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Recent Progress on Nutraceutical Research in Prostate Cancer

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Abstract

Recently, nutraceuticals have received increasing attention as the agents for cancer prevention and supplement with conventional therapy. Prostate Cancer (PCa) is most frequently diagnosed cancer and second leading cause of cancer-related death in men in US. Growing evidences from epidemiological studies, *in vitro* experimental studies, animal studies, and clinical trials have shown that nutraceuticals could be very useful for the prevention and treatment of PCa. Several nutraceuticals including isoflavone, indole-3-carbinol, 3,3'-diindolylmethane, lycopene, (-)-epigallocatechin-3-gallate, and curcumin are known to down-regulate the signal transductions in AR, Akt, NF-κB, and other signal transduction pathways which are vital for the development of PCa and the progression of PCa from androgen-sensitive to castrate-resistant PCa. Therefore, nutraceutical treatment in combination with conventional therapeutics could achieve better treatment outcome in prostate cancer therapy. Interestingly, some nutraceuticals could regulate the function of cancer stem cell (CSC) related miRNAs and associated molecules, leading to the inhibition of prostatic CSCs which are responsible for drug-resistance, tumor progression, and recurrence of PCa. Hence, nutraceuticals may serve as powerful agents for the prevention of PCa progression and they could also be useful in combination with chemotherapeutics or radiotherapy. Such strategy could become a promising newer approach for the treatment of metastatic PCa with better treatment outcome by improving overall survival.

Keywords

nutraceuticals; prostate cancer; AR; Akt; NF-κB; cancer stem cell

1 Introduction

Although the incidence of prostate cancer (PCa) changed from 2005 with a decreasing trend by 1.9% per year, prostate cancer is still one of the most frequently diagnosed cancers in men in US and European countries [1]. American Cancer Society has estimated 238,590 new cases and 29,720 deaths of PCa in 2013 [1]. However, the incidences of PCa in Asian

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countries are much lower compared to US. One major reason that have been considered important for the low incidence of PCa in Asian countries is that peoples in Asian countries consume large amount of vegetables, fruits and other naturally occurring components in their diets [2, 3]. The bioactive dietary constituents in Asian diets have been considered as chemopreventive components which could block, delay, or reverse the process of prostatic carcinogenesis.

Furthermore, experimental studies have shown that these dietary chemopreventive components could also help to inhibit cancer cell growth, invasion, and metastasis. Therefore, these components have also been considered as nutraceuticals having therapeutic effects on prostate cancer. Nutraceutical from the words “nutrition” and “pharmaceutical” was coined by Dr. Stephen L. DeFelice in 1979 [4]. He defined the nutraceutical as “a food, or parts of food that provides medical or health benefits, including the prevention and/or treatment of a disease”. The investigated nutraceuticals having inhibitory effects on PCa include isoflavone, 3,3’-indole-3-carbinol, diindolylmethane , lycopene, (−)-epigallocatechin-3-gallate, curcumin, etc.

Isoflavones largely exist in Leguminosae family. Soybean is the major source of isoflavones. Genistein is the major soy isoflavone found in soybeans and soy products. Indole-3-carbinol (I3C) is derived from glucosinolates in vegetables of Cruciferae family including broccoli. In human stomach, I3C condenses to form 3,3’-diindolylmethane (DIM). Lycopene exist in tomatoes and is responsible for the red color of tomato. Tomatoes and tomato products are excellent sources of lycopene. Epigallocatechin-3-gallate (EGCG) is produced from green tea. Green tea contains several catechins including EGCG which is the most potent constituent for chemoprevention. Curcumin is derived from Curcuma longa. Curcumin shows strong activities in anti-inflammation and chemoprevention. All of these natural agents possess anti-oxidant feature, which could be responsible for the anti-carcinogenic activity of these agents (Figure 1). Moreover, these agents also show anti-cancer effects through regulation of many important cell signaling pathways including AR, Akt, and NF-κB which are critical for the development and progression of PCa. Therefore, the nutraceuticals with anti-cancer and non-toxic features could be used as chemopreventive agents for the prevention of PCa or in combination with conventional therapies for the treatment of PCa, especially hormone refractory and metastatic PCa.

2 Nutraceuticals and reduced risk of PCa

Because of the high incidence of PCa in US, the chemoprevention of PCa is an important strategy for fighting against PCa. Although two drugs, finasteride and dutasteride which reduce androgen production, have been found to lower the risk of PCa with potential side effects as shown in clinical trials, a committee to the FDA has recommended against the approval for both drugs for the prevention of PCa based on risk-benefit analyses. Therefore, nutraceuticals with non-toxic feature as food supplements may be excellent strategies for the prevention of PCa.

Indeed, high consumption of foods from which nutraceuticals are produced could lower the risk of PCa development. Epidemiological studies have shown that Asian countries have low

rates of PCa incidence and high rates of soy consumption [3]. It has been found that consumption of soy foods is associated with lower risk of PCa in men; however, the protection could be dependent on the type and quantity of soy foods consumed [5]. Frequent intake of soymilk has been connected with a significant decrease in PCa risk [6]. In a population-based prospective study in 43,509 Japanese men, consumption of soy product and isoflavone was found to be associated with a reduced risk of localized prostate cancer [7]. In a case-control study in Chinese men, similar results were observed showing decreased risk of PCa associated with high consumption of soy foods and isoflavones [8]. In addition, the results from two case-controlled studies of meta-analysis also showed that intake of higher dose of isoflavone genistein was associated with the lower risk of PCa with one statistical significance and another with marginal significance [3], suggesting the protective effects of isoflavone against PCa.

