Molecular Basis of Prostate Cancer and Natural Products as Potential Chemotherapeutic and Chemopreventive Agents

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Prostate cancer is the second most common malignant cancer in males. It involves a complex process driven by diverse molecular pathways that closely related to the survival, apoptosis, metabolic and metastatic characteristics of aggressive cancer. Prostate cancer can be categorized into androgen dependent prostate cancer and castration-resistant prostate cancer and cure remains elusive due to the developed resistance of the disease. Natural compounds represent an extraordinary resource of structural scaffolds with high diversity that can offer promising chemical agents for making prostate cancer less devastating and curable. Herein, those natural compounds of different origins and structures with potential cytotoxicity and/or in vivo anti-tumor activities against prostate cancer are critically reviewed and summarized according to the cellular signaling pathways they interfere. Moreover, the anti-prostate cancer efficacy of many nutrients, medicinal plant extracts and Chinese medical formulations were presented, and the future prospects for the application of these compounds and extracts were discussed. Although the failure of conventional chemotherapy as well as involved serious side effects makes natural products ideal candidates for the treatment of prostate cancer, more investigations of preclinical and even clinical studies are necessary to make use of these medical substances reasonably. Therefore, the elucidation of structure-activity relationship and precise mechanism of action, identification of novel potential molecular targets, and optimization of drug combination are essential in natural medicine research and development.

Keywords: prostate cancer, natural compounds, apoptosis, androgen receptor, mechanism

INTRODUCTION

It is nowadays evident that prostate cancer (PCa) is recognized as the second most common cancer and the fifth cause of cancer death in males (Torre et al., 2015). Initially, the usual therapy for prostate cancer is prostatectomy or radiation, which aims to remove or kill the malignant cells that have not spread or metastasized (Feldman and Feldman, 2001). However, numerous patients cannot be cured thoroughly by this treatment, and then followed by cancer recurrence and/or metastasis. The
Majority of prostate cancer growth is androgen dependent. Androgen deprivation therapy (ADT) such as surgery or gonadotropin-releasing hormone (GnRH) analog treatment, is the main therapeutic and dramatically effective intervention for the treatment of androgen dependent prostate cancer (ADPC) in putting patients with tumors in remission, as documented by the work on castration of Huggins, who was awarded the Nobel prize in 1966 (Huggins, 1978). Nevertheless, after this therapy, most of these prostate cancer patients gradually become androgen independent, go on to progress, metastasize and resist to ADT within 13–24 months accompanied by increased levels of prostate-specific antigen (PSA). Siegel et al. reported that failure of ADT is responsible for the ∼27,000 metastatic prostate cancer deaths in the United States annually (Siegel et al., 2017). This stage of prostate cancer is called castration-resistant prostate cancer (CRPC), which has poor prognosis (Small et al., 2004). At present, there is no effective therapy for CRPC besides docetaxel, which has been demonstrated to prolong overall survival in this patient population. However, the efficacy of docetaxel is not satisfactory and there are many severe adverse effects such as anemia, neutropenia, diarrhea, and sensory neuropathy. Although, therapeutic options have expanded rapidly since 2011, including AR inhibitors (enzalutamide, abiraterone), immunotherapy (sipuleucel-T), bone seeking radionuclides (radium-223), and second-line chemotherapy (cabazitaxel), all of these agents or interventions only have shown a median survival benefit of 2–5 months (Ritch and Cookson, 2016). So searching for more effective anti-prostate cancer drugs, especially with high efficacy and low toxicity, remains an urgent problem that needs to be resolved. Natural compounds represent an irreplaceable resource of structural scaffolds that can offer chemical agents for making prostate cancer less devastating and curable. In recent years, many natural products and extracts have been scientifically investigated in vitro and/or in vivo and proved as potential anti-prostate cancer agents, which are currently scattered across various publications. So a systematic summary and knowledge of future prospects are necessary to facilitate further chemical and pharmacological studies for anti-prostate cancer agents.

Herein, we reviewed the detailed molecular causes of prostate cancer and critically summarized the natural products for prostate cancer.
compounds (or extracts and Chinese herb preparations) that have been reported to inhibit prostate cancer cells proliferation/tumor growth, induce prostate cancer cells apoptosis or exhibit effects on specific signaling pathways involved in prostate cancer in vivo and in vitro. In addition, we also provided possible novel targets for screening natural compounds (or extracts or Chinese herb preparations) with anti-prostate cancer activity and discuss the future prospects for the application of these compounds and extracts and the novel available approaches and technological improvements that should be explored to treat prostate cancer.

OVERVIEW OF THE MOLECULAR BASIS OF PROSTATE CANCER

Molecular Basis of Androgen Dependent Prostate Cancer

Androgens, principally testosterone (T) and dihydrotestosterone (DHT), are synthesized from cholesterol as the initial 27-carbon substrate via multiple enzymatic steps (Wadosky and Koochekpour, 2016). As a member of the ligand-activated nuclear hormone receptors superfamily, androgen receptor (AR) is a modular protein with four functional domains: an N-terminal regulatory domain (NTD), a DNA-binding domain (DBD), a small hinge region (H) and a ligand-binding domain (LBD) (Ho and Dehm, 2017). Upon binding to androgens, AR undergoes a conformational change, leading to nuclear translocation, phosphorylation, homodimer, and interaction with DNA (Li and Al-Azzawi, 2009). Subsequently, AR dimer binds to androgen-response elements (AREs), recruits essential cofactors and regulates the expression of androgen-regulated genes (Ho and Dehm, 2017).

The development and maintenance of the prostate is inseparable from androgen acting through the AR. Since Huggins and Hodges first demonstrated the responsiveness of prostate cancer to androgen deprivation, it has been clear that prostate cancer is dependent on androgen and AR activation for growth and survival (Huggins and Hodges, 1941). From then, hundreds of studies have demonstrated that androgen withdrawal results in initial regression of essentially all prostate cancers, albeit for a finite period, with the ultimate development of castration-resistant disease. Androgen deprivation therapy, via either orchidectomy or use of a gonadotropin-releasing hormone (GnRH) agonist has become the cornerstone of therapy in the treatment of prostate cancers. Newer agents, such as abiraterone, which block androgen synthetic pathways, have added clinical benefit in disseminated disease, demonstrating that even in “castration resistant disease” androgens may still be supporting prostate cancer growth.

