Developing New Small Molecular Drugs for Prostate Cancer Therapy

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ABSTRACT

Most of the early prostate cancer has no obvious symptoms, but its malignancy metastasis will cause largely deaths. The treatment options for patients with prostate cancer include traditional surgery, external beam therapy, hormone therapy, small molecular drug and cryosurgery. It was considered non-traditional treatments also can be used in alternative medicines for prostate cancer therapy. There are well-known molecular mechanisms and their pathogenesis, which provide potential targets for drug screening on the prostate cancer. Currently, natural plant extracts or human tissues active ingredients are widely used for the treatment of cancer. Then isolated effective substances in the extract, and further prepared large amounts of small molecule drugs by chemical synthesis. In this review, we summarized four small molecular drugs, abiraterone, docetaxel, isochaihulactone and butylidenephthalide, and their detailed anti-tumor mechanisms. These indicate that small molecular drug is a very efficient way and can be used for prostate cancer treatment.

Keywords: Prostate Cancer; Small Molecular Drugs; Abiraterone; Docetaxel; Isochailuactone; Butylidenephthalide

1. Introduction

Prostate cancer nearly occurs in the prostate, a gland found in the male reproductive organs, and its carcinogenesis procedures is relative slowly; however, there are cases of aggressive prostate cancer spread more rapidly than others [1-3]. Early prostate cancer has similar symptoms with benign prostatic hyperplasia, including micturition, urination obstacle, hematuria and dysuria [4,5]. Prostate cancer itself does not cause severe symptoms, however, metastatic prostate cancer can spread through body and have fatal symptoms [6].

There are several currently known mechanisms for the prostate cancer pathogenesis [7]. Mutation of P53, common in prostate cancer, influenced its downstream effectors, which have been proved mediating prostate cancer processing and causing aberrant nuclear protein accumulation [8-10]. Loss of the tumor suppress gene PTEN, implying with advanced prostate tumors in clinically [9,11,12]. The c-met and HER2/neu (c-erbB2) oncogene also play important roles in prostate carcinogenesis [13-15]. Besides, RUNX2 can prevent cancer cell leading to apoptosis and contribute in prostate cancer development [16]. Furthermore, androgen signaling involved in development and homeostasis of the prostate, and cancer initiation and progression correlated with activation of androgen receptor [17,18].

Treatments of prostate cancer involved surgery, external beam therapy, hormone therapy, small molecular drug and cryosurgery [19-24]. Currently, natural plant extracts or human tissues active ingredients are widely used for the treatment of cancer, and further isolated effective substances in the extract [25,26]. With the advances in drug design and chemical synthesis, small molecule drugs become more popular in drug screening and clinical trial [27]. The small molecular drugs have
irreplaceable characteristics in easy to chemical synthesis, drug save, oral absorption and molecules modify and design [28,29]. In this review, we summarized four kinds of prostate cancer treated small molecular drugs, abiraterone, docetaxel, isochaihulactone and butylidenephthalide [30-33].

2. Abiraterone
Androgen receptor, a ligand-inducible transcription factor and member of the steroid hormone, enhance prostate cancer growth and progression through activation of target genes [34,35]. There have been proved that androgen ablation can control metastatic prostate cancer growth through reduction in serum acid phosphatase by surgical or medical castration [36,37]. Escalating studies showed abiraterone play a role in inhibiting of CYP17, a androgen synthesis suppressor, which has potential therapeutic effects in aggressive castration-resistant prostate cancer [38-41]. Abiraterone already is a Food and Drug Administration (FDA) drug used in prostate cancer, extended survival time up to 14.8 months, and its formulation form as abiraterone acetate [33,42,43].

3. Docetaxel
Androgen-independent prostate cancer defined as lower levels of testosterone found in tissue during carcinogenesis, it cannot cured by surgery [33,44-46]. Several studies pinpointed precise mechanisms progression and tried to offer new cure for androgen-independent prostate cancer [47-49]. Docetaxel, a member of the taxane family, has been used extensively and treated with many cancers, including breast, ovarian and certain forms of lung cancer [50,51]. The mechanism of docetaxel to inhibit prostate cancer is associate with tubulin and then promotes microtubule assembly, this can cause mitotic-dependent cell cycle arrest [52-54]. Further, docetaxel induced cell death through activation of caspase and lysosomal pathways and function as medication drugs for prostate cancer [55,56].

4. Isochaihulactone
Previously indicated isochaihulactone, isolating from Bursera microphylla, has potential inhibiting ability in A549 cell through cell cycle arrest at the G2/M phase and induced apoptosis [26, 57-59]. Besides, isochaihulactone also can inhibits cell proliferation via downregulation of the checkpoint proteins cdc25c, cyclin B1, and cdc2 in LNCaP cell; resulting in apoptotic death through enhanced p53 and p21 expression [30,59]. The apoptotic signal were controlled by activating EGR-1 and NAG-1 in JNK-dependent manner [30,60]. Indicating reduced androgen receptor expression in isochaihulactone treated LNCaP cell [30,60]. These results proved that isochaihulactone may has potential therapeutic efficient for prostate cancer therapy.

5. Butylidenephthalide
Butylidenephthalide (BP), isolated from Angelica sinensis, showed a dramatic therapeutic effect in against glioblastoma multiforme and its derivative also inhibit cell growth in hepatocellular carcinoma and lung adenocarcinoma cells [61-63]. Furthermore, butylidenephthalide could inhibit cell proliferation and induce cell death in human prostate cancer cells (PC-3 and LNCaP) [31]. The mechanisms were involved change expression levels of G0/G1 regulatory proteins, its cytotoxicity is mediated by endoplasmic reticulum stress and induction of death receptor pathway [31]. Theses indicated that butylidenephthalide also has potential therapeutic effect in aggressive prostate cancer.

6. Conclusion
In this review, we summarized four different small molecular drugs and their therapeutic effects and mechanisms on prostate cancer. Through the analysis of the extracts, which contain anti-tumor ability, we can isolate effective substance and rule out their therapeutic mechanisms. These methods provide a convenient way to find out new potential anti-tumor drugs.

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REFERENCES


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