Molecular Mechanisms of Curcumin and Its Semisynthetic Analogues in Prostate Cancer Prevention and Treatment

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Abstract

Primary prostate cancer, also known as prostate adenocarcinoma (PCa), is a devastating cancer in men worldwide. Europe and developing countries of Asia have fewer reported cases of prostate cancer compared to increasing cases in the United States with higher incidence in Black men. Risk factors associated with prostate cancer are aging, genetics, lifestyle, high body mass index as well as carcinogenic exposure to carbon-containing fuels, tobacco, and charbroiled meats. Hormone therapy and radical prostatectomy are commonly implemented treatments. The more than 20,000 prostate cancer deaths of 2013 suggest there exists a need for enhanced chemopreventive and therapeutic agents for prostate cancer treatment. Fruits, vegetables, and red wines contain high levels of polyphenolic levels. Consumption of these products may provide chemoprevetion of PCa. Curcumin, the major compound from the turmeric rhizome *Curcumin Longa* has long been used for medicinal purposes as an antiseptic and wound healing. This review focuses on curcumin's therapeutic effectiveness *in vitro* and *in vivo* in prostate cancer models. The review will highlight the mechanisms of actions of curcumin in the signaling pathways of prostate cancer.
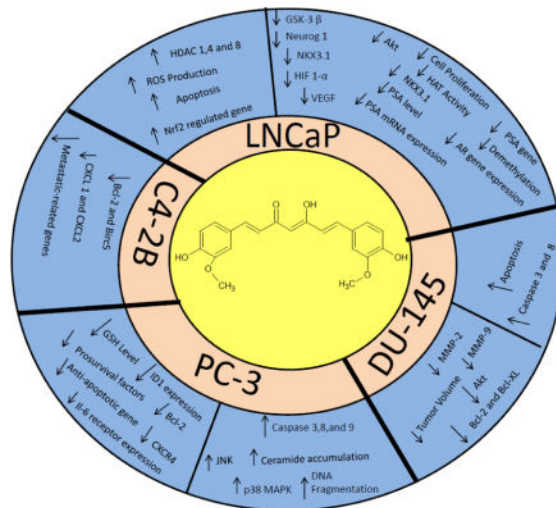
Graphical Abstract

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Conflicts of interest

The authors declare that there are no conflicts of interest.

1. Introduction

Primary prostate cancer (PCa), prostate adenocarcinoma, is second to skin cancer in its frequency of diagnosis and first in cancer deaths in American men. In 2013, 29,720 deaths were attributed to the malignancy in the United States. There continues to a be a steady decline in the numbers of prostate cancer deaths, however the death rate among Black men as a result of prostate cancer is two times greater [1]. Common PCa risk factors are increased age, elevated BMI and α-linolenic acid levels, and family history. Genetic predisposition contributes to 5% to 10% of prostate cancers. Incident rates of men of African descent are higher worldwide in comparison to men of other races. The annual incidence rate for Native American/Alaska Natives is 77.8; Caucasian is 144.9 and 228.5 per 100,000 for men of African descent (Fig. 1). The incidence and mortality is lower in Asia [2, 3], but predicted to increase because of economic development and western lifestyle influence [4, 5]. In 2010, the United States invested an estimated 11.85 billion dollars in the health care cost of PCa. Limited PCa prevention and treatment modalities are expected to increase future health care expenditures [6]. Prostate cancer is a malignancy with 10% to 20% castration-resistant development within approximately 5 years of survival and 50 % recurrence at 10 years after treatment with prostatectomy or radiation therapy [7–11]. Active surveillance, radical prostatectomy, and radiotherapy are alternative prostate cancer treatment options that are limited in their use when prostate-specific antigen (PSA) levels [12–14] and Gleason score (GS) are elevated [15, 16]. Average PSA levels are lower for members of most Asian countries for men between 60–80 years of age [17, 18]. More than 220,000 new cases of prostate cancer were anticipated to be diagnosed in the United States in 2015 [19]. An effective therapeutic approach to address the malignancy is an active area of research. There are several types of cancer that start in the prostate: sarcoma, small cell carcinoma, neuroendocrine tumors, transitional cell carcinoma, and adenocarcinoma. Prostate adenocarcinoma represents the documented deaths associated with PCa. The molecular mechanisms such as androgen receptor signaling, NF-κB, PI3K, Akt, JAK/STAT, MAPK, TGF-β/SMAD, and Wnt pathways of PCa are the targets of established therapeutic

agents implemented in the prevention and treatment of prostate cancer [20]. A study performed by Terlikoswska *et al.* [21] reported more than twenty signaling pathways mediated by curcumin; PPAR, COX-2, EGFR, and NF-κB. To date, finasteride and dutasteride (Fig. 2) are administered to treat benign prostate enlargement and reduction of male hormones. Clinical trials have demonstrated that two drugs are effective in lowering the risk of PCa by 25%.