![Non-nuclear AR signaling in CRPC](image-url)
| Natural compound | Sort | Name of microorganisms | Cell type | Observation | Activity | Mechanism of action | Refs |
|------------------|------|------------------------|-----------|-------------|----------|---------------------|------|
| C-phycocyanin    | Proteins | Limnothrix sp. | LNCaP | In vitro | Induction of apoptosis | Increase of radical oxygen species (ROS) generation; increase of caspase-9 and caspase-3 activities. | Gantar et al. (2012) |
| Eusynstylamide B(1) | Alkaloids | Didemnum candidum | LNCaP | In vitro | Antiproliferation | Induction of G2 cell cycle arrest; increase of CHK2 phosphorylation; upregulation of p21CIP1/WAF1; decrease of CDC2 expression. | Liberio et al. (2015) |
| Frondoside A(2) | Triterpene glycosides | Cucumaria okhotensis | DU145 LNCaP PC3 22Rv1 VCaP | In vivo | Antiproliferation | Induction of apoptosis Inhibition of metastasis Inhibition of tumor growth | Induction of G2/M cell cycle arrest; upregulation of Bax, Bad, PTEN, cleavage of PARP and caspase-3; downregulation of anti-apoptotic proteins (survivin and Bcl-2); inhibition of pro-survival autophagy by upregulation of phospho-mTOR. Dyshlovoy et al. (2016) |
| Galiellalactone(3) | Ketones | Galiella ruffle | DU145 LNCaP PC3 | In vivo | Induction of apoptosis Inhibition of tumor growth | Inhibition of Stat3 activity; downregulation of the expressions of Bcl-2, Bcl-xl, c-myc and cyclin D1. | Hellsten et al. (2008) |
| Chaetocin(4) | Ketones | Trichoderma virens | PC3 | In vivo | Antiangiogenesis | Disruption of the HIF-1α/p300 complex. | Cook et al. (2009) |
| Chetomin(5) | Ketones | Trichoderma virens | PC3 | In vivo | Antiangiogenesis | Disruption of the HIF-1α/p300 complex. | Cook et al. (2009) |
| Glutoxin(6) | Ketones | Trichoderma virens | PC3 | In vivo | Antiangiogenesis | Disruption of the HIF-1α/p300 complex. | Cook et al. (2009) |
| Halichondramide(7) | Trisoxazol-e macrolides | Chondrosia corticata | PC3 | In vivo | Antiproliferation inhibition of metastasis | The suppression of PRL-3 via downregulation phosphoinositide 3-kinase (P3K) subunits p85 and p110 the expression; downregulation of matrix metalloproteases (MMPs). | Shin et al. (2013) |
| Lejimalide B(8) | Macrolide-s | Eudistoma cf. rigida | LNCaP PC3 | In vivo | Antiproliferation induction of apoptosis | Induction of G0/G1 cell cycle arrest and expression of p21waf1/cip1; downregulation of the expression of cyclin A, E, D survivin, p21B and BNIP3. Wang et al. (2008a) |
| Jasplakinolide(9) | Cyclopentapeptides | Jaspis johnstoni | LNCaP PC3 | In vitro | Antiproliferation | Not investigated. Senderowicz et al. (1995) |
| Malformin A1(10) | Cyclopentapeptides | Aspergillus niger | LNCaP PC3 | In vitro | Antiproliferation induction of apoptosis necrosis | Induction of mitochondrial damage and autophagy. Liu et al. (2016) |
| Stellettin A(11) | Triterpene-s | Geodia japonica | LNCaP | In vivo | Antiproliferation induction of oxidative stress and apoptosis | Upregulation of FasL and caspase-3 expression. Liu et al. (2006) |
| Niphatenone B(12) | Glycerol ethers | Niphates digitalis | LNCaP PC3 | In vitro | Antiproliferation | Binding with the activation function-1 (AF1) region of the AR N-terminus domain (NTD). Meimitis et al. (2012) |
| 4H-1,3-dioxin-4-one-2,3,8-trimethyl | Dioxin | Trichoderma atroviride | PC3 | In vitro | Induction of apoptosis | Increase of expression of caspase -3 | Ks et al. (2019) |

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(Morgenthaler, 2009). These data support the notion that prostate cancer, in most cases, is a hormone (androgen) sensitive disease.

**Overview of the Mechanisms of Castration-Resistant Prostate Cancer**

Historically, there are much debate about the mechanisms of castration resistance, which are mainly summarized as the following by recent studies: canonical AR signaling, relying on AR nuclear translocation and AR-DNA binding, and non-nuclear AR signaling which requires neither AR nuclear translocation nor AR-DNA binding(Qin and Bin, 2019; Pisano et al., 2021).

**Canonical AR Signaling**

The potential mechanisms of canonical AR signaling that lead to CRPC can be categorized into three parts. 1) common alterations in AR, which can lead to AR increase its sensitivity to very low levels of androgens or constitutive activation of AR signaling; 2) AR activation by androgens converted from adrenalandrogens or synthesized intratumorally via the de novo route; 3) alterations in cofactors of the AR pathway (Figure 1).

**Common Alterations in AR**

One possible mechanism by which the prostate cancer becomes resistant to androgen deprivation therapy is alterations in AR, including AR amplification or overexpression, AR mutations and truncated AR lacking ligand-binding domains (ARΔLBD). Thus, these changes in AR increase its sensitivity to very low levels of androgens or lead to constitutive activation of AR signaling. Strictly speaking, this mechanism of prostate cancers is not androgen-independent and the responses still depend on AR and androgen.

**AR Amplification or Overexpression.** Despite low circulating androgens in the CRPC patients, one potential mechanism that would allow tumor cell proliferation is by promoting the expression of the AR itself, which increases ligand-occupied receptor content (Feldman and Feldman, 2001). Plenty of studies have shown that approximately 50% of tumors that become castration resistant after ADT have amplified the AR gene, the most frequent genetic alteration reported for CRPC tumors, whereas none of the untreated primary tumors before androgen ablation had an AR gene amplification (Robinson et al., 2015; Djusberg et al., 2017). Numerous studies provide the simplest explanation of how increased androgen receptor expression leads to resistance to anti-androgen therapy. According to one study, a three-to-five-fold increase in receptor levels could compensate for low ligand levels and restore androgen receptor signaling in xenotransplantation models. (Chen et al., 2004). Although tumors with AR amplification have

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**TABLE 1 | (Continued) Natural compounds obtained from marine organisms or microorganisms with anti-prostate cancer activities.**

| Natural compound | Sort | Name of microorganisms | Cell type | Observation | Activity | Mechanism of action | Refs |
|-----------------|------|------------------------|-----------|-------------|----------|--------------------|------|
| Alternol        | unknown | mutant fungus | PC-3; 22Rv1; LNCaP; PC3 | in vitro | Antiproliferation; Induction of apoptosis | Interaction with multiple Krebs cycle enzymes | Li et al. (2019) |
| Hapalinol H (13) | indole-alkaloid | Fischerella muscicola | PC-3 | in vitro | Antiproliferation; | Through the intrinsic mitochondrial pathway | Acua et al. (2018) |
| Heteronemin (14) | sesterterpenoid | Hyrtios sp. | LNCaP; PC3 | in vitro | Induction of apoptosis | Oxidative and ER Stress Combined with the Inhibition of Topoisomerase II and Hsp90 | Lee et al. (2018) |
| xanthoquinolin | Quinolines | Parengyodontium album MEXU 30064 | PC-3 | in vitro | Induction of apoptosis | Though intrinsic and extrinsic apoptotic pathways | Anaya-Eugenio et al. (2019b) |
| Glutetin (16) | alkaloid | Aspergillus terreus P63 | PC-3 | in vitro | Antiproliferation | Not investigated | Gubiani et al. (2019) |
| Erythromycin (17) | antibiotic | Actinomycete streptomycyes | 22Rv1; VCaP | in vitro | blocking RORg transcriptional regulation activities | Inhibition of the expression of RORg target genes AR and AR variant | Zheng et al. (2020) |
| Urupocidin C (18) | bicyclic guanidine alkaloid | Monanchora pulchra | 22Rv1; LNCaP | in vitro | Induction of apoptosis | Though mitochondria targeting | Dyshlovoy et al. (2020) |
| Pseudopterosin H | diterpene glycosides | Pseudopterogorgia elisabethae | PC-3 | in vitro | reducing PC-3 cell viability | Inducing apoptosis and downregulating the production of intracellular reactive oxygen species | Bowers et al. (2021) |
| Naidixic acid (19) | quinolone antibiotic | Streptomyces sp. (C-7) | PC3 | in vitro | cytotoxic effect | Not investigated | Arora et al. (2018) |
| Discorbain L (20) | alkaloid | Latrunacula sp. | in vivo | Inhibition of cell growth | Not investigated | Harris et al. (2018) |
increased levels of AR, the signal for cell proliferation presumably continues to require androgen (Visakorpi et al., 1995). Maybe this can explain why tumors with castration resistance have increased sensitivity to androgens in a low androgen environment.

**AR Mutations.** In CRPC, the frequency of AR mutations in pretreated tumors is 5–30% (Grasso et al., 2012; Robinson et al., 2015; Kumar et al., 2016). Most mutations identified in CRPC were located in the AR-LBD. These alterations could facilitate AR signaling in CRPC by offering: 1) ligand facilitation, thereby inducing AR activation even in the presence of low or absent levels of androgens and 2) agonist properties to AR antagonists (Coutinho et al., 2016). In addition, mutations can also occur in the AR-NTD that account for about a third of all alterations that contribute to AR transactivation, such as facilitated recruitment of co-factors and other components of the transcriptional machinery, promoted N/C interaction, increased response to DHT activation and enhanced protein stability and nuclear retention (Network C. G. A., 2015; Coutinho et al., 2016).

