevalent (constituting 24% of all cancer cases). It is believed that if Nigerians begin a proper diet (diet comprised with foods such as tomatoes, citrus fruits, soy beans, capsicum species and tea which have important phytochemicals) early in life that the incidence could be reduced, and the time-to-onset delayed (66). No human trials have been reported on efficacy or safety of capsaicin in the clinical setting. There is one case report of a 66-year-old man with a PSA relapse after radiotherapy for a T2b, Gleason score 7 adenocarcinoma of the prostate. He had a continual rise in PSA and discontinued medication therapy due to intolerable side-effects. Prior to initiation of capsaicin, the PSA level was doubling every four weeks. The patient started taking 2 ml of habanera chili sauce, containing 454 μg/ml capsaicin, one or two times per week. Upon testing the level of PSA (five consecutive time points), it was found that the doubling time increased from 4 to 7.3 weeks, with PSA calculated to be 13.26 ng/ml six months later. At this time, he began taking 2 ml of the sauce daily and within three months, the PSA level dropped to 11.3 ng/ml. The patient decided to stop taking the habanera sauce, and the PSA level rose to 13.57 ng/ml in a month and a half. He restarted the treatment increasing the amount of sauce to 15 ml daily, his PSA level was stable for nine more months before deciding to discontinue the treatment again. Within two months, his PSA level had reached 22.3 ng/ml. The patient never reported any side-effects from the intake of capsaicin. Based on this case, one may conclude that capsaicin has the potential to reduce and stabilize the PSA level in humans, and further clinical studies are needed to substantiate the role of capsaicin on PSA level (67).

In conclusion, capsaicin appears to have a role in the prevention and management of PCa. It is inexpensive and appears harmless when administered at appropriate concentrations, although there is still some controversy concerning its clinical use, some studies showing that it can induce pain and inflammation at higher concentrations (64). Some investigators even believe that capsaicin has the potential to be carcinogenic at certain concentrations (64, 67). Nonetheless, capsaicin may potentially be used for those patients who are refractory to hormonal therapy (59). This would be helpful as there is currently no successful therapy for this population group (67). There is much work to be done in understanding the role of capsaicin in PCA prevention and treatment and hence it is essential to conduct more preclinical and clinical studies to determine its safety and efficacy.

Curcumin

Curcumin (diferuloylmethane; Figure 4), a major yellow pigment of turmeric (Curcuma longa Linn.) is the most common spice in the Indian subcontinent, adding flavor and yellow color to foods. Turmeric also has a long history of medicinal use and has been used for centuries throughout Asia, especially in the Hindu, Ayurvedic and Chinese cultures, where it is used to treat a variety of inflammatory conditions and chronic diseases (68). Many of its traditional properties, including its anti-carcinogenic activity, have been validated in various cellular and animal models of diseases. Curcumin and its active metabolites, such as tetrahydrocurcumin, have been widely studied for their anti-inflammatory and anti-carcinogenic effects (69, 70).

Several in vitro studies employing different PCA cell lines have provided evidence that curcumin may inhibit the development of PCa at different stages (71-76). Early studies involving LNCaP and PC-3 cells showed that curcumin is a potent inhibitor of epidermal growth factor receptor (EGFR) signaling (77). Treatment of cells with curcumin suppressed both constitutive (DU145) and inducible (LNCaP) NF-κB activation, and potentiated TNF-induced apoptosis. These effects appeared to be mediated via down-regulation of BCL2 and BCL-XL and the activation of procaspase-3 and procaspase-8 (78). Curcumin arrests cell movements and alters cell shape more potently in PC-3 cells compared to LNCaP cells (79). Chendel et al. also demonstrated the ability of curcumin to inhibit TNF-α-mediated NF-κB activity, resulting in BCL2 protein down-regulation in PC-3 cells. This enhanced radiation-induced apoptosis by releasing cytochrome c and activating caspasas (80). Studies also demonstrated the ability of curcumin to trigger DNA damage and cell death of PCa cells. Curcumin induced the expression of various pro-apoptotic factors, including the p53 tumor suppressor protein, p53 up-regulated modulator of apoptosis (PUMA) and BIM (75, 76). The latter study (76) reported a reduced expression and activity of CC motif ligand-2 (CCL2) and matrix metalloproteinase-9 (MMP-9) proteolytic activity, causing reduced PC-3 cell adhesion, motility and invasion. In a recent study, it was shown that curcumin suppressed EGF-stimulated and heregulin-stimulated PC-3 cell invasion, as well as androgen-induced LNCaP cell invasion (81). Curcumin treatment also reduced MMP-9 activity and down-regulation of cellular matriptase, a membrane-anchored serine protease with oncogenic roles in
tumor formation and invasion (81). Another study demonstrated that curcumin up-regulated the mitogen-activated protein kinase phosphatase-5 (MAPK-5), subsequently reducing cytokine-induced p38-dependent pro-inflammatory changes in normal prostatic epithelial cells. In contrast, PCa cells (DU145, PC-3, LNCaP and LAPC-4) retained the ability to up-regulate MAPK-5 following curcumin treatment (82). A study of the oncprotein murine double minute (MDM2), a major ubiquitin E3 ligase of tumor suppressor p53, identified that curcumin down-regulates MDM2 independently of p53, especially in PC3 (p53null) cells. Curcumin reduced both protein and mRNA levels of MDM2 in a dose- and time-dependent manner, while enhancing the expression of the tumor suppressor p21WAF1/CIP1 (83). Along with other dietary agents, curcumin was shown to inhibit Hedgehog signaling and expression of the glioblastoma (GLI) protein in PCa cells (84). The role of curcumin on the wingless integration (WNT)/β-catenin signaling pathway also revealed a marked suppression of β-catenin and its targets implicated in cell-cycle regulation only in androgen-dependent cell lines; further analysis showed that levels of cyclin-D1 and cellular homolog of retroviral v-myc oncogene (c-MYC), the target gene of the β-catenin/T-cell factor transcriptional complex, were also decreased (85-87).