Turmeric, a yellow spice common in India and Southeast Asia, is derived from the plant rhizome *Curcuma longa Linn*. Its diverse pharmacology action toward various diseased targets attracts great interest from the medicinal chemistry community [22–31]. Turmeric is safely tolerated at a dose of 12 grams a day as a spice, coloring agent, or as a dietary supplement. Natives of Southeast Asia have traditionally used turmeric for medicinal purposes as an antiseptic and wound healing compound. The turmeric powder contains 77% curcumin, 17% demethoxycurcumin and 5% bisdemethoxycurcumin (Fig. 3) [32]. Curcumin, (1,7-bis(4-hydroxy-3 methoxphenyl)-1,6-heptadiene-3,5-dione) has diverse biological activities, such as anti-inflammatory [33–35], antioxidant [36–40], anti-diabetic [41, 42], anti-coagulant [43, 44], antibacterial [45–47], anti-fungal [48–51], and anti-allergic [52–56]. Curcumin has been investigated for its anti-cancer activity in various cancer cell lines such as breast [57–64], prostate [65, 66], lung [67–70], liver [71] and skin [72–74].

Curcumin's lack of aqueous solubility, rapid clearance, hepatic and intestinal metabolism explains why the consumption of high doses is required to achieve therapeutic effect. Studies of curcumin have addressed its poor bioavailability, absorption, metabolism and tissue distribution [75–78]. *In-vivo* studies reveal the oral administration of curcumin undergoes metabolic O-conjugation to curcumin glucuronide and curcumin sulfate and bio-reduction to tetrahydrocurcumin, hexahydrocurcumin, and hexahydrocurcuminol (Fig. 4) [75–78].

2. Curcumin and Prostate Cancer: *In Vitro* Studies

Curcumin's modulation of various signaling pathways leads to cytotoxicity, antiproliferation, and induced apoptosis in LNCaP (androgen dependent), PC-3 (androgen independent) and DU-145 prostate cancer cell lines. Choi et al. [79] determined curcumin is a cytotoxic agent in prostate cancer cells and inhibitor of androgen receptor (AR) expression and transcription activity of the Wnt/β-catenin signaling pathway. The team determined curcumin suppresses the phosphorylation of downstream targets GSK-β and Akt protein in LNCaP cells when exposed to 20 μM of curcumin for 24 and 48 h. Curcumin has demonstrated the inhibition of the accumulation of β-catenin and down regulation of cyclin D1 and c-myc in LNCaP cells. Chaudhary et al. [80] performed an investigation of curcumin's cytotoxicity in LNCaP, PC-3, and DU145 cells. The study determined Akt is activated in 5% LNCaP serum and 10% in PC-3 cells when exposed to 35 μM of curcumin. The experiment demonstrated that curcumin performs as an inhibitor of Protein kinase B (PKB/Akt) in a dose-dependent manner and inhibits complete activation of Akt in a time-dependent manner. A DU145 and LNCap study determined curcumin inhibits cell proliferation, induces apoptosis, induces procaspase-3 and procaspase-8 in DU145 and caspase-3 and caspase-8 in LNCaP at 50μM and 10 μM of curcumin respectively [81]. Piantino et al. [82] demonstrated LNCaP and PcBra 1 cells undergo apoptosis at the rates of

90% and 55% respectively when exposed to curcumin. Curcumin has demonstrated anti-androgenic activity through the inhibition of PSA reporter vectors at 20 µM in a dose-dependent manner [83]. Yang et al. [84] performed an LNCaP study to discover the mechanisms responsible for curcumin's inhibition of cell proliferation and induction of apoptosis. The study revealed curcumin's ability to target, suppress cell proliferation and improve apoptosis in LNCaP cells when exposed to 40µM of curcumin. Curcumin performs as an inhibitor of prolyl 4-hydroxylase in a dose-dependent manner and modulates hypoxia by downregulation of AR activity and PSA expression in LNCaP cells. At concentration of 10 µM, curcumin blocks HIF1-α overexpression and significantly decreases protein levels of AR by 26% and 31% under normoxia and hypoxia conditions [85]. Du et al. investigated curcumin's role in cancer associated fibroblasts (CAF) and epithelial to mesenchymal transition (EMT) in PC-3 cells. The study determined curcumin abated CAF invasion and EMT activity and inhibited the production of ROS. The study further identified downregulated receptor expression of CXCR4 and IL-6 by curcumin inhibition of MAOA/mTOR/HIF-α signaling pathway [86]. In an investigation performed by Ling Yu, PC-3 cells treated with 20 µM of curcumin for 30 days displayed more than 50 % of ID1 mRNA reduction, performs as an inhibitor of DNA binding 1 (Id1) in a dose-dependent manner, and modulates the expression of ID1 mRNA and protein in prostate cancer cells [87]. A study of hormone refractory C4-2B prostate cancer cells exposed to curcumin revealed the inhibition of growth factor receptor signaling pathway and activation of NF-kB [88].