**Truncated AR Lacking Ligand-Binding Domains (ARΔLBD).** Latest RNA sequencing data from big data sets, strongly suggests that constitutively active ARΔLBD may play a role in 40–50% of patients with CRPC (Robinson et al., 2015). Compared with hormone naïve PCs, ARΔLBDs are frequently upregulated in CRPC, and may serve as an adaptive response to therapies targeting the androgen/AR-signaling axis (Guo et al., 2009; Li et al., 2013). The recent genomic data on unique exon junctions reveals that at least 12 distinct AR-V mRNA species are detectable in primary PCa and 23 in CRPC (Abeshouse et al., 2015). However, among these variants, AR-V3/AR-V7 appears to be one of the most abundantly and ubiquitously expressed isoforms in our screening of a panel of human prostate cancer cell lines and tissues (Guo et al., 2009; Schweizer and Plymate, 2016). In addition, nonsense mutations leading to premature chain termination (Q641X, formerly Q640X) as well as enzymatic cleavage (tr-AR) were also shown to induce ARΔLBDs (Haile and Sadar, 2011). F. Zengerling et al. reported that inhibition of IGF-1R signaling pathway (2018) was downregulated in the Akt/mTOR/MMP-9 signaling pathway, resulting in a down-regulation of AR, Q641X and AR-V7 (2011). F. Zengerling et al. reported that inhibition of IGF-1R

**TABLE 2 | Alkaloids obtained from plants with anti-prostate cancer activities.**

| Natural compound | Botanical name | Cell type | Observation | Activity | Mechanism of action | Refs |
|------------------|----------------|-----------|-------------|----------|---------------------|------|
| Anibamine(21)    | Aniba panurensis | DU145 M12 PC3 | In vitro | Antiproliferation | Binding to the chemokine receptor CCR5 | Zhang et al. (2010b) |
| Berberine(22)    | Coptis chinensis Franch. | DU145 LNCaP PC3 | In vitro | Induction of apoptosis and programmed necrosis | Inhibition of p63-Cyp-D association via decreasing the ROS production; downregulation of HIF-1α and VEGF expression; induction of G1 and G2/M cell cycle arrest by activating ATM-Chk1; induction of caspase-3 and -9 activation; upregulation of bax/bcl-2 expression. | Wang et al. (2012), Zhang et al. (2014) |
| Pipernaïne(23)   | Piper longum L. | DU145 LNCaP PC3 | In vitro | Induction of apoptosis | | Lee et al. (2013b) |
| Piperlongumine(24) | Piper longum L. | LNCaP PC3 | In vitro | Antiproliferation | Induction of G2/M phase cell cycle arrest; upregulation of bax/bcl-2 expression; activation of caspase-3; downregulation of PARP expression. | Kong et al. (2008) |
| Sanguinarine(25) | Argemone mexicana L. | PC3E RNPE1 TEM4-18 | In vitro | Cytotoxicity | Inhibition of RGS17 activity. | Bodle et al. (2017) |
| Piperine(26)     | Piper nigrum L. and Piper longum L. | DU145 | In vitro | Inhibition of migration progression | downregulating the Akt/mTOR/MMP-9 signaling pathway | Yuan and Ying (2018) |
| Neferine(27)     | Nelumbo nucifera Gaerth. | PC3, CD44+ CSCs ; LNCaP | In vitro | Inhibition of proliferation and migration | through p38 MAPK/JNK activation | Erdogan and Turkekul (2020) |

**AR Activation by DHT Synthesized Intratumorally via the de novo Route or Converted From Adrenal Androgens.** There are two possible ways for the initial substrates to convert to intratumoral DHT in CRPC. The first way is that androgens are synthesized intratumorally via the de novo route and the second is that androgens are converted from adrenal androgens.
| Natural compound | Botanical name                  | Cell type | Observation | Activity                  | Mechanism of action                                                                                                                                                                                                 | Refs                                                                 |
|------------------|--------------------------------|-----------|-------------|---------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------|
| Apigenin(28)     | Distributed in various plants  | C4-2B     | In vitro    | Antiproliferation         | Binding with IκKa; inhibition of NF-κB/p65 activity; inhibition of apoptosis proteins and Ku70-Box interaction; inhibition of tumor suppressor ER-β degradation; inhibition of class I HDACs expression; inhibition of ABCB1 expression and sensitivity improvement of docetaxel-resistant prostate cancer cells to docetaxel treatment. | Zhu et al. (2013), Salmani et al. (2017) |
|                  |                                | DU145     |             |                           |                                                                .short                                                                 |                                                                        |
|                  |                                | PC3       |             |                           |                                                                                                          |                                                                      |
|                  |                                | 22Rv1     |             |                           |                                                                                                          |                                                                      |
|                  |                                |           | In vivo     | Anti-invasion             | Suppression of prostate cancer growth                                                                                                                      |                                                                      |
| Baicalein(29)    | Scutellaria baicalensis Georgi | LNCaP     | In vitro    | Antiproliferation         | Induction of G1 cell cycle arrest; inhibition of androgen receptor (AR) expression.                                                                        | Haimson et al. (2005)                                                |
|                  |                                | PC3       | In vivo     |                           |                                                                                                          |                                                                      |
| Cajanol(30)      | Cajanus cajan (L.) Huth        | PC3       | In vitro    | Induction of apoptosis    | Induction of G1 and G2/M cell cycle arrest; modulation of the ERα-dependent PI3K pathway and induction of GSK3 and CyclinD1 activation.                        | Haimson et al. (2005)                                                |
| Cryptocaryone(31)| Cryptocarya wightiana Thwaites | PC3       | In vitro    | Antiproliferation         | Induction of caspase-8 and 3 activation; upregulation of DR5 surface expression; induction of Fas clustering and the association of downstream signaling molecules, including FADD and procaspase-8; induction of DR4 and DR5 aggregation. | Chen et al. (2010)                                                   |
| CG901(32)        | Artocarpus altibis (Parkinson) Fosberg | C4-2B     | In vitro    | Antiproliferation         | Selective inhibition of prostate cancer cell lines proliferation and mouse xenograft growth by inhibiting the expression of STAT3 target genes.                                                                 | Jeon et al. (2015a)                                                 |
|                  |                                | DU145     |             |                           |                                                                                                          |                                                                      |
|                  |                                | PC3       |             |                           |                                                                                                          |                                                                      |
| Daidzein(33)     | Glycine max (L.) Merr.         | DU145     | In vitro    | Antiproliferation         | Decrease the expression of VEGF and AR genes; induction of G2/M phase in the PC3 cells by downregulating Cyclin B1 and CDK1, and upregulating CDK inhibitors (p21 and p27); upregulation of Fas ligand (FasL) and the expression of proapoptotic Bim; downregulation of the expression of p-FOXO3a and increase of the nuclear stability of FOXO3a. | Labow and Layne, (1972)                                              |
|                  |                                | LNCaP     | In vivo     |                           |                                                                                                          |                                                                      |
|                  |                                | PC3       |             |                           |                                                                                                          |                                                                      |
| Fisetin(34)      | Distributed in various plants  | DU145     | In vitro    | Antiproliferation         | Downregulation of the expression of NucO protein; downregulation of MMP-2 and MMP-9 expressions.                                                           | (Shimoi, 1998; Afaq et al., 2008; Khan et al., 2008; Chien et al., 2010; Suh et al., 2010; Mukhtar et al., 2015) |
|                  |                                | LNCaP     |             |                           |                                                                                                          |                                                                      |
|                  |                                | PC3       |             |                           |                                                                                                          |                                                                      |
|                  |                                | 22Rv1     | In vivo     | Inhibition of tumor growth|                                                                                                          |                                                                      |
| Formononetin(35)| Trifolium pratense L.          | PC3       | In vitro    | Antiproliferation         | Induction of G0/G1 phase cell cycle arrest; inhibition of the IGF-1/IGF-1R pathway and alteration of the Bax/Bcl-2 ratio; downregulation of expression levels of cyclin D1 and CDK4. | (Huang et al., 2013; Bi, 2014; Li et al., 2014)                       |
|                  |                                | RWPE1     | In vivo     | Induction of apoptosis    |                                                                                                          |                                                                      |
| Flavokawain B(36)| Piper methysticum G.Forst.     | DU145     | In vitro    | Antiproliferation         | Selective inhibition on androgen receptor (AR)-negative prostate cancer cell growth; induction of apoptosis with associated increased expressions of proapoptotic proteins: death receptor-5, Bim, Puma and downregulation of XIAP and survivin expressions. | Tang et al. (2010)                                                  |
|                  |                                | PC3       |             |                           |                                                                                                          |                                                                      |
|                  |                                | LNCaP     |             |                           |                                                                                                          |                                                                      |
|                  |                                | LAPC4     |             |                           |                                                                                                          |                                                                      |
| Natural compound         | Botanical name                  | Cell type      | Observation | Activity                             | Mechanism of action                                                                                                                                                                                                                   | Refs |
|-------------------------|--------------------------------|----------------|-------------|--------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|
| Genistein (37)          | Glycine max (L.) Merr.         | DU145 PC3 PC-3M| In vitro    | Inhibition of migration              | Prevention of metastasis by directly binding to MEK4 and downregulation of p38 expression; downregulation of expression and activity of MMP-2.                                                                                         | Li and Sarkar, 2002; Hsu et al., 2010 |
| Ginkgetin (38)          | Ginkgo biloba L.               | DU145 LNCaP PC3| In vitro    | Induction of apoptosis               | Induction of G0/G1 cell cycle arrest; selective suppression of STAT3 Tyr705 phosphorylation but not through inhibiting upstream tyrosine kinases and tyrosine phosphatase.                                                                  | Jeon et al. (2015b) |
| Isoliquiritigenin (39)  | Distributed in various plants  | D4-2B LNCaP    | In vitro    | Inhibition of tumor growth           | Downregulation of the expression of NudC protein; downregulation of MMP-2 and MMP-9 expressions.                                                                                                                                       | Zhang et al. (2010a) |
| Isoangustone A (40)     | Ginkgo biloba L.               | DU145 PC3      | In vitro    | Inhibition of apoptosis              | Induction of p27kip1 tumor suppressor gene accumulation by attenuating p27kip1 at Thr 187 phosphorylation; inhibition of CDK2 activation through binding with the CDK2 complex; inhibition of mTOR kinase activity by binding with the mTOR complex. | Lee et al. (2013a) |
| Luteolin (41)           | Distributed in various plants  | LNCaP PC3      | In vitro    | Inhibition of apoptosis              | Inhibition of ANO1 expression; inhibition of the expression and/or function of ARs via regulation of prostate derived Ets transcription factor(PDE5); inhibition of IGF-1/IGF-1R system; decrease of the expression of E-cadherin through MDM.           | Seo et al. (2017) |
| Licochalcone A (42)     | Glycyrrhiza glabra L.          | LNCaP          | In vitro    | Induction of apoptosis               | Induction of G2/M cell cycle arrest; downregulation of cyclin B1 and cdc2 expression; inhibition of phosphorylation of retinoblastoma (Rb); decrease of expression of transcription factor E2F, cyclin D1, CDKs 4 and 6; increase of expression of cyclin E. | Su et al. (2017) |
| Quercetin-6-C-b-D-      | Ulmus wallichiana Planch.      | DU145 LNCaP PC3 RWPE1 | In vitro    | Induction of apoptosis               | Induction of apoptosis via induction of cleaved PARP and Cas-3; induction of G0/G1 cell cycle arrest; inhibition of reactive oxygen generation and AKT/ mTOR survival pathway via directly binding with aryl hydrocarbon receptor. | Hamidullah et al. (2015) |
| glucopyranoside (43)    |                                |                |             |                                      |                                                                                                                                                                                                                                          |      |
| Quercetin (44)          | Distributed in various plants  | DU145 LNCaP PC3| In vitro    | Induction of apoptosis               | Increase of expression of c-Jun and its phosphorylation; decrease of expression of HSP72; intervention of BaP toxicity.                                                                                                                                 | Asea et al. (2001), Yuan et al. (2004), Chaudhary et al., (2007), Aalinkeel et al. (2008) |
| Xanthohumol (45)        | Humulus lupulus L.             | BPH-1 PC3      | In vitro    | Induction of apoptosis               | Induction of S and Sub G1 cell cycle arrest; inhibition of NFkB activity and expression. Upregulation of pro-apoptotic proteins Bax and p53 expression.                                                                                      | Colgate et al. (2007) |