Moreover, a multicenter case-control study of African-American, white, Japanese, and Chinese men has been performed to determine the relationship between risk of PCa and vegetables, fruits, and legumes consumption. It was found that legumes not limited to soy products could prevent the development of PCa [2]. Consumption of yellow-orange and cruciferous vegetables was also inversely related to risk of PCa, especially advanced PCa [2]. Similar to these results, other studies also showed a significantly reduced risk of PCa in the group with consumption of vegetables, particularly cruciferous vegetables [9, 10] from which I3C and DIM are produced. Furthermore, cruciferous vegetable also showed its inhibitory effects on the progression of PCa. In a study focused on finding relationship between vegetable/fruit intake and prostate cancer outcomes, post-diagnostic cruciferous vegetable intake significantly decreased the risk of PCa progression [11]. Similarly, another study also showed that the risk of extra-prostatic PCa including stage III or IV was decreased with increasing consumption of cruciferous vegetables, especially broccoli [12]. These results suggest that I3C and DIM obtained from cruciferous vegetables could protect against PCa development and progression.

The reported effects of tomato on PCa are still controversial. In as early as 1999, a prospective analysis showed that increased consumption of tomato products and other lycopene-containing foods could inhibit PCa progression or occurrence [13]. From then on, more studies have investigated the effects of lycopene from tomatoes on the risk of PCa. In a study including 65 patients with PCa and 132 cancer-free controls, level of plasma lycopene was measured and bivariate/multivariate analyses were conducted. A significantly inverse association of PCa with plasma concentrations of lycopene was observed [14], suggesting the protective effects of lycopene against PCa. Several other studies also showed that frequent consumption of tomato products or lycopene intake was associated with a lower risk of PCa [15] and that tomato products could prevent PCa; however, this effect could be modest and restricted to high consumption of tomato [16]. Opposite results were also reported in a large prospective study showing that no association was observed between serum lycopene and PCa [17], suggesting that lycopene or tomato may not be effective for the prevention of PCa. Nevertheless, more recent studies support that higher intake of tomato sauce or other tomato products have a protective effect against PCa [18, 19]. In summary, although there may exist some controversy as to the health benefit of lycopene

against PCa, the majority of studies suggest that lycopene could serve as a chemopreventive agents against the development and progression of PCa.

To investigate the relationship between green tea, from which EGCG is produced, and risk of PCa, a case-control study has been conducted which showed that the risk of PCa was decreased with increasing frequency, duration and quantity of consumption of green tea [20]. In a prospective study, 49,920 Japanese men aged 40–69 years were included starting in 1990 and ending in 2004. It was found that green tea consumption was not correlated with localized PCa; however, the intake of green tea was correlated with a dose-dependent reduction of risk of advanced PCa [21]. In an earlier report including smaller group of PCa patients, opposite results were reported showing no association between green tea and PCa risk in Japanese men [22], which could be partly due to the smaller sample size. A meta-analysis supported that green tea but not black tea could exert protective effect against PCa, especially in Asian populations [23]. Moreover, a case-control study was conducted using combination of tea and lycopene. The results showed that the protective effect of green tea or lycopene was significant and that the protective effect from consumption of both tea and lycopene was synergistic [24], suggesting that combinational use of nutraceuticals could be potent and promising strategy for the prevention of PCa.

Although there is no report on the relationship between risk of PCa and consumption of turmeric or ginger from which curcumin is produced, curcumin have still received much attention in PCa prevention because of its anti-oxidant and anti-inflammatory effects. A randomized, double-blind, placebo-controlled clinical trial was conducted using isoflavones and curcumin in patients who had prostate biopsy because of elevated PSA but had neither cancer nor prostatic intraepithelial neoplasia [3]. The patients were grouped based on their PSA level. After 6 months of administration of isoflavone and curcumin, PSA level in high baseline PSA group was significantly decreased compared to placebo administration, demonstrating preventive effects of isoflavone and curcumin on PCa.

It is important to note that the incidence of PCa in Asian countries is increasing although it is still low compared to Western countries. One reason for this increase could be partly due to changes in life style especially because the people in Asian countries are adopting Westernized life style in recent years [3]. Moreover, it was found that the immigrants from Asian countries to US have higher incidence of PCa compared to the native Asians [3, 25]. These results suggest that dietary factors influence the incidence of PCa and that nutraceuticals could prevent the development of PCa through their anti-oxidant and anti-carcinogenic activity (Figure 1).

3 The role of nutraceuticals in the inhibition of PCa

It is well known that most patients with PCa progress from androgen-dependent status to castrate-resistant (hormone resistant) PCa after failure of androgen-deprivation therapy. Tumor invasion and metastasis occur subsequently after castrate-resistant PCa which contribute to high mortality of PCa. To improve the efficacy of PCa therapy and stop PCa progression, combination treatments using combined therapeutics with distinct targets and low toxicity are believed to be more promising for the treatment of PCa. Therefore, design

of combination treatment strategies targeting important signaling in PCa is critical for the successful treatment of PCa. Growing evidences suggest that the mechanisms involved in the progression of PCa include the deregulation of androgen receptor (AR), Akt, NF-κB, and other signaling [26–29]. Among them, AR signaling is more critical for the development of PCa and the progression of androgen-dependent PCa to castrate-resistant PCa [28, 29]. The nutraceuticals including isoflavone, I3C, DIM, lycopene, EGCG, and curcumin have been found to have the inhibitory effects on the signaling of AR, Akt, and NF-κB in PCa (Figure 2). Moreover, some nutraceuticals could target signaling that are critical for prostate cancer stem cells (CSCs) which are responsible for the drug resistance, tumor progression, and recurrence of PCa. Therefore, these nutraceuticals combined with conventional therapies could show better anti-PCa activity by synergic action. The effects of these nutraceuticals on PCa cells and tumors in experimental studies and clinical trials are reviewed below.