In a study performed by Zhang et al. [89] it was observed that NKX3.1, NK-class homeobox gene, and AR expression are significantly down-regulated when exposed to 40µM of curcumin. Shu et al. [90] reported demethylation levels decrease from 37% to 8% when exposed to 5µM of curcumin. The study also observed curcumin, alone or in combination with trichostatin A, demonstrated an increase in histone acetyltransferase activity and inhibition of histone deacetylase. Hong and team [91] performed an investigation of curcumin's anti-cancer nature in androgen-independent prostate cancer cell line DU-145. The study determined exposure to curcumin concentrations of 25–100 µg resulted in decreased MMP-9 and MMP-2 secretion with significant inhibition of tumor volume and cell proliferation. In PC-3 cells, curcumin has displayed cytotoxicity, apoptotic induced cellular ceramide accumulation (an intermediate in sphingolipid metabolism that leads to apoptosis), activation of MAPK, JNK, cytochrome c, apoptosis-inducing factor (AIF), and caspase-3, 8, and 9 [92]. Chendil [93] demonstrated downregulation of prosurvival factors and anti-apoptotic genes when exposed to 5 µM of curcumin in PC-3 cells and a significant decrease in clonogenic expression when curcumin is administered along with radiation as a therapeutic agent. The administration of curcumin alone resulted in an increase of apoptosis, 7.23% to 11.56%, at 24 and 48h whereas the curcumin-radiation treatment combination yielded apoptotic increase of 21.39 % to 27.57%.

3. *In-vivo* studies

Curcumin has been remarkably well investigated its anti-prostate cancer activity in *in vitro* models, but its bioavailability is poor. Several animal models have been employed to investigate the anti-prostate cancer activity of curcumin. Hong et al. [94] investigated the effectiveness of curcumin in a LNCaP xenograft model administered 500 mg/Kg orally three

times a day for one month. The study revealed a 27% delay in tumor growth and significant suppression of AR expression. A study with the implementation of a PC-3 cell suspension was placed subcutaneously in male SPF BALBB/c nude mice to generate prostate tumors. 25–100 mg/kg of curcumin was administered by injection every 2 days resulting in decreased PC-3 tumor growth, volume, and weight. The study also revealed efficacy in the induction of apoptosis by significant downregulation of Bcl-2 expression and upregulation of Bax expression [95]. Dorai et al. [96] observed curcumin's ability to halt cell proliferation and induce apoptosis in LNCaP. Male nude mice inoculated with LNCaP cells were treated with a diet made of curcumin and PICO 5053 for 6 weeks. Curcumin demonstrated significant reduction of tumor growth in a statistically significant manner (P < 0.008). In an interesting study with PC-3 prostate cancer cells, Killian and co-worker [97] demonstrated that exposure to 15 µM of curcumin for 24 h inhibited CXCL1 and CXCL-2 transcription expression to 40 % and 25 % respectively, reduced tumor growth rate by 50 % and inhibited apoptosis genes BCL2 and BIRC5. Induced necrosis rate, apoptosis rate, and down regulation of COX2 by 50 %, SPAC by 25 %, ALDH3A1 by 25 % and EFEMP by 40 % were also observed.
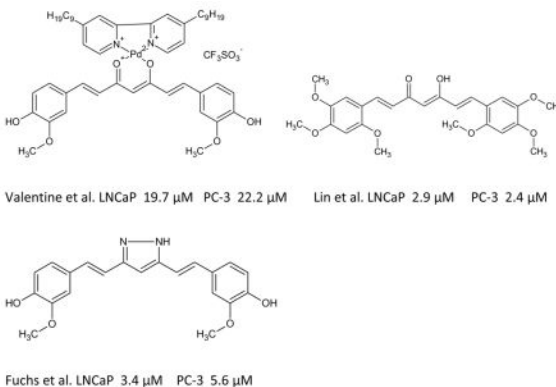
4. Curcumin Delivery and Prostate Cancer

The oral administration of curcumin results in rapid metabolism and undergoes enterohepatic circulation requiring a larger dose of curcumin in order to provide therapeutic effects. Studies of curcumin's cytotoxic effects on prostate cancer with the implementation of nanoemulsions, nanoparticles, and liposomes have demonstrated increased therapeutic efficacy compared to curcumin administered alone. Thangavel et al. [98] studied Redox nanoparticles (RNP) containing curcumin. Their experiment demonstrated significant increases in cellular uptake, induced apoptosis and cytotoxicity and the suppression of more than 40 % of tumor cell proliferation at 100 µmol/L. RNP-curcumin complex exhibited anti-cancer therapeutic activities in a mouse model displaying significant reduction in tumor volume growth rate. Yallapu et al. [65] formulated a poly (lactic-co-glycolic acid) nanoparticle with curcumin (PLGA-NP) by using a nano-precipitation method that exhibited effective anti-cancer activity in C4-2 (LNCaP cell type) androgen dependent and androgen independent PC-3 and DU-145 cells. The curcumin encapsulated nanoparticle inhibits STAT3 and AKT phosphorylation activity, induces apoptosis, alters expression of miR-21 and miR-205, decreases cell proliferation, and inhibits clonogenic potential in PC-3, DU-145 cells.