(Continued on following page)
TABLE 3 | (Continued) Flavonoids obtained from plants with anti-prostate cancer activities.

| Natural compound | Botanical name | Cell type | Observation | Activity | Mechanism of action | Refs |
|------------------|----------------|-----------|-------------|----------|---------------------|------|
| Vitexicarpin(46) | Vitex rotundifolia L.f. | PC3 | In vitro | Induction of apoptosis | Induction of G2/M cell cycle arrest. | Meng et al. (2012) |
| 2′,4′- dihydroxychalcone (47) | Herba oxytropis | PC3 | In vitro | Induction of apoptosis | Induction of G1/S cell cycle arrest. | Sheng et al. (2015) |
| Auriculasin (48) | Flemingia macrophylla var. philippinensis (Merr. & Rolfe) H. Ohashi | LNCaP, FGC, RWPE-1 | In vitro | Induction of apoptosis; antiproliferation | Regulation of the P38/AKT/mTOR pathway in LNCaP prostate cancer cells; ROS accumulation | Cho et al. (2018) |
| Narigenin (49) | citrus fruits and tomatoes | MAT-LyLu cells | In vitro | Inhibition of metastasis | Blocking voltage-gated sodium channels | Gurnushan Aktas and Akgun (2018) |
| Casticin (50) | Vitex rotundifolia L.f., tomatoes | DU 145 | In vitro | Inhibition of prostate cancer cell metastasis | Inhibition of the protein levels of AKT, GSK3β, Snail, and MMPs (MMP-2, -9, -13, and -7); diminution of the expressions of NF-κB p65, GRB2, SOS-1, MEK-p-ERK1/2, and p-JNK1/2 | Lin et al. (2019) |

DHT Intratumorally via the de novo Route. The use of cholesterol for de novo steroidogenesis requires the components of the steroidogenic machinery present in the adrenal and gonads, including steroidogenic acute regulatory proteins, CYP11A1 and CYP17A1 (Miller and Auchus, 2011), which may play important roles in prostate cancer (Locke et al., 2008). Comparisons between primary prostate cancer and CRPC demonstrate that the transcription levels of these proteins are upregulated in CRPC (Montgomery et al., 2008) and CYP17A1 protein is detectable in a subset of metastatic CRPC cases (Efstathiou et al., 2012). In contrast to steroidogenesis in the adrenals and gonads, CRPC expresses steroid-5α-reductase (SRD5A1) with obvious 5α-reductase activity (Chang et al., 2011). One of the functions of robust SRD5A enzyme activity is that any de novo steroidogenesis would likely occur through the back door pathway that bypasses the requirement for T and involves 5-reduction of a 21-carbon steroid (pregesterone or 17α-hydroxyprogesterone) instead of a 19-carbon androgen (Shaw et al., 2000; Auchus, 2004). Although this biochemical pathway may be engaged in CRPC, the relatively lengthy eight enzymatic steps required for conversion from cholesterol to DHT, the abundance of adrenal precursors present in serum, and the much closer pathway proximity of adrenal precursors to DHT, together suggest that adrenal precursors serve as the major substrate pool.

DHT Converted From Adrenal Androgens. There are two possible pathways from adrenal precursor steroids to DHT (Luu-The et al., 2008; Chang and Sharifi, 2012). The canonical adrenal pathway is the route that results in T synthesis as the penultimate metabolite, which undergoes 5-reduction to DHT (Scher and Sawyers, 2005; Ryan and Tindall, 2011; Hoffland et al., 2012; Stein et al., 2012). This pathway is probably favored in the field because of the general notion that T must be the precursor to DHT and T is frequently detectable at concentrations greater than DHT in CRPC, as occurs with gonadal androgen physiology (Titus et al., 2005; Montgomery et al., 2008). In this pathway, DHEA is converted by 3β-hydroxysteroid dehydrogenase (3βHSD) to androstenedione (AD), which is then 17-keto reduced by aldo-keto reductase 1C3 (AKR1C3) or 17βHSD3 to T, the immediate precursor to DHT. The second possible pathway is that AD, like T, a 3-keto, Δ4-steroid, is also a potential substrate for SRD5A (Tomkins, 1957). AD is reduced to 5α-androstanedione (5α-dione), which then becomes the immediate precursor to DHT. The 5α-dione pathway is the major pathway for the synthesis of DHT in CRPC (Chang et al., 2011).