3.1 Isoflavone

Soy isoflavones include genistein, daidzein, and glycitein. Among them, genistein has been extensively investigated for inhibition of PCa. Isoflavone genistein exerts its effects by regulation of multiple signaling pathways. We and other investigators have found that isoflavone could significantly inhibit the activation of AR, Akt, and NF-κB in PCa cells and interrupt the crosstalk between these three signaling pathways *in vitro* [30–35]. By *in vivo* studies, isoflavone has been found to inhibit prostate tumor growth through inhibition of AR activation and AR downstream gene expression [36, 37]. Moreover, isoflavone could inhibit the growth of Epithelial-to-Mesenchymal Transition (EMT) type of PCa cells through inhibiting Wnt signaling [38] and decrease the stemness properties of PCa cells though suppression of Hedgehog signaling [39], suggesting that isoflavone could eliminate prostatic EMT-type cells and CSCs which are the major source for drug resistance, invasion, and metastasis of PCa.

Isoflavone could also increase anti-cancer activity of chemotherapeutic agents in PCa cells. We have found that genistein significantly enhanced growth inhibition and apoptosis triggered by docetaxel in PCa cells [34]. The molecular mechanism underlying the enhanced inhibition of PCa cells in the combination treatment was found to be due to the inactivation of NF-κB. Other investigators also reported that isoflavone genistein could synergistically increase the anti-cancer effects of different chemotherapeutics and radiotherapy on PCa cells through differential mechanisms [38, 40–42]. We and other investigators found that isoflavone could also potentiate the efficacy of radiotherapy through the inactivation of NF-κB and HIF-1 signaling in PCa cells [43, 44]. These results suggest that isoflavone genistein could be a promising nutraceutical for combination treatment with other therapeutics for the treatment of PCa.

Several phase I and phase II clinical trials have been conducted for assessing the toxicity and pharmacokinetics of isoflavones in healthy men and patients with PCa [45–50]. It was revealed that the high dose of isoflavone administration only caused minimal clinical toxicity [45, 46]. The bioavailability of isoflavones has also been detected. The maximum plasma genistein concentration after oral administration could reach up to 27.4 μM which is

the concentration showing anti-cancer activity *in vitro* [45, 50], suggesting that isoflavone is a safe and bioavailable nutraceutical.

More importantly, isoflavone administration could also alter the levels of serum testosterone and PSA in PCa patients. A clinical trial has been performed to determine the effectiveness of isoflavone administration in patients with early stage of PCa [47]. The results showed that serum free testosterone and PSA were reduced in the isoflavone group compared to the placebo group. Nineteen percent of patients in the isoflavone group had reduced total PSA by two points or more [47], suggesting that isoflavone could decrease the production of testosterone and, in turn, reduce the expression of PSA. We also performed a phase II trial to test the efficacy of isoflavone in patients with PSA recurrent prostate cancer after prior therapy. We found that PSA was increased up to 56% per year before the study, and it was only increased up to 20% per year in the study period after isoflavone intervention [51]. The slope of PSA after study entry was significantly lower than that before study entry in 6 patients, suggesting that isoflavone has inhibitory effects on recurrent PCa [51]. Based on the results from experimental studies, more phase I/II trials are being conducted by using isoflavone alone or in combination with conventional therapy or other nutraceuticals in the prevention of PCa or treatment of PCa at different stages of PCa progression (Table 1). The results from these clinical trials will reveal the true value of isoflavone in PCa prevention and treatment.

3.2 I3C and DIM

In experimental studies, I3C and DIM have shown their potent inhibitory effects on the growth of PCa cells. By molecular mechanistic studies, we and other investigators have found that I3C and DIM could inhibit the activation of AR, Akt, and NF-κB signaling in PCa [52–57], similar to the effects of isoflavone. However, DIM showed much stronger inhibitory effects on the expression of AR and the activation of AR signaling. I3C and DIM have also shown their ability to down-regulate IGF-1/Akt signaling which also crosstalk with AR signaling [55, 58]. In addition, I3C and DIM could regulate the signal transduction in uPA, Par-4, HDAC, AMPK, c-Met, and Wnt signaling [55, 59–64], resulting in the inhibition of PCa cell proliferation. More importantly, we found that DIM increased the expression level of let-7 and, in turn, suppressed the expression of its target EZH2, causing the down-regulation of CSC signature in PCa cells [65]. These results suggest that DIM could have clinical impact for the inhibition of PCa cells and prostatic CSCs.

We and other investigators found that I3C or DIM combined with chemotherapeutics or other nutraceuticals could decrease the proliferation of PCa cells more effectively than monotreatment in PCa [66–69]. It was found that I3C could increase the anti-cancer efficacy of cisplatin in PC-3 PCa cells [67]. I3C could also induce the expressions of BRCA1 and BRCA2 in PCa cells, providing tumor suppressive proteins to inhibit PCa growth [66]. Moreover, combination of I3C and isoflavone caused much higher expression of BRCA1 and BRCA2, suggesting the synergic effects of these nutraceuticals. Furthermore, DIM could enhance docetaxel-induced apoptotic cell death of PCa cells though the inhibition of survivin, AR, and NF-κB signaling [70], suggesting that DIM could be used in combination treatment with conventional chemotherapeutic agents for better treatment of PCa.