The study further identified the delivery systems ability to inhibit tumor growth, enhance recruitment of macrophage, and damage free red blood cell membrane in a C4-2 mouse xenograft model. Curcumin nanolipid carriers (CUR-NLC) fabricated by nanoemulsion were investigated in a comparison study of curcumin versus curcumin-genistein nanolipids, The investigation demonstrated an increase in loading efficiency and cell growth inhibition in PC3 cells, cell viability decrease up to 71% in the presence of curcumin only and 50% inhibition of prostate cancer cells in the presence of a curcumin-genistein combination of 20 and 45µM of respectively [99]. Shukla et al. [100] developed an optimal composition of etoposide and curcumin containing nanoemulsion prepared by ultra-sonication which demonstrated enhanced cytotoxicity in PC-3. A curcumin and resveratrol liposome has

shown enhanced anticancer activity in PTEN (phosphatase and tensin homolog) knockout mice. The synergistic relationship induces apoptosis and inhibits cell growth, downregulates p-Akt and cyclin D, and significantly decreases prostatic adenocarcinoma *in vivo* [101]. Yallapu et al. performed studies on β-cyclodextrin (CD) self-assembled curcumin encapsulated delivery systems. The CD system demonstrated greater anti-proliferative activation in both metastatic and nonmetastatic prostate cancer cells in a time-dose-dependent manner [102, 103].

5. Curcumin Structure Activity Relationship and Prostate Cancer

Recent studies have investigated the structural activity relationship of synthesized curcumin analogues. Enhancement of curcumin's anticancer activity can be achieved through modifications of its chemical structure. The most successful analogues synthesized are pyrazole-curcumin analogue. This section will display the structural activity relationship of curcumin and its semisynthetic analogs. Curcumin-complex, a heteroleptic palladium II complex composed of curcumin and bipyridine has been synthesized by valentine et al. The analogue effectively induces apoptosis and inhibits cell growth in hormone independent prostate cancer cell lines greater than the administration of curcumin alone. In 2005, Lin and team reported the synthesis of more than 40 curcumin analogues, 18 of the synthesized analogues demonstrated cytotoxic behavior in LNCaP and PC-3 prostate cancer cell lines. Fuchs el at. synthesized 13 curcumin analogues with pyrazole ring. The heterocycle modified analogue showed more potency.

Valentine et al. LNCaP 19.7 μM PC-3 22.2 μM   Lin et al. LNCaP 2.9 μM   PC-3 2.4 μM

Fuchs et al. LNCaP 3.4 μM   PC-3 5.6 μM

6. Synergistic Curcumin combinations

Curcumin administered *in vitro* and *in vivo* in synergistic combination with established anti-cancer agents yields enhanced efficacy in prostate cancer cell cytotoxicity and decreased cell viability. Detail information is presented in Table 4.

7. Clinical Trial Studies

Curcumin's therapeutic efficacy has been explored and reported in more than 45 completed clinical trials and 39 curcumin trials are scheduled to investigate its efficacy in several disease states. Only one completed clinical study explored curcumin's activity in prostate cancer and two more are scheduled. A one-year trial conducted by Rastmanesh et al. [114]

explored the radioprotective and radiosensitivity of curcumin in patients diagnosed with prostate cancer administered 3 gm daily for up to 8 weeks. A Phase II study lead by Hakim Mamammedi [115], Center Jean Perrin, in the recruiting stage will explore the synergistic relations of Taxotere with curcumin versus Taxotere alone as a first-line treatment of patients with metastatic castration-resistant prostate cancer. Yair Lotan [116], University of Texas Southwestern Medical Center, is in the recruiting stage of a Phase II study to investigate the administration of curcumin and its ability to improve recurrence free survival. Detail information is presented in Table 5.

8. Conclusion

A steady decline in prostate cancer related deaths since the 1990s may be attributed to early detection by increased implementation of prostate-specific antigen (PSA) screening blood test. The chemopreventive and chemotherapeutic nature of curcumin as a therapeutic agent for the treatment of prostate cancer is promising. Curcumin's anti-tumor and anti-cancer activity is extensive and identified as potent in liver, breast, ovarian, pancreatic, and prostate cancers. The natural compound's therapeutic properties are highlighted in its regulation of transduction and inflammatory pathway, cell cycle arrest induction, and apoptotic characteristics. Efficacious *in vivo* application of curcumin is limited in prostate cancer. The compound is chemically unstable, has poor aqueous solubility, narrowed systemic distribution, and experiences severe biotransformation when administered orally. Curcumin analogs, synergistic therapy, and innovative drug delivery techniques must be implemented to address the pharmaceutical *in vivo* application hurdles and overcome the aggressive and metastatic nature of cancer. Delivery vessels with encapsulated curcumin have demonstrated alternatives for efficacious oral administration. The chemopreventive and cytoprotective potency character of curcumin is retained in nanoparticle and liposome formulations. The administration of curcumin in a synergistic relationship with established prostate cancer therapeutics such as docetaxel and phenethyl isothiocyanate improves the cytotoxicity and chemotherapeutic characteristics.