Alterations in Cofactors of the AR Pathway

Resistance to AR-targeted therapies in CRPC was also associated with genomic and transcriptomic alterations in coregulators of the AR pathway. Expression of 50 of the ~200 AR-associated coregulators is aberrant in clinical CRPC specimens (Liu et al., 2017). For example, a higher frequency of mutations in FOXA1, the gene encoding a pioneer factor that facilitates AR chromatin binding and transcriptional activation, was found in CRPC (12%) than in primary prostate cancer (4%) (Watson et al., 2013; Abeshouse et al., 2015). In addition, as one class of coregulators, steroid receptor coactivators (SRC-1, SRC-2 and SRC-3) play a key role in facilitating aberrant AR signaling in CRPC e. There have been studies reported that all 3 SRCs is elevated in CRPC (Taylor et al., 2010; Grasso et al., 2012; Abeshouse et al., 2015; Beltran et al., 2016; Bernemann et al., 2016). GATA2, another AR pioneer factor in the AR signaling axis, is aberrant expressed in CRPC and associated with poor outcome (He et al., 2014; Yan et al., 2014). Gupta et al. detected genomic copy number changes of circulating tumor cells from 16 patients with CRPC resistant to abiraterone or enzalutamide and revealed that multiple genes encoding AR coregulators had copy number alterations, including copy number gains BRD4 (43.75%) (Gupta et al., 2017). Moreover, changes of AR corepressors also play a key role in CRPC. For example, loss of activity of the key nuclear receptor corepressors NCOR1 and NCOR2, is prevalent...
| Natural compound | Botanical name | Cell type | Observation | Activity | Mechanism of action | Refs |
|------------------|----------------|-----------|-------------|----------|---------------------|------|
| Artemisinin(51)  | Artemisia annua L. | DU145 PC3 | In vitro | Induction of apoptosis | Increase of synthesis, and cleavage of procaspase-9, cleavage of caspase-3, and PARP-1 degradation. | Nakase et al. (2009) |
| Betulinic Acid(52) | Bacopa monnieri (L.) Wettst. | LNCaP | In vitro | Induction of apoptosis | Activation of selective proteasome-dependent degradation of the transcription factors specificity protein 1(Sp1), Sp3, and Sp4; regulation of survivin and VEGF expression; downregulation of NF-kappaB expression. | Chinthariapalli et al. (2007) |
| Celastrol(53)     | Tripterygium wilfordii Hook.f. | LNCaP PC3 | In vitro | Induction of apoptosis | Accumulation of ubiquitinated proteins and three natural proteasome substrates IKB-A, Bax, and p27. | Wolfram et al. (2014) |
| Caseamembrin C(54) | Casearia membranacea | PC3 | In vitro | Antiproliferation | Downregulation of Bcl-2 and Bcl-xL expression; upregulation of Mcl-1 protein and activation of caspase-9 and caspase-3. | Huang et al. (2004) |
| Glycyrrhizin(55)  | Glycyrrhiza glabra L. | DU145 LNCaP | In vitro | Antiproliferation | Downregulation of the expression of caspase-3 and caspase-8. | Thirugnanam et al. (2008) |
| Lycopene(56)      | Distributed in various plants | PC3 | In vitro | Antiproliferation, Antimetasis | Inhibition of the androgen receptor element, resulting in decreased PSA velocity; inhibition signaling of insulin-like growth factor-I (IGF-I); decrease of the expression of αvβ3 and αvβ5 integrin. | (Eureyko et al., 2009; Wertz, 2009; Tang et al., 2011; Holzapfel et al., 2013) |
| Oridonin(57)      | Isodon rubescens (Hemsfl.) H.Hara | PC3 | In vivo | Induction of apoptosis | Increase of expression of P21 and the mRNA level of beclin; increase of caspase-3 activity. | (Deepak and Handa, 2000; Xiang et al., 2012; Ming et al., 2016) |
| Pachymic acid(58) | Poria cocos | DU145 LNCaP | In vitro | Antiproliferation | Decrease of prostaglandin synthesis and AKT activity. | Gapter et al. (2005) |
| Pseudolaric acid B(59) | Larix kaempferi (Lamb.) Carrière | DU145 LNCaP | In vitro | Antiproliferation | Increase of ROS generation and Bcl-2 degradation. | Zhao et al. (2012) |
| Sugiol(60)        | Salvia prionitis Hance | DU145 LNCaP PC3 | In vitro | Antiproliferation | Induction of G0/G1 cell cycle arrest; downregulation the expression of STAT3; interaction with TKT. | Jung et al. (2015) |
| Triptolide(61)    | Tripterygium wilfordii Hook.f. | DU145 LNCaP PC3 22Rv1 | In vitro | Antiproliferation | Decrease of CDK7-mediated phosphorylation; disruption of the phosphorylation of AR through XRS/CDK7. | Fei et al. (2016) |
| Ursolic Acid(62)  | Distributed in various plants | DU145 LNCaP | In vitro | Antiproliferation | Upregulation of DRS activation of JNK, inhibition of NF-κB and STAT3 pathways. | (Deepak and Handa, 2000; Shamnugam et al., 2011; Meng et al., 2019) |
| Zerumbone(63)     | Zingiber zerumbet (L.) Roscoe ex Sm. | DU145 HRPCC PC3 | In vitro | Antiproliferation | Increase of MPM-2 expression; increase of Bcl-2 and Bcl-xL phosphorylation; induction of Cdk1 activity; induction of Cdk25C downregulation. | Chan et al. (2015) |
| β-elemene(64)     | Distributed in various plants | DU145 PC3 | In vitro | Antiproliferation | Increase of cytochrome c; activation of PARP and caspase-3, -7, -9, and -10. | Li et al. (2010) |

(Continued on following page)
in CRPC due to mutation and/or deletion (Grasso et al., 2012; Abeshouse et al., 2015; Kumar et al., 2016).

Non-nuclear AR Signaling

Trafficking from the nucleus into the cytoplasm, AR may have unexpected consequences because AR has known functions in the cytoplasm, which is called non-genomic signaling (Foradori et al., 2008). One of the main characteristics of non-nuclear signaling is its rapidity with which it occurs. When steroid receptors stay in the cytosol, they can undergo several protein–protein interactions within seconds to minutes after steroid stimulation, which activates a variety of signaling pathways to promote the development of CRPC (Figure 2).