BioResponse 3,3'-diindolylmethane (BR-DIM), which is a DIM with higher bioavailability, has been evaluated in several clinical trials. A phase I clinical trial has been conducted to determine the safety, tolerability, and pharmacokinetics of BR-DIM in healthy men and women [71]. The doses administered were 50, 100, 150, 200, and 300 mg. No adverse effects related to BR-DIM were found at doses up to 200 mg. At the dose of 300 mg, only minimal toxicity was found. Therefore, the clinical trial demonstrates that BR-DIM is well tolerated. We have also conducted a dose-escalation, phase I clinical study in using BR-DIM to determine the maximum tolerated dose, toxicity profile, and pharmacokinetics of BR-DIM, and to assess its effects on serum PSA and quality of life in patients with castrate-resistant, non-metastatic, PSA relapse PCa [72]. We also observed minimal toxicity consistent with previous report. The maximum tolerated dose was 300 mg and the recommended phase II dose of BR-DIM was 225 mg twice daily which was non-toxic. One patient with 225 mg BR-DIM experienced a 50% PSA decline. Another patient had PSA stabilization. Ten patients had an initial deceleration of their PSA rise (decrease in slope), suggesting that modest efficacy was obtained [72]. In our phase II clinical trial, we found that the expression of let-7 family was lost and the level of EZH2 was up-regulated in PCa tissues, especially in higher Gleason grade PCa, suggesting that loss of let-7 and gain of EZH2 contribute to PCa aggressiveness [65]. BR-DIM intervention significantly increased the expression of let-7 family and down-regulated EZH2 expression in PCa tissue, suggesting the clinical impact of BR-DIM for the treatment of PCa. Recently, more clinical trials are being conducted using I3C or DIM in patients with different stages of PCa to test the inhibitory effects of DIM on PCa growth and PSA recurrence (Table 1).

3.3 Lycopene

Lycopene is a potent antioxidant. It has been found that lycopene could exert its anti-oxidant and anti-inflammatory effects through the regulation of NF-κB activation [73]. In PCa, lycopene has been found to inhibit cell growth and induce apoptosis through the modulation of multiple signaling pathways. Experimental studies have revealed that lycopene could down-regulate the expression of Ras, NF-κB, cyclin D, p-Akt, and Bcl-2, and up-regulate the expression of p21, p27, p53, and Bax in PCa cells [74], demonstrating that lycopene modulates the signaling that controls cell growth and apoptotic cell death pathways. Lycopene also inhibited IGF-I signal transduction in normal prostate epithelial cells through down-regulation of DHT-stimulated IGF-1 production [75]. Lycopene also showed the inhibitory effects on AR signaling in PCa. One study showed that lycopene could inhibit the activity of AR gene element and the AR expression in a dose-dependent manner [76]. Consistent with AR inhibition, the suppression of PSA expression by lycopene was also observed, suggesting that dietary lycopene could have clinical impact in PCa.

Indeed, lycopene has been found to potentiate the anti-tumor activity of docetaxel in PCa *in vitro* and *in vivo* [77]. The down-regulation of insulin-like growth factor 1 receptor (IGF-1R) activation was found in lycopene treated PCa cells. Lycopene enhanced anti-cancer effect of docetaxel through the inhibition of IGF signaling transduction by down-regulation of IGF-1R, suppression of IGF stimulation, and up-regulation of IGF-BP3, leading to the inhibition of Akt and survivin signaling. In animal study, docetaxel treatment combined with lycopene resulted in 38% increase in tumor regression compared with

docetaxel alone [77]. These results suggest that lycopene and docetaxel combination treatment could be a promising therapeutic approach for the treatment of PCa.

Several clinical trials have been conducted to investigate the effects of lycopene in PCa patients. In a phase II clinical trial, the safety and effect of lycopene at different concentrations have been tested in patients with localized PCa. The patients were supplemented with lycopene during the time of biopsy to prostatectomy. It was found that the plasma lycopene increased while the level of serum free testosterone decreased after lycopene administration [78], suggesting that lycopene could suppress PSA expression. Indeed, lycopene supplements did reduce the expression of PSA in localized PCa [79]. Another phase II clinical trial showed that plasma PSA level was decreased by 18% in lycopene group whereas the PSA was increased by 14% in the control group [79], suggesting the promising effect of lycopene on PCa treatment. Moreover, lycopene intervention group showed lower mean plasma PSA and smaller PCa tumors compared to control group [80]. These results demonstrate the beneficial value of lycopene in the treatment of PCa; however, further definitive therapeutic trial is warranted.

Furthermore, lycopene could show stronger anti-PCa effects when combined with other nutraceuticals. A clinical trial was conducted to test the effects of lycopene combined with soy protein in patients with recurring PCa and rising PSA [81]. The results showed that no grade 2 through grade 4 toxicity was observed and that both serum lycopene and isoflavone were increased. Importantly, serum PSA was decreased and mean serum VEGF was reduced after lycopene and soy protein supplementation [81]. These results indicate that consumptions of tomato and soy products could have beneficial effects for the prevention and treatment of PCa. Recently, more clinical trials are being designed and conducted to investigate the antioxidant and anti-cancer effects of lycopene on the prevention of PCa and the treatment of different stages of PCa (Table 1).