Acknowledgments

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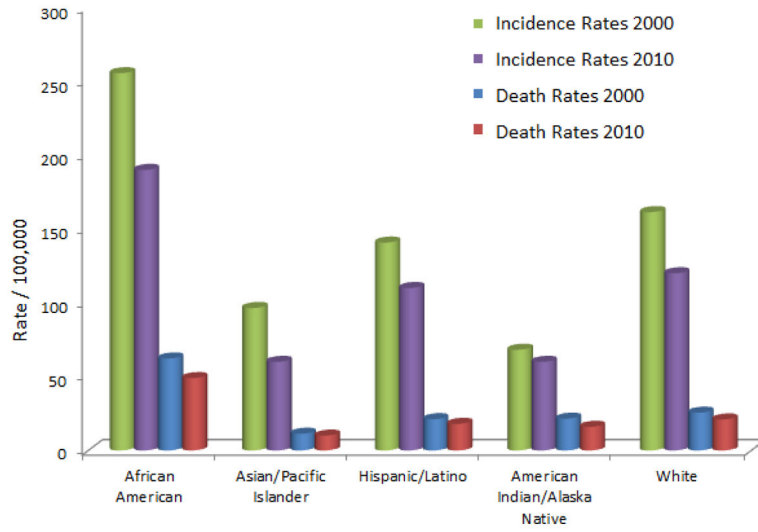
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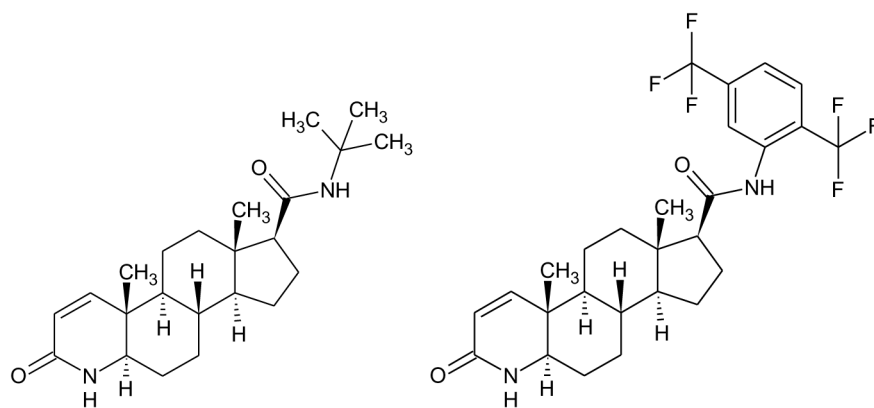
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