### PI3K/AKT Signaling Pathway
The PI3K/AKT pathway is one of the most frequently activated signal transduction pathways in human cancer, including prostate cancer (Hoxhaj and Manning, 2020; Park et al., 2018; Braglia et al., 2020). Alterations of the PI3K/AKT pathway, including altered expression, mutation, and copy number alterations, have been reported in 42% of primary prostate tumors and 100% of metastatic tumors (Taylor et al., 2010). Alterations of the PI3K/AKT pathway, including altered expression, mutation, and copy number alterations, have been reported in 42% of primary prostate tumors and 100% of metastatic tumors. Androgens induce the accumulation of TORC2 complex, rapamycin insensitive chaperone of mTOR and stress activated protein kinase interacting protein 1 in the nucleus, thus stimulating TORC2 to activate Akt (Fang et al., 2012). Activated AKT can stimulate many downstream functions via
| Natural compound | Botanical name | Cell type | Observation | Activity | Mechanism of action | Refs |
|------------------|----------------|-----------|-------------|----------|---------------------|------|
| Atraric acid (76) | Prunus africana (Hook.f.) Kalkman | LNCaP | In vitro | Inhibition of prostate cancer cell growth | Inhibition of AR nuclear translocation. | Schleich et al. (2006) |
| Curcumin (77)    | Curcuma longa L. | DU145 PC3 | In vitro | Antiproliferation | Increase of the expression of MT1-MMP and MMP2 proteins; inhibition of the DNA-binding ability of NCo. | Yang et al. (2017) |
| Ellagic Acid (78) | Distributed in various plants | LNCaP | In vitro | Antiproliferation Induction of apoptosis | Increase of Bax/Bcl2 ratio and increase caspases 3, caspases 6, caspases 8, and caspases 9 and PARP cleavage; inhibition of mT0R activation and reduction of intracellular levels of β-catenin; downregulation of the expressions of anti-apoptotic proteins, silent information regulator 1 (SIRT1), human antigen R (HuR) and heme oxygenase-1 (HO-1). | Vanella et al. (2013) |
| Gallic Acid (79)  | Toona sinensis (Juss.) M.Roem. | DU145 PC3 22Rv1 | In vitro | Inhibition of migration Induction of apoptosis | Activation of Chk1 and Chk2 and inhibition of Cdc25C and Cdc2 activities; blocking of the p38, JNK, Pkc and P38/AKT signaling pathways and downregulation of NF-kB protein level; inhibition of MMP2 and MMP 9 gene expression. | Hask et al., 2003; Kaur et al., 2009 |
| Gossypol (80)     | Gossypium hirsutum L. | DU145 PC3 | In vitro | Induction of apoptosis | Downregulation of Bcl-2 and Bcl-xl and the upregulation of Bax; activation of caspase3, caspase8 and caspase9 through the ROS-independent mitochondrial dysfunction pathway and the increase of PARP cleavage; suppression of the expression of AP-1 and NF-kB blocked the activation of VEGF receptor 2 kinase. | Huang et al. (2006) |
| Honokiol (81)     | Magnolia officinalis | PC3 LNCaP Myc-CaP | In vitro | Induction of apoptosis | Inhibition of prostate tumor growth | Shigemura et al. (2007) |
| Nordihydroguaiaretic acid (82) | Larrea tridentata (DC.) Coville Magnolia obovata Thunb. | PC3 LNCaP | In vitro | Antiproliferation | Suppression of NRP1 function. | Li et al. (2016) |
| Obovatol (83)     | Reynoutria japonica Houtt. | DU145 | In vitro | Induction of apoptosis | Inhibition of TNF-α and TPA-induced DNA binding activity of NF-kB; translocation inhibition of p65 and p50 into nucleus via decreasing kB phosphorylation; increase of the apoptotic genes expression: Bax, caspase-3, caspase-9; inhibition of the anti-apoptotic genes expression: Bcl-2, inhibitor of apoptosis protein (IAP-1) and X chromosome IAP (XIAP). | Suyong et al. (2009) |
| Procyanidin (84)  | Arachis hypogaea L. | DU145 | In vitro | Antiproliferation | Downregulation of Bcl-2 and Bcl-xl and upregulation of Bax; activation of caspases-3, -8 and -9 and increased PARP cleavage. | Chang et al. (2013) |
| Sinapic acid (85) | various vegetables and fruit species | PC3; LNCaP | In vitro | Antiproliferation; Induction of apoptosis; Inhibition of migration invasion | Increase of the expression of BAX, CASP3, CASP8, CYCS, FAS, TIMP-1 and CDH1, decrease of expression of MMP-9 in PC-3 cells; decrease of in the expressions of CDH2, MMP-2 and MMP-9 in LNCaP cells; increase of caspase-3 activity | Eroğlu et al. (2018) |

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its kinase activity, including glycogen synthase kinase 3 (GSK3), tuberous sclerosis complex (TSC), FOXO transcription factors, NF-kappa-B and Bcl-2 family members BAD, which regulate a range of cellular processes (Liu et al., 2009; Courtney et al., 2010). It is estimated that genomic phosphatase and tensin homolog gene (PTEN) alterations, which is a negative inhibitor of PI3K/AKT pathway, occur in 9–45% of high-grade prostate intra-epithelial neoplasia (HG-PIN), 20–60% of localized prostate cancer, and up to 100% of cases of metastatic prostate cancer (Taylor et al., 2010; Jia et al., 2013).

### Src Signaling Pathway

Preclinical studies have confirmed that non receptor tyrosine kinase c-Src and Src family kinase (SKF) regulate a complex signal network, driving the development of castration-resistance prostate cancer and bone metastasis. (Cai et al., 2011). After the establishment of bone metastasis, prostate cancer cells destroy the balance of osteoclasts and osteoblasts by secreting a variety of molecules, such as growth factors and cytokines that disrupt the normal process of bone maintenance and reconstruction (Yang et al., 2001; Mundy, 2002). The balance is in favor of

| Natural compound | Botanical name | Cell type | Observation | Activity | Mechanism of action | Refs |
|------------------|----------------|-----------|-------------|----------|---------------------|------|
| Carvacrol (86)   | Origanum and Thymus | Human OSCC Tca-8113, SCC-25 | In vitro | Antiproliferation, inhibition of metastasis and invasion; Induction of apoptosis | Regulating the cell cycle-associated proteins (P21, CCND1 and CDK4) and apoptosis-associated proteins (Cox2, Bcl-2, and Bax); inhibiting P-FAK, and reducing β-catenin, ZEB1, and MMP-2/9 expression | Dai et al. (2016) |

| Hispolon (87) | Phellinus linteus | DU145 | In vitro | Induction of apoptosis | Via modulation of mitochondrial and STAT3 pathways | Masood et al. (2019) |