3.4 EGCG

Similar to other nutraceuticals, EGCG also exerts anti-oxidant and anti-tumor effects through the regulation of multiple signaling pathways. Experimental studies have shown that EGCG could slow PCa cell proliferation and induce apoptotic cell death mediated through the stabilization of p53 and down-regulation of NF-κB, leading to decreased expression of Bcl-2 and increased expression of $p21^{WAF1}$ and Bax [82]. EGCG could also inactivate c-Jun, NF-κB, ERK1/2, and p38 signaling, resulting in decreased expression of MMP-2 and MMP-9 in PCa cells [83]. Moreover, EGCG also inactivated PI3K/Akt and c-Met signaling, causing the inhibition of PCa cell growth [63, 84]. Furthermore, the molecular mechanistic studies revealed that EGCG could significantly inhibit the expression, transactivation, and nuclear translocation of AR and, in turn, suppress the expression of AR target gene PSA, leading to the inhibition of PCa cell proliferation [85, 86]. In addition, EGCG could also regulate histone acetyl-transferase activity, resulting in the suppression of androgen-mediated AR activation and AR target gene transcription [87]. Therefore, EGCG targets AR, Akt, and NF-κB signaling, which are important signaling pathways in PCa progression, in addition to other signaling such as p53 and MAPK signaling.

More importantly, EGCG could also potentiate the anti-tumor activities of conventional chemotherapeutic agents in PCa. It was found that EGCG combined with lower doses of doxorubicin could exert synergistic effects on the reduction of colony-forming capacity of PCa cells *in vitro* and prostate tumor growth *in vivo* in an animal model [88]. EGCG combined with paclitaxel or docetaxel also showed a synergistic activity in the suppression of PCa cell proliferation *in vitro* and *in vivo* [89]. Combination treatment with EGCG and paclitaxel or docetaxel significantly increased the expression of p53, p73, p21, and caspase 3, resulting in the induction of apoptotic cell death. The animal study showed that the combination treatment significantly inhibited the growth of PCa tumors implanted, and also blocked metastases after intravenous administration of PCa cells in the animals [89]. Experimental studies have also found that EGCG could sensitize PCa cells to TRAIL-mediated apoptosis, and could also synergistically down-regulate the levels of VEGF, uPA, angiopoietin, and MMPs which are related to angiogenesis and metastasis [90]. Moreover, EGCG treatment combined with COX-2 inhibitors *in vitro* showed synergistic inhibition of PCa cell growth and induction of apoptotic cell death which was mediated through down-regulation of NF-κB and up-regulation of Bax, pro-caspase-6, and pro-caspase-9 [91]. Animal study showed that EGCG treatment combined with celecoxib, a COX-2 inhibitor, caused enhanced tumor growth inhibition with increased expression of IGFBP-3 and decreased expression of IGF-1 and PSA [91]. All of these results suggest that EGCG could synergistically potentiate anti-tumor activity of chemotherapeutic agents in PCa.

Several clinical trials were conducted to determine the bioavailability, safety and effects of EGCG in PCa patients. In a clinical study testing the metabolism and bioactivity of EGCG in human prostate tissue, patients with localized PCa consumed six cups of green tea daily for 3 to 6 weeks before radical prostatectomy [92]. The EGCG and methylated EGCG were identified in prostatectomy tissue from patients consuming green tea and the majority of EGCG was not conjugated, suggesting the bioavailability of EGCG in the prostate tissue. EGCG was not detectable in prostate tissue or urine from patients consuming water [92]. These results suggest that a short-term green tea intervention could increase the level of EGCG in prostate tissues. Another clinical study was conducted to determine the effects of EGCG in green tea on serum biomarkers in patients with PCa [93]. The PCa patients scheduled for radical prostatectomy were administrated with Polyphenon E containing 800 mg of EGCG until undergoing radical prostatectomy. No increased liver enzyme in serum was observed, suggesting no toxicity of EGCG. Importantly, they found that serum levels of PSA, HGF, and VEGF in patients with PCa were reduced after administration of EGCG [93], suggesting the beneficial effects of EGCG for the supplementary treatment of PCa. Recently, more clinical trials are being conducted to investigate the inhibitory effects of EGCG on the growth of PCa in the patients with high-grade prostatic intraepithelial neoplasia or different stages of PCa (Table 1). Moreover, the effects of EGCG combined with lycopene or fish oil on the prevention or treatment of PCa are also being tested in clinical trials (Table1).

3.5 Curcumin

Curcumin also exerts strong anti-oxidant and anti-tumor effects through regulation of signal transduction in multiple signaling pathways. Curcumin showed very strong inhibitory effect

on NF-κB pathway. It was found that curcumin could inhibit both constitutive and inducible activation of NF-κB and enhance TNFα-induced apoptosis associated with decreased expression of Bcl-2 and Bcl-xL and the increased expression of procaspase-3 and procaspase-8 [94]. Curcumin also showed the inhibitory effect on the activation of Akt in PCa cells [95]. Moreover, a curcumin analogue, 4-hydroxy-3-methoxybenzoic acid methyl ester (HMBME), has been found to decrease the level of activated Akt and suppress the Akt kinase activity in PCa cells [96]. In addition, HMBME treatment also inhibited the DNA binding activity, transcriptional activity, and expression of NF-κB, suggesting the potent effects of curcumin analogue on Akt/NF-κB signaling. An experimental study found that curcumin could inhibit the activation and expression of AR, AP-1, NF-κB, and CREB in PCa cells [97]. Curcumin could also suppress the PSA expression stimulated by the activation of AR and interlukin-6 in PCa cells [98]. Furthermore, we found that CDF, a synthetic analogue of curcumin, could inhibit AR expression and interrupt the signal transduction in the AR/TMPRSS2-ERG/Wnt signaling network, leading to the inactivation of Wnt signaling and the inhibition of PCa cell invasion [56]. Similar results were also reported showing that curcumin could interrupt the interaction between AR and Wnt/β-catenin signaling pathways in PCa cells [99]. All these reports suggest the potent inhibitory effects of curcumin or its synthetic analogue on PCa.