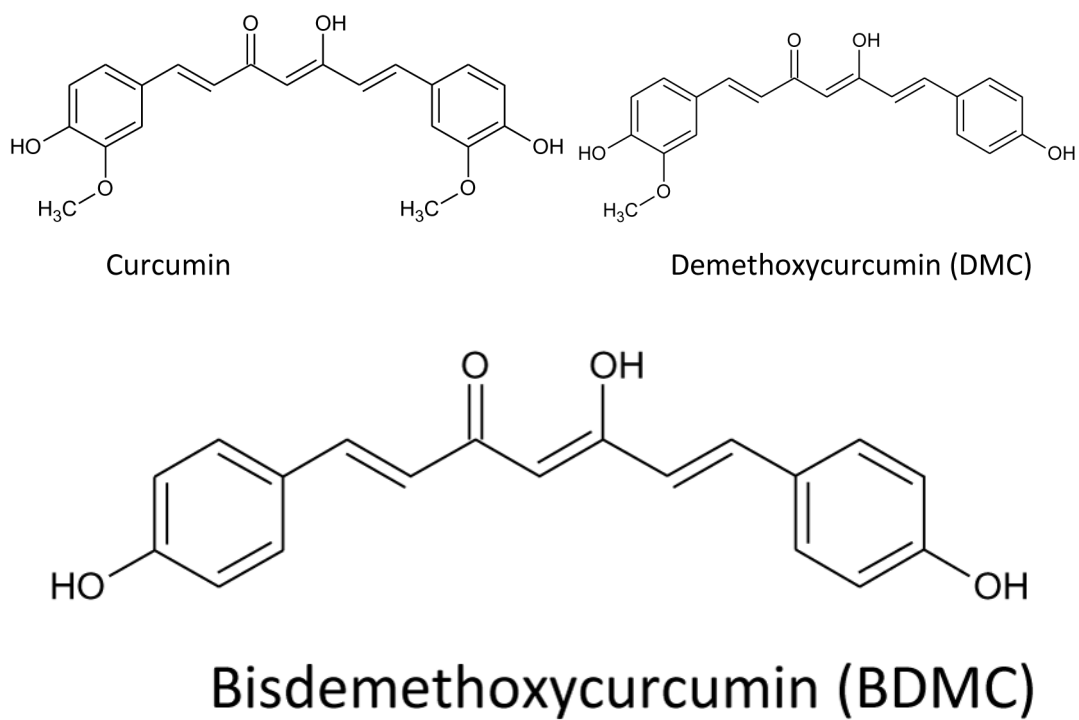https://clinicaltrials.gov/ct2/show/NCT02095717?tern=curcumin+and+prostate&rank=3
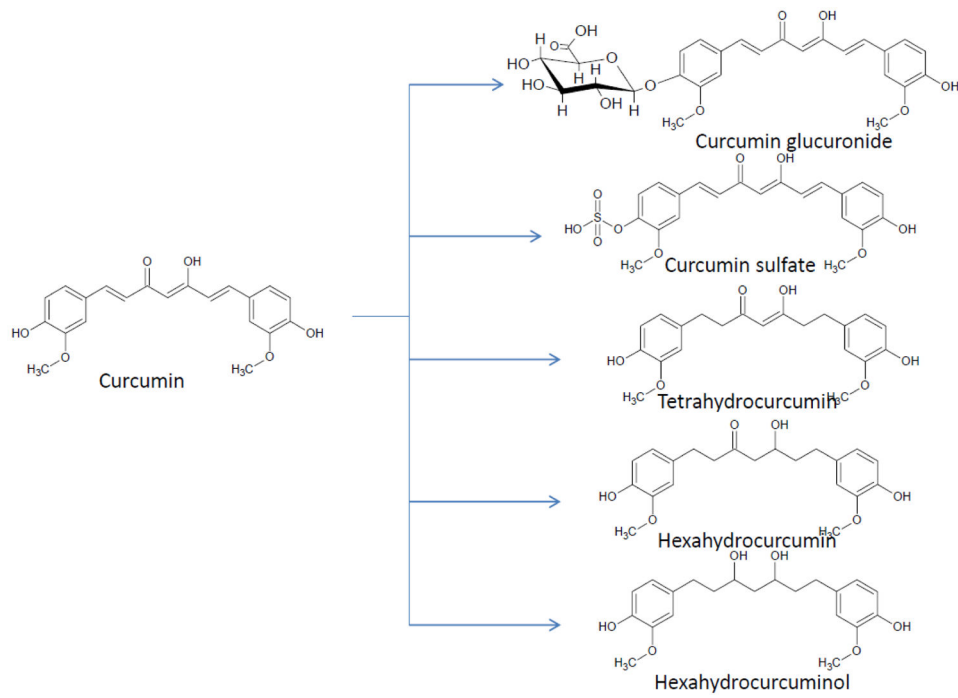
Figure 1.
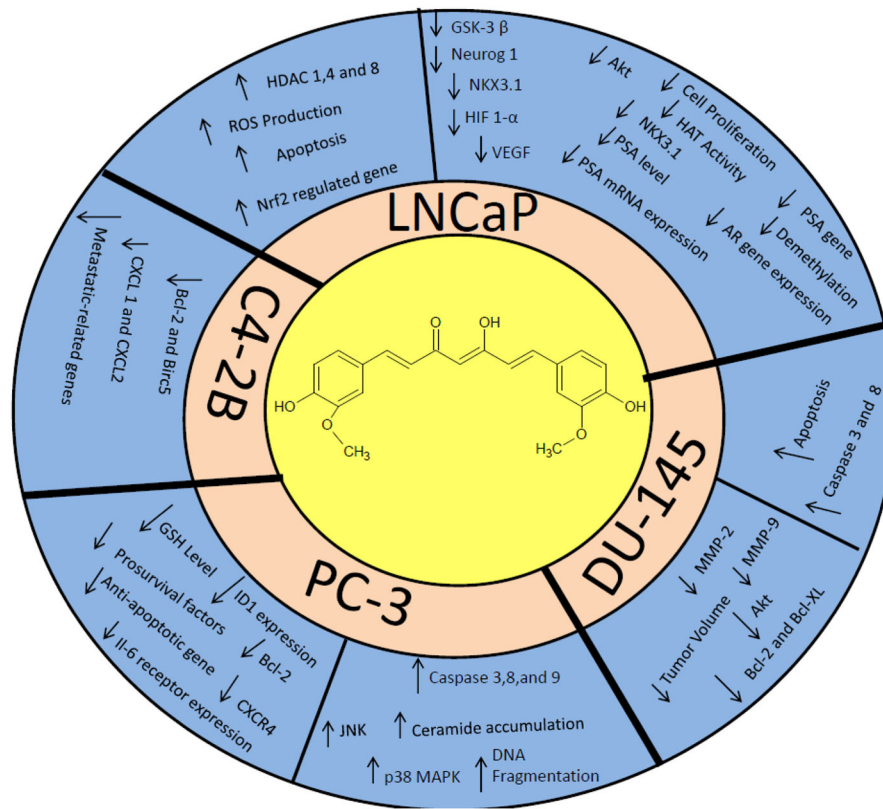Prostate cancer incidence and death rates