### TABLE 5 | (Continued) Polyphenols obtained from plants with anti-prostate cancer activities.

| Natural compound | Botanical name | Cell type | Observation | Activity | Mechanism of action | Refs |
|------------------|----------------|-----------|-------------|----------|---------------------|------|
| Deoxypodophyllotoxin (88) | Anthriscus sylvestris (L.) Hoffm. | LNCaP PC3 | In vitro | Antiproliferation | Accumulation of the reactive oxygen species, intracellular Ca²⁺; increase of mitochondrial membrane potential. | Kim et al. (2013) |
| Magnolol (89) | Magnolia officinalis Rehdeter & E.H.Wilson PřEC | PC3 | In vivo | Induction of apoptosis | Decrease of MMP-2 and MMP-9 expression; decrease of the level of phosphorylated AKT. | Lee et al. (2009) |
| Silibinin (90) | Stilbium marianum (L.) Gaerthn. | LNCaP 22Rv1 | In vitro | Antiproliferation | Activation of acetyl-CoA carboxylase; reduction in hypoxia-induced NADPH oxidase (NOX) activity; increase of the lipid accumulation and NOX activity; downregulation of HIF-1α expression, lipid levels, clonogenicity and NOX activity. | Ting et al. (2016) |
| VB1 (91) | Vitex negundo L. | PC3 | In vitro | Induction of apoptosis | Activation of PARP cleavage. | Zhou et al. (2009) |
| Magnolone (92) | Phellodendri amurenensis cortex | 22RV1 | In vitro | Antiproliferation | Disturbance of nutrition metabolism and energy metabolism | Sun et al. (2018) |
| Arctigenin (93) | Arctium lappa L. | PC-3M | In vitro | Induction of apoptosis and autophagy | Via PI3K/Akt/mTOR inhibition | Sun et al. (2021) |
| 2-(5′-allyl-3″,5″,9″-trihydroxy-4″-methoxyphenyl-furan)-3-hydroxy-7,8-furan-ring-chromen-4-one (94) | Hosta plantaginea (Lam.) Aschers | LNCaP | In vitro | Inhibition of cell growth | Not investigated | Wei et al. (2020) |
| 2,3-dehydrosilychristin (96) | Hosta plantaginea (Lam.) Aschers | LNCaP | In vitro | Inhibition of cell growth | Not investigated | Wei et al. (2020) |
| 2-(5′-allyl-4″,9″-dihydroxyphenyl-furan)-3-hydroxy-7-methoxy-8-(6″,7″-dimethyl-furan-2″-one)-chromen-4-one (94) | Hosta plantaginea (Lam.) Aschers | LNCaP | In vitro | Inhibition of cell growth | Not investigated | Wei et al. (2020) |
| 2,3-dehydrolychristin (98) | Hosta plantaginea (Lam.) Aschers | LNCaP | In vitro | Inhibition of cell growth | Not investigated | Wei et al. (2020) |
| silchristin A (97) | Hosta plantaginea (Lam.) Aschers | LNCaP | In vitro | Inhibition of cell growth | Not investigated | Wei et al. (2020) |
| Natural compound     | Sort               | Botanical name               | Cell type | Observation | Activity                        | Mechanism of action                                                                                                                                   | Refs                                      |
|---------------------|--------------------|------------------------------|-----------|-------------|---------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|
| Aloe-emodin(98)     | Anthraquin-ones    | *Rheum palmatum* L.         | PC3       | *In vitro*  | Suppression of prostate cancer   | Binding with mTOR complex2; inhibition of mTORC2 kinase activity and downstream substrates of mTORC2, AKT and PKCa activity.                      | Liu et al. (2012a)                        |
| Calcitriol(99)      | Secosteroids       | Distributed in various plants | C4-2B     | *In vitro*  | Antiproliferation                | Upregulation of Vitamin D receptor (VDR) expression; induction of BAX expression; increase of cleaved caspase-3 and downregulation of cdk2 expression, induction of [Ca2+] rise by evoking phospholipase C-dependent Ca2+ release from the endoplasmic reticulum and Ca2+ entry via phospholipase A2-sensitive store-operated Ca2+ channels; regulation of FOXO3a/β-catenin/GSK-3β signaling; regulation of estrogen metabolism and acting as an antiandrogen, finally leading downregulation of the AR and PSA. | Ben-Eltikri et al. (2016)                 |
| Diallyl Trisulfide(101) | Trisulfides        | *Allium sativum* L.         | DU145     | *In vitro*  | Induction of apoptosis           | Downregulation of XAP protein expression.                                                                                                               | Kim et al. (2011)                         |
| Embelin(102)        | Quinones           | *Embelia ribes Burm.f.*     | CA-2B     | *In vitro*  | Antiproliferation                | Induction of G1 cell cycle arrest; induction of apoptosis by triggering caspase 3 activation and PARP cleavage; inhibition of survivin expression by inhibiting AKT/NF-κB pathway. | Xu et al. (2017)                          |
| ESK246(103)         | Glycosides         | *Pittosporum venulosum*     | LNCaP     | *In vitro*  | Antiproliferation                | Inhibition of leucine uptake, leading to reduced mTORC1 signaling, cell cycle protein expression and cell proliferation.                     | Wang et al. (2014)                       |
| Ginsenoside Rg3(104) | Steroids           | *Panax ginseng C.A.Mey.*    | PC-3M     | *In vitro*  | Antiproliferation                | Suppression of aquaporin 1 (AQP1) water channel protein expression by activating p38 MAPK.                                                            | Pan et al. (2012)                        |
| Natural compound | Sort | Botanical name | Cell type | Observation | Activity | Mechanism of action | Refs |
|------------------|------|----------------|-----------|-------------|----------|---------------------|------|
| Guggulsterone(105) | Steroids | Commiphora mukul (Hook. ex Stocks) Engl. | DU145 LNCaP PC3 | in vitro | Antiproliferation | Induction of apoptosis | Singh et al. (2005) |
| | | | | | | Increase of Bax expression, downregulation of Bcl-xl and Bcl-2 expression; increase of caspase-9 and caspase-8 cleavage; increase of ROI generation by activating JNK; selective inhibition of androgen receptor promoter activity in LNCaP cell. |
| Guttiferone F(106) | Prenylated benzophenones | Allanblackia stuhlmannii (Engl.) Engl. | LNCaP PC3 | in vitro | Induction of apoptosis | Increase of sub-G1 fraction and DNA fragmentation; down-regulation of androgen receptor expression and phosphorylation of ERK1/2. | Li et al. (2015c) |
| Indole-3-carbinol (I3C)(107) | Indoles | Distributed in various plants | LNCaP | in vitro | Antiproliferation | Induction of G1 cell-cycle arrest and downregulation of AR expression and inhibition of AR promoter activity. | Hsu et al. (2005) |
| Juglone(108) | Quinones | Juglans mandshurica Maxim. | LNCaP | in vitro | Antiproliferation | Induction of apoptosis | Jiang et al. (2013) |
| Marchantin M(109) | Diphenyls | Asterella angusta | DU145 LNCaP PC3 | in vitro | Induction of apoptosis | Inhibition of the 20S proteasome activity; induction of microtubule-associated protein-1 light chain-3 beta (LC3B) expression and conversion; induction of RNA-dependent protein kinase-like ER kinase activity; suppression of the PI3K/AKT/mammalian target of rapamycin axis through preventing the activation and expression of AKT. | Jiang et al. (2013) |
| Moniliformediquinone (110) | Phenanthradiquinones | Dendrobium moniliforme (L.) Sw. | DU145 PC3 | in vitro | Antiproliferation | Induction of apoptosis | Hsu et al. (2014) |
| | | | | | | Inhibition of tumor growth | | |

(Continued on following page)
TABLE 7 (Continued) Other compounds obtained from plants with anti-prostate cancer activities.

| Natural compound | Sort       | Botanical name                  | Cell type   | Observation | Activity                      | Mechanism of action                                                                                   | Refs                                                                 |
|------------------|------------|---------------------------------|-------------|-------------|-------------------------------|--------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------|
| Oleuropein (111) | Glycosides | Olea europaea L.                | LNCaP       | In vitro    | Anti-oxidation Cytotoxicity    | Inhibition of tumor cell growth and invasiveness                                                       | Acquaviva et al. (2012)                                              |
|                  |            |                                 | DU145 BPH-1 | In vivo     |                               |                                                                                                         |                                                                      |
| Physapubescin B (112) | Steroids | Physalis pubescens L.          | PC3         | In vitro    | Antiproliferation             | Downregulation of Cdc25C protein expression; induction of G2/M cell cycle arrest; decrease of Cdc25C level and increase of levels of CyclinB1, P21 and p-Cdk1 (Tyr15). | Ding et al. (2015)                                                  |
| Pristimerin (113) | Esters     | Distributed in various plants   | PC3         | In vitro    | Induction of apoptosis        | Inhibition of proteasomal chymotrypsin-like activity assay and polyubiquitinated protein accumulation; Interaction with the proteasomal β5 subunit in a conformation suitable for proteasome inhibition; increase of caspase-3 activation. | Yang et al. (2008)                                                   |
|                  |            |                                 | LNCaP       | In vivo     |                               |                                                                                                         |                                                                      |
|                  |            |                                 | C4-2B       | In vitro    |                               |                                                                                                         |                                                                      |
| Phenethyl-      | Isothiocyanates | Distributed in various plants   | C4-2B       | In vitro    | Antiproliferation             | Increase in the G2-M phase; downregulate AR expression through inhibition of the transcription factor Sp1 and p300/CBP-associated factor (PCAF); upregulation of miR-194 via directly targeting BMP1, and downregulation of BMP1 led to decrease expression of key oncogenic matrix metalloproteinase, MMP2 and MMP9. | Wang et al. (2006), Yin et al. (2009), Jiang et al. (2013), Zhang et al. (2016) |
| Isothiocyanat(PEITC) (114) |            |                                 | DU145       | In vivo     |                               |                                                                                                         |                                                                      |
|                  |            |                                 | LNCaP       | In vivo     |                               |                                                                                                         |                                                                      |
| Putrescine-1,4- | Phenylprop-anoids | Distributed in various plants   | DU145       | In vitro    | Induction of apoptosis        | Increase the caspase-3 activity; increase of ROS generation.                                              | Russo et al. (2007)                                                  |
| dicinnamide (115) |            |                                 |             |             |                               |                                                                                                         |                                                                      |
| Physalins A(116) | Secosteroids | Physalalekekei var. franchetii | C4-2B 22Rv1 | In vitro    | Antiproliferation             | Inhibition of JNK and ERK activation; downregulation of AR expression and PAS expression.                  | Han et al. (2011)                                                   |
|                  |            |                                 |             |             |                               |                                                                                                         |                                                                      |

(Continued on following page)
### TABLE 7 | (Continued) Other compounds obtained from plants with anti-prostate cancer activities.