Pre-clinical studies employing various animal models provided evidence regarding the role of curcumin in preventing or reducing the development of prostate cancer. A curcumin-supplemented diet has been shown to inhibit tumor growth of DU145 xenografts in addition to reducing the number of metastatic nodules in lungs by inhibiting the activity of MMP-2 and MMP-9 (73). Curcumin also inhibited growth of LNCaP xenografts in nude mice by inducing apoptosis and inhibiting cell proliferation, and also sensitized these tumors to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-induced apoptosis. Moreover, in xenografted tumors, curcumin up-regulated the expression of TRAIL-R1, TRAIL-R2, BAX, BAK, p21/WAF1, and p27/KIP1, and inhibited the activation of NF-κB and its gene products such as cyclin-D1, vascular endothelial growth factor (VEGF), urokinase plasminogen activator (uPA), MMP-2, MMP-9, BCL2 and BCI-XL (88). Intaperitoneal administration of a combination of curcumin (3 μM) and phenethyl isothiocyanate (PEITC, 2.5 μM) inhibited well-established PC-3 tumor xenografts in nude mice more effectively than administration of PEITC or curcumin alone at higher doses (72). A further study conducted by the same group in the TRAMP model revealed that a diet supplemented with 2% curcumin or 0.05% PEITC, or a combination of 1% curcumin and 0.025% PEITC for a period of 10 or 16 weeks significantly reduced the incidence of the development of high-grade PIN and PCa, at least in part, by down-regulating the AKT pathway (89). In a different study, it was shown that curcumin may inhibit or delay the onset of PCa via the activation of protein kinase D1 (PKD1) and synergize conventional chemotherapy by activating PKD1 and inhibiting β-catenin transcriptional activity both in cell culture and xenograft models (86). In a recent study employing an orthotopic mouse model of hematogenous metastasis, it was shown that treatment with curcumin yielded statistically significant inhibition of the formation of lung metastases by disrupting the prometastatic feedback loop between NF-κB and CXCL1/2 (90). The antitumor properties and ability of curcumin to inhibit the proliferation of various tumor cells in culture, and its role in preventing carcinogen-induced cancer in rodents, the growth of human tumors in xenografts or orthotransplanted animal models, either alone or in combination with chemotherapeutic agents or radiation, has been well documented [reviewed (91)].

Results from preclinical models have shown that curcumin is rapidly metabolized, conjugated in the liver, and excreted in the feces, therefore having limited systemic bioavailability [reviewed (92)]. Several phase I and phase II clinical trials indicate that curcumin is quite safe and may exhibit therapeutic efficacy (91, 93). A phase I clinical trial which attempted to determine the toxicity of curcumin demonstrated that curcumin was well tolerated at dose levels up to 3600 mg for up to four months in patients with advanced colorectal cancer (94) and up to 8000 mg for up to three months in 25 patients with various precancerous lesions (95). These results hold promise, and interest in curcumin as a preventive and therapeutic agent continues to grow. A number of human trials investigating the chemopreventive or therapeutic potential of curcumin in various pre-malignant and cancer conditions have been completed or are underway, however, none of those trials specifically target PCa prevention or treatment. The data from all the pre-clinical studies clearly provide evidence for curcumin as a potential antitumor agent; however, more studies are required to identify the mechanism(s) through which its bioavailability may be enhanced and explore possible combination regimens for prevention and treatment of PCa.

Conclusion

The main focus of this article was to review recent advances in studies of the chemopreventive properties of four major phytochemicals against PCa development and summarize the in vitro and in vivo findings, including results of available and or completed clinical trials. A PubMed search was carried out with the search terms “lycopene and prostate cancer” and likewise with other phytochemicals. Based on the results from pre-clinical and epidemiological studies, it is evident that administration of naturally-occurring phytochemicals may have a protective effect against the
development of PCa. However, there are certain limitations, such as bioavailability and the concentration of the agent required to exert beneficial effects. Therefore, better epidemiological and controlled studies are warranted to confirm the exact role of these phytochemicals used alone and in combination with other agents in PCa prevention and treatment.

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