Figure 2.
Finasteride and Dutasteride

Curcumin

Demethoxycurcumin (DMC)

Bisdemethoxycurcumin (BDMC)

Figure 3.
Structures of Natural Curcumins

Figure 4.
Structures of curcumin metabolites

Figure 5.
Curcumin on Prostate Cancer Signaling Pathways

Table 1

Biological Activities of Curcumin Prostate Cancer Signaling Pathways

Biological Effects	Mechanism of Action	Concentration	Ref.
Curcumin inhibited the phosphorylation of downstream targets of LNCaP cells	↓Phosphorylation of GSK-3β/Akt ↓AR Expression	20 μM	79
Curcumin inhibits protein kinase B activation in DU-145 cells	↓AKT	35 μM	80
Curcumin inhibits NFKb-regulate gene products in DU-145 cells	↓Bcl-2 and Bcl-XL ↑Caspase 3 and 8, ↑Apoptosis	50 μM	81
Curcumin inhibits proliferation of LNCaP and other obstructive prostate cancer cell lines	↑Apoptosis	10–50 μM	82
Curcumin inhibits the activation of androgen and other transcription factors	↓AR gene expression ↓PSA Level ↓PSA secretion	20 μM	83
Curcumin inhibits expression of androgen receptor of LNCaP cells	↓Cell proliferation ↓PSA promoter gene	10–40 μM	84
Curcumin inhibits hypoxia and HIF1 alpha expression on PSA promoter activity	↓PSA level ↓AR protein level	10 μM	85
Curcumin inhibits ROS production and receptor expression of cancer-associated fibroblasts in prostate cancer cells	↓IL-6 receptor expression ↓CXCR4	25 μM	86
Curcumin inhibits cell viability and induce apoptosis by decrease mRNA and protein expression in prostate cancer cells	↓ID1 mRNA expression ↓Cell viability	20μM	87
Curcumin augments down-regulation of gene expression in prostate cancer cells	↓NKX3.1 ↓AR expression ↓ARE Binding activity	10,20,40 μM	89
Curcumin inhibits methylation through CpG Island of LNCaP	↓Demethylation, ↑Neurog 1, ↑HDAC 1,4 and 8 ↓HAT activity	5 μM	90
Curcumin inhibited proliferation and tumor volume of DU-145 cells	↑Apoptosis ↓MMP-9 secretion ↓MMP-2 secretion	10–100 μg/ml	91
Curcumin augments ceramide accumulation and induce apoptosis in PC-3 cells	↑Ceramide accumulation ↑p38 MAPK ↑JNK ↑Caspase 3,8, and 9 ↓GSH Level ↑DNA Fragmentation	25–100 μM	92
Curcumin, alone or in combination with radiation inhibits regulation of pro-survival factors and anti-apoptotic genes in PC-3 cells	↓Prosurvival factors ↑Procaspase-9 ↑Caspase 9 and 3	5 μM	93

Table 2

Biological Effects of Curcumin in *In Vivo* Models of Prostate Cancer

Biological Effect	Mechanism of Action	Dose/Duration	Ref.
Curcumin inhibited proliferation and tumor volume of DU-145 cells	↓Tumor Volume ↓MM-9 Secretion ↓MMP-2 Secretion	5 mg/kg/3x week	90
Curcumin inhibited AR activity and expression in LNCaP xenograft models	↓Transcriptional Activtiy of AR mRNA	500 mg/kg for 4 weeks	94
Curcumin induce apoptosis and apoptosis related protein in nude mice of prostate cancer cells	↓Bcl-2	25–100 mg/kg for 30 days	95
Curcumin inhibit LNCaP tumor angiogenesis of *in vivo* models	↓Tumor volume ↓Tumor mass ↓Vessel formation ↓Tumor Growth ↓Microvessel	2%/ for 2 weeks	96
Curcumin inhibit pro-inflammatory cytokines and increase apoptosis and necrosis rate in prostate cancer cells.	↓Bcl2 and Birc5 ↓Metastatic-related genes, ↓CXCL1 and CXCL2	15 μM	97