More importantly, several studies have demonstrated that curcumin could potentiate the anti-tumor efficacy of chemotherapeutics in PCa cells. In combination with taxane, curcumin treatment decreased resistance of PCa cells to taxane and increased the inhibitory efficacy of taxane in hormone-refractory PCa cells, suggesting that the combination treatment with curcumin and taxane could have beneficial effects for the treatment of hormone-refractory PCa [100]. Curcumin treatment also enhanced TRAIL-induced apoptosis in PCa cells *in vitro* [101] and sensitized TRAIL-resistant xenograft of PCa, suggesting that the combination treatment with curcumin and TRAIL could have better clinical efficacy in the treatment of PCa [102]. Moreover, curcumin could also sensitize PCa cells to radiotherapy. In PCa cells, radiation could up-regulate the expression of TNFα and, in turn, induce NF-κB activity, leading to the induction of Bcl-2 protein and resistance to radiation. Importantly, curcumin in combination with radiation therapy caused significant inhibition of TNFα-induced NF-κB activity with down-regulation of Bcl-2, resulting in significant induction of apoptosis [103]. These results indicate that the combination of curcumin with conventional therapeutics could be an effective therapeutic approach for the treatment of PCa with drug or radiation resistance.

Chronic inflammation in prostate could promote the development of PCa and induce an elevated PSA in the prostate gland. A clinical trial has been designed to test whether combination treatment with curcumin and isoflavone could improve the PSA and prevent the development of PCa by anti-inflammatory effects of curcumin and isoflavone in patients who had high PSA and underwent prostate biopsies, but were not found to have PCa [104]. The results showed that the levels of PSA were significantly reduced by the combination treatment of curcumin and isoflavones in patients with high PSA expression, suggesting that curcumin synergizes with isoflavones to suppress PSA expression in PCa through the anti-AR properties of these nutraceuticals. Thus far, no promising data reported from clinical

trials documenting the inhibitory effects of curcumin on PCa. One reason for the limitation of curcumin usage in the clinical trial is partly due to its poor bioavailability. Therefore, it is important to synthesize curcumin analogues or nanoparticles with high bioavailability and efficacy so that they can be used in future clinical trials for the prevention or treatment of PCa.

4 Conclusion and perspective

In conclusion, nutraceuticals have recently received much attention as the agents for cancer prevention and also adjuncts to conventional therapy. Growing evidence from epidemiological studies, *in vitro* and *in vivo* experimental studies, and limited clinical trials demonstrate that nutraceuticals may be promising agents for the prevention and treatment of PCa. Several nutraceuticals such as isoflavone, DIM, I3C, lycopene, EGCG, and curcumin are known to regulate multiple cell signal transductions in the AR, Akt, NF-κB, and other signaling pathways which are vital for the development of PCa and the progression of PCa from androgen-sensitive to castrate-resistant PCa. Therefore, nutraceuticals could be used in combination treatment with conventional therapeutics for better treatment of PCa. Interestingly, some nutraceuticals have been found to regulate CSC-related miRNAs and associated molecules, leading to the inhibition of prostatic CSCs which are responsible for PCa drug-resistance, progression, and recurrence (Figure 2). Hence, using nutraceuticals in combination with chemotherapeutics or radiotherapy may be a promising therapeutic approach for the treatment of PCa, especially for castrate-resistance metastatic PCa. However, the limitation of utilizing nutraceuticals in the clinical setting is because of their low bioavailability, at least, for some nutraceuticals in humans. Therefore, synthetic analogues or nanoparticle formulation of nutraceuticals are needed for the treatment of PCa patients. Further in-depth *in vitro* and *in vivo* mechanistic studies and clinical trials are also needed to test the value of nutraceuticals in the prevention and/or treatment of PCa, especially metastatic PCa for which newer innovative treatment is warranted.

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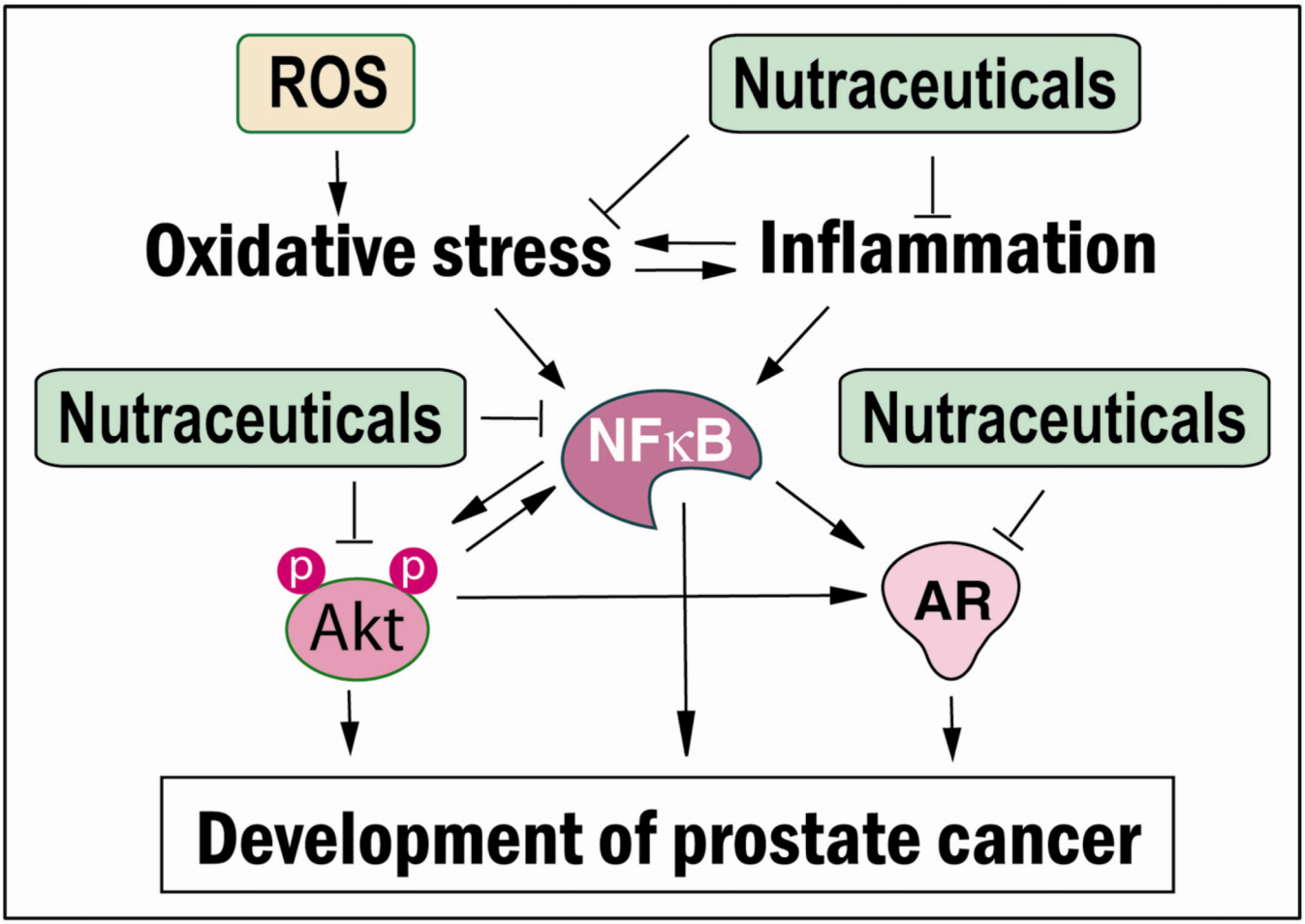