Table 3

Curcumin Drug Delivery Systems on prostate cancer models

Biological effect	Delivery Vessel	Mechanism of Action	Cell line	Ref.
Curcumin in PLGA nano-encapsulation enhance anti-cancer activity in mouse xenograft model of prostate cancer	Poly(lactic-co-glycolic acid) (PLGA) 2.5–40 μM	↑Accumulation and Retention Protrusion of cell membrane ↑Shrinkage and Aggregation ↑Disrupt Cytoskeleton Micro and spherical nucleation	C4-2 xenograft DU145	65
Curcumin in oxidative degradable nanoparticle enhance apoptotic cell death, cytotoxicity and inhibits acid ceramidase in prostate cancer cells	Curcumin-loaded pH sensitive redox nanoparticle (Cur-RNP) (10 mg/kg Cur to 20 mg/kg of RNP)	↑Cellular uptake ↓Tumor volume growth rate ↑Stability ↑Solubility	PC-3	98
Curcumin in lipid nanoparticles enhance drug delivery system and cell growth inhibition in prostate cancer cells.	Curcumin co-loaded nanostructured lipid carrier (Cur-NLC) (1200 μg alone) (700 μg/w genistein)	↑Intracellular uptake Solubility to 70% ↑Stability to 100% for 2 h ↑*In vitro* drug release to 55% for 8 h	PC-3	99
Curcumin in nanoemulsion enhance cytotoxicity of etoposide in prostate cancer cells	Nanoemulsion (ETP 5 μM + CUR 25 μM)	↑AUC ↑Bioavailability ↑Cellular uptake ↑Intracellular availability	DU-145 PC-3	100
Curcumin and resveratrol combination in liposome encapsulation inhibit prostatic adenocarcinoma and cell viability in PTEN knockout mice	Lipo-curcumin (2.5 mg/kg/bw each)	↑Bioavailability 5 fold increase for rate of apoptosis	PTEN-CaP8	101
Curcumin loaded β-cyclodextrin inclusion complex enhance anti-proliferative activity in prostate cancer cells	β-cyclodextrin-curcumin (CD-CUR) 5–40 μM	↑Aqueous Solubility ↑Apoptosis ↑Intracellular uptake ↑*In vitro* stability	C4-2 DU145	102
PCD/CUR self-assembly enhance anti-cancer activity in prostate cancer cells	Poly(β-cyclodextrin)/Curcumin self-assembly 20 μM	↑Bioavailability and delivery ↓Cell growth 3–4 fold increase in cellular uptake ↑Stability and Solubility	C4-2 DU145 PC3	103

Table 4

Synergistic Effects of Curcumin on prostate cancer models

Biological effect	Mechanism of Action	Dose	Cell line	Ref.
Curcumin and nelfinavir co-exposure with docetaxel increase apoptosis, enhance ER-stress transducers and associated death sensors in castration resistant prostate cancer cells (C4-2B)	↑Caspase 3 activity ↑p-eIF2µ ↑CHOP/ATF4/TRIB3 ↓colony forming unit (CFU)	Curcumin (5 µM) Nelfinavir (5 µM) Docetaxel (10 nM)	CRPC subline (C4-2B)	107
Curcumin in combination with bicalutamide enhance cell groth inhibition in prostate cancer cells	↑Phosphorylation of ERK1/2 and SAPK/JNK ↓MUC1-C and NF-kβ	Curcumin (30µM) Bicalutamide (40 µM)	PC-3 DU145	108
Epigallocatechin gallate (EGCG) in combination with curcumin improve cell cycle arrest in androgen-independent prostate cancer cell lines	↓S and G2/M phase of cell cycle	Curcumin (50 µM) EGCG (50 and 100 µM)	PC-3	109
Curcumin in combination with phenethyl iosthicyante inhibit tumor growth and weight of prostate xenograft mouse	↑Apoptosis ↓Tumor volume	Curcumin (3 and 6 µM) Phenethyl isothiocyanate (2.5 µM)	PC-3 xenograft	110
Curcumin in combination with isoflavones enhance expression of androgen receptor inhibition	↓PSA	Curcumin (25 µM) Isoflavones (10 µg/ml)	LNCaP	111
Curcumin, alone or in combination with TRAIL induce apoptosis on mitochondria pathway prostate cancer cells	↓Cell viability ↑Apoptosis ↑Mitochondria pathway ↓Procaspase 8 and 3 ↑Cytochrome C ↓DNA Fragmentation	Curcumin (10–40 µM) TRAIL (20 ng/ml)	LNCaP PC-3 Du145	112
Curcumin, alone or in combination with TRAIL induce cytotoxic effects on prostate cancer cells	↓Cell viability ↓Clonal Growth	Curcumin (20–40 µM) TRAIL (20 ng/ml)	LNCaP	113

Table 5

Curcumin-prostate Cancer Clinical Trials

Clinical trials gov. identifier no.	Year started	Phase	Patient condition	Curcumin Dose	Purpose
NCT01917890	Aug. 2013	Completed	Prostate cancer/Radiation therapy	3 gm once daily for 7–8 weeks	Determine curcumin radioprotective and radiosensitizing activity for prostate cancer treatment in
NCT02064673	May 2014	Phase II/recruiting	Prostate cancer	500 mg 2x Daily for 6 months	Curcumin vs. placebo for treatment of patient after going radical prostatectomy
NCT02095717	March 2014	Phase II/recruiting	Metastatic Castration Resistant		Curcumin vs placebo combine with Taxotere for treatment in prostate cancer metastatic castration resistant patients