Figure 1.
The role of nutraceuticals in the prevention of PCa.

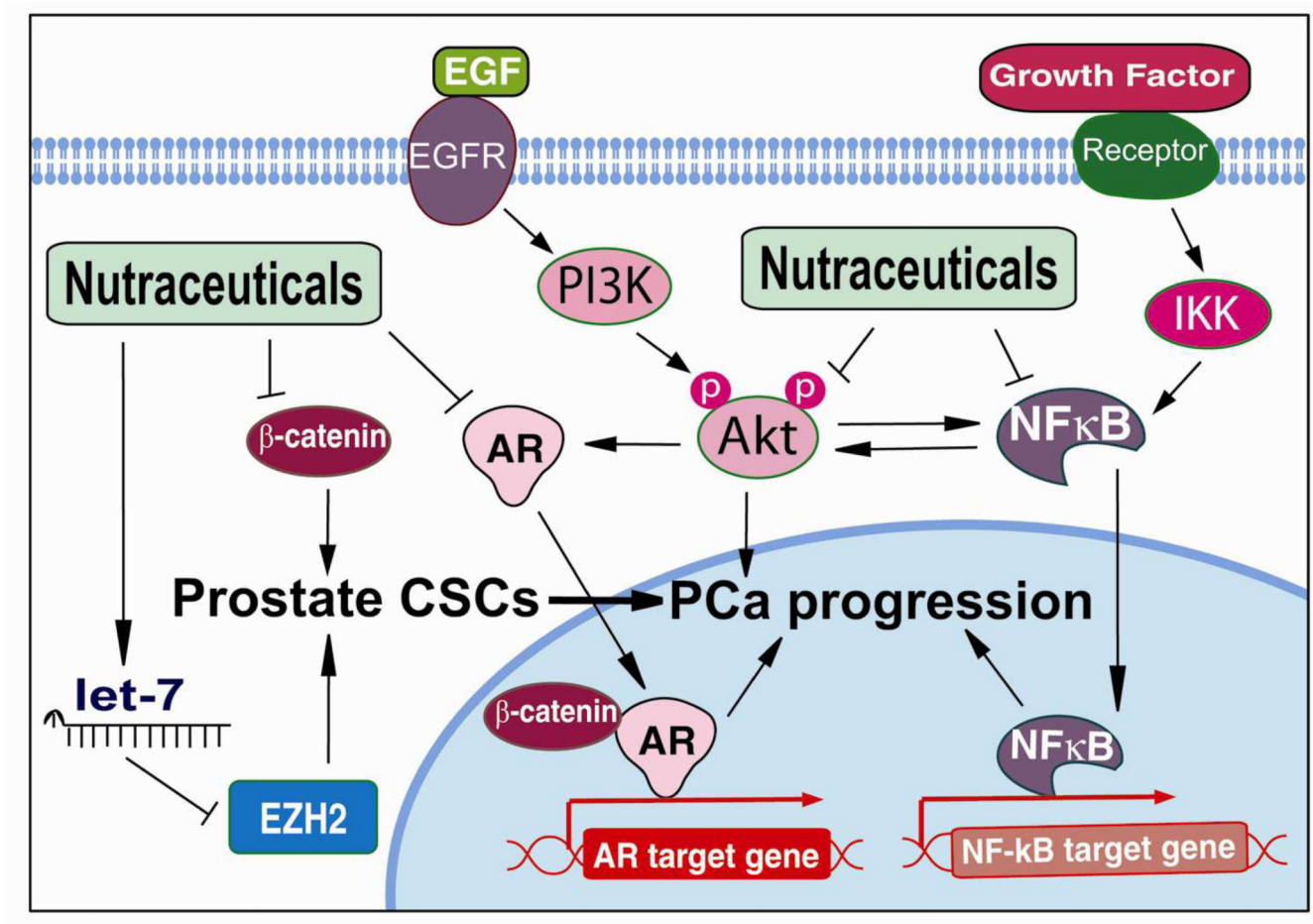

Figure 2.

The major signal transductions in PCa and the effects of nutraceuticals on the signaling pathways in the treatment of PCa.

Table 1

Ongoing clinical trials using nutraceuticals in the prevention or treatment of PCa

NCT Number	Title
Isoflavone	
NCT01682941	Soy Isoflavones in Treating Patients With Recurrent Prostate Cancer or Rising Prostate-Specific Antigen
NCT00596895	Isoflavone in Prostate-specific Antigen Recurrent Prostate Cancer
NCT01036321	Phase II Clinical Trial of Purified Isoflavones in Prostate Cancer: Comparing Safety, Effectiveness
NCT00042731	Isoflavones & Lycopene in Localized Prostate Ca:Prior to Radical Prostatectomy
NCT00617617	The Specific Role of Isoflavones in Reducing Prostate Cancer Risk
NCT00861588	Effects of Isoflavone in Patients With Watchful Waiting Benign Prostate Hyperplasia
NCT00078923	Soy Isoflavones in Treating Patients Who Are Undergoing Radical Prostatectomy for Stage I or Stage II PCa
NCT00243048	Isoflavones and Radiation Therapy in Treating Patients With Localized Prostate Cancer
NCT00200824	Effects of Soy Compounds on Breast Cancer, Prostate Cancer, and Bone Health
NCT00255125	Role of Soy Supplementation in Prostate Cancer Development
NCT00245518	Effect of Soy on Cognition and Hot Flashes in Men With Prostate Cancer Undergoing Testosterone Suppression Therapy
NCT00499408	Vitamin D and Soy Supplements in Treating Patients With Recurrent Prostate Cancer
NCT00594620	Soy Derivatives for Control of Hot Flashes in Men on Androgen Deprivation Therapy
NCT00345813	Soy Supplements in Treating Patients Undergoing Surgery for Localized Prostate Cancer
NCT00765479	Soy Protein in Preventing Recurrent Cancer in Patients Who Have Undergone Surgery for Stage II Prostate Cancer
NCT01009736	Effects of Tomato-Soy Juice on Biomarkers in Patients With Prostate Cancer Undergoing Prostatectomy
NCT00031746	Soy Protein Supplement in Preventing Prostate Cancer in Patients With Elevated Prostate-Specific Antigen Levels
I3C and DIM	
NCT00607932	Brassica Vegetables or Indole-3-Carbinol in Treating Patients With PSA Recurrence After Surgery for Prostate Cancer
NCT00579332	Effects of Brassica or Indole-3-Carbinol on Prostatectomy Patients With PSA Recurrence
NCT00888654	Diindolylmethane in Treating Patients With Stage I or Stage II Prostate Cancer Undergoing Radical Prostatectomy
NCT00305747	Diindolylmethane in Treating Patients With Nonmetastatic PCa That Has Not Responded To Previous Hormone Therapy
NCT00450229	Diindolylmethane in Treating Patients Undergoing Surgery for Stage I or Stage II Prostate Cancer
Lycopene	
NCT00450749	Lycopene in Treating Patients Undergoing Radical Prostatectomy for Prostate Cancer
NCT00416325	Lycopene in Preventing Prostate Cancer in Patients Who Are at High Risk of Developing Prostate Cancer
NCT00416390	Lycopene in Treating Patients With Prostate Cancer or Benign Prostatic Hyperplasia
NCT00322114	Lycopene in Preventing Prostate Cancer in Healthy Participants
NCT01443026	The Effects of Lycopene on High Risk Prostatic Tissue
NCT00042731	Isoflavones & Lycopene in Localized Prostate Ca:Prior to Radical Prostatectomy
NCT00844792	Study of Antioxidants on Prostate Tumors in Men Undergoing Radical Prostatectomy for Prostate Cancer
NCT00402285	Lycopene or Omega-3 Fatty Acid Nutritional Supplements in Treating Patients With Stage I or Stage II Prostate Cancer
NCT00068731	Lycopene in Treating Patients With Metastatic Prostate Cancer
NCT00178113	A Pilot Study of Lycopene Supplementation in Prostatic Intraepithelial Neoplasia
NCT00093561	Lycopene in Preventing Prostate Cancer in Healthy Participants
NCT01105338	Lycopene or Green Tea in Treating Patients With Prostate Cancer
NCT00006078	Lycopene In Preventing of Prostate Cancer

NCT Number	Title
NCT00744549	Study of Antioxidants on MRI Detectable Early Stage Prostate Cancer Among Men on Active Surveillance
NCT00450957	Lycopene in Healthy Male Participants
NCT00154843	A Clinical Study to Determine Factors Affecting Absorption and Serum Levels of Lycopene After Supplementation
NCT01692340	Novel 13C Carotenoids for Absorption and Metabolism Studies in Humans
EGCG	
NCT00459407	Defined Green Tea Catechins in Treating Patients With Prostate Cancer Undergoing Surgery to Remove the Prostate
NCT01340599	Defined Green Tea Catechin Extract in Treating Patients With Localized Prostate Cancer Undergoing Surgery
NCT00596011	Study of Polyphenon E in Men With High-grade Prostatic Intraepithelial Neoplasia
NCT00676780	Green Tea Extract and Prostate Cancer
NCT00253643	Fish Oil and Green Tea Extract in Preventing Prostate Cancer in Patients Who Are at Risk for Developing Prostate Cancer
NCT01105338	Lycopene or Green Tea in Treating Patients With Prostate Cancer

Information collected from ClinicalTials.gov on May 14, 2013