| Natural compound | Sort          | Botanical name                  | Cell type | Observation | Activity | Mechanism of action | Refs                        |
|------------------|---------------|---------------------------------|-----------|-------------|----------|---------------------|-----------------------------|
| Physalins B (117) | Secosteriods  | Physalis alkekengi var. franchetii | C4-2B 22Rv1 | *in vitro*  | Antiproliferation | Inhibition of JNK and ERK activation; downregulation of AR expression and PAS expression. | Han et al. (2011) |
| Physachenolide C (118) | Steroids | Distributed in various plants | LNCaP PC3 | *in vitro* | Cytotoxicity | Inhibition of tumor cell growth | Xu et al. (2015) |
| Reevesioside A (119) | Glycosides | Reevesia formosana | DU145 PC3 | *in vitro* | Antiproliferation | Induction of G1 cell cycle arrest by the downregulation of several related cell cycle regulators, including cyclin D1, cyclin E and CDC25A; increase of association between RB and E2F1 and the subsequent suppression of E2F1 activity via decreasing RB phosphorylation. | Leu et al. (2014) |
| Scopoletin(120) | Coumarins | Erycibe obtusifolia | LNCaP | *in vitro* | Antiproliferation | Induction of apoptosis | Li et al. (2015a) |
| Sulforaphane(SNF) (121) | Sulphides | Distributed in various plants | TRAMP C1 | *in vitro* | Anti-oxidation | Regulation of Nrf2's CpGs demethylation and reactivation. | Zhang et al. (2013) |
| Thymoquinone (122) | Quinones | Nigella sativa | C2-2B DU145 LNCaP PC3 | *in vitro* | Induction of apoptosis | Not investigated. | Trang et al. (1993) |
| Wedelolactone(123) | Esters | Wedelia sinensis | DU145 PEC PC3 LNCaP | *in vitro* | Induction of apoptosis | Increase of c-JNK and caspase-3 activity by downregulation of PKCε without AKT inhibition. Increase of Nrf2 expression via the Nrf2 promoter CpGs demethylation. Induction of [Ca\textsuperscript{2+}]\textsuperscript{i} rise through PKC-regulated store-operated Ca\textsuperscript{2+} channels and PLC-dependent Ca\textsuperscript{2+} release from the endoplasmic reticulum. | Koka et al. (2010), Sarveswaran et al. (2012) |
| Z-Ligustilide(124) | Esters | Angelica sinensis (Oliv.) Diels | TRAMP C1 | *in vitro* | Cytotoxicity | Increase of [Ca\textsuperscript{2+}]\textsuperscript{i} rise through PKC-regulated store-operated Ca\textsuperscript{2+} channels and PLC-dependent Ca\textsuperscript{2+} release from the endoplasmic reticulum. | Su et al. (2013) |
| 2,5-dimethylphenol(125) | Phenols | Chlaenius cordicolli | PC3 | *in vitro* | Cytotoxicity | | Wang et al. (2016a) |
| 3-oxo-trucallic acid (126) | Lupanic acids | Boswellia carteri Birdw. | LNCaP PC3 | *in vitro* | Induction of apoptosis | | Estrada et al. (2010) |

(Continued on following page)
TABLE 7 | (Continued) Other compounds obtained from plants with anti-prostate cancer activities.

| Natural compound | Sort     | Botanical name        | Cell type | Observation | Activity                      | Mechanism of action                                                                                     | Refs                        |
|------------------|----------|-----------------------|-----------|-------------|-------------------------------|---------------------------------------------------------------------------------------------------------|-----------------------------|
| 3-α-acetoxy-triucallic acid(127) | Lupanic acids | *Boswellia carteri* Birdw. | LNCaP PC3 | *in vitro* | Induction of apoptosis         | Inhibition of Akt activity and Akt signaling pathways, including glycogen synthase kinase-3β and BAD phosphorylation, and nuclear accumulation of p65, androgen receptor, β-catenin, and c-Myc. | Estrada et al. (2010) |
| 3-β-acetoxy-triucallic acid(128) | Lupanic acids | *Boswellia carteri* Birdw. | LNCaP PC3 | *in vitro* | Induction of apoptosis         | Inhibition of Akt activity and Akt signaling pathways, including glycogen synthase kinase-3β and BAD phosphorylation, and nuclear accumulation of p65, androgen receptor, β-catenin, and c-Myc. | Estrada et al. (2010) |
| 6a-acetoxyanopterine(129) | Esters   | *Anopterus macleayanus* | LNCaP PC3 | *in vitro* | Antiproliferation              | Interaction with tubulin.                                                                                   | Levrier et al. (2016) |
| 24-epibrassinolide(130) | Brassinosteroids | Distributed in various plants | DU145 LNCaP | *in vitro* | Antiproliferation; Induction of apoptosis | Induction of G1 cell cycle arrest accompanied by reductions in cyclin D1, CDK4/6 and pRb expression in LNCaP cells; induction of G2/M cell cycle arrest by reductions in cyclin A; cyclin expression in DU145 cells. | Steigerova et al. (2012) |
| 25-OH-PPD (131) | Saponins | *Panax ginseng* C.A.Mey. | LNCaP PC3 | *in vitro* | Antiproliferation              | Induction of G1 cell cycle arrest by downregulation of MDM2, E2F1, Bcl2, cdk2/4/6, and cyclin D1 expressions; increase of p21, p27, and Bax expressions; induction of PARP cleavage and caspases activation. | Wang et al. (2008a) |
| 28-homocastasterone(132) | Brassinosteroids | Distributed in various plants | DU145 LNCaP | *in vitro* | Antiproliferation; Induction of apoptosis | Induction of G1 cell cycle arrest accompanied by reductions in cyclin D1, CDK4/6 and pRb expression in LNCaP cells; induction of G2/M cell cycle arrest via reductions in cyclin A expression. | Steigerova et al. (2012) |

(Continued on following page)
| Natural compound | Sort | Botanical name | Cell type | Observation | Activity | Mechanism of action | Refs |
|------------------|------|----------------|-----------|-------------|----------|---------------------|------|
| 2′-Hydroxycinnamaldehyde (133) | Aldehydes | Cinnamomum verum J.Presl | DU145; LNCaP | In vitro; In vivo | Antiproliferation; Induction of apoptosis | Signal transducer and activator of transcription 3 inactivation and reactive oxygen species generation | Yoon et al. (2019) |
| Methylucidone (134) | cyclopentenedione | Lindera erythrocarpa Makino (Lauraceae) | DU145 | In vitro | Inhibition of cell growth; Induction of apoptosis | Arrest of the cell cycle at G1 phase; regulation of the expression of the protein tyrosine phosphatase MEG2 | Jin et al. (2018) |
| Ophiopogon D′ (135) triterpenoid saponins | Radix Ophiopogonis | PC3; DU145; DU-145 | In vitro | Induction of apoptosis | Via a RIPK1-related pathway | Lu et al. (2018) |
| Corchorusoside C (136) steroid | Streptocaulon juventas Merr. (Apocynaceae) | DU-145 | In vitro | Induction of apoptosis | Inhibition of activity and protein expression of NF-κB (p50 and p65), IKKα and β, and ICAM-1; decrease of protein expression of Bcl-2 and increase of expression of PARP-1; increase of caspases 3 and 7; downregulation of cell cycle proteins (cdk1, pcdk1, cyclin A and B) in DU145 and PC3 cells; downregulation of cdk2 in PC3 cells; downregulation of Akt, pAKT 18 and Bcl-2 proteins; upregulation of Bax | Anaya-Eugenio et al. (2019a) |
| Daucosterol (137) steroid saponin | Crataeva adansonii DC (Capparaceae) | LNCaP; DU145;PC3 | In vitro | Antiproliferation; inhibition of cell growth; induction of apoptosis | Downregulation of cell cycle proteins (cdk1, pcdk1, cyclin A and B) in DU145 and PC3 cells; downregulation of cdk2 in PC3 cells; downregulation of Akt, pAKT 18 and Bcl-2 proteins; upregulation of Bax | Zingue et al. (2019) |
| Cyanidin 3-glucoside (138) Glycosides | The dark purple glutinous rice (Oryza sativa L.) cultivar Luem Pua (LP) | PC3 | In vitro | Inhibition of progressive cancer cell behaviors | Inhibit EMT through Smad signaling pathway(s) mediating Snail/ E-cadherin expression | Jongsomchai et al. (2020) |
| Germacrone (139) Ketones | Rhizoma Curcuma | PC-3;22RV1 | In vitro | Antiproliferation; Induction of apoptosis | Inhibiting the Akt/mTOR signaling pathway | Yu et al. (2020) |
| Ineupatolide (140) Esters | Carpesium cernuum L. | PC-3 | In vitro | Antiproliferation | Promoting apoptosis and arresting the cell cycle in the G2 and S phases; | Huang et al. (2021) |
| Jegosaponin A and B (141 and 142) Saponins | Styrax japonica Siebold et al. Zuccarini. | PC-3 | In vitro | Exhibiting cell membrane disruptive properties | Not investigated | Nishimura et al. (2021) |
| Isolobetyol (143) polyacetylene | Platycodon grandiflorus (Jacq.) A.DC. | PC-3 | In vitro | Antiproliferation | Not investigated | Li (2020) |
| Lobetol (144) Alkynes | Platycodon grandiflorus (Jacq.) A.DC. | PC-3 | In vitro | Antiproliferation | Not investigated | Li (2020) |
| Lobetyolin (145) Alkynosides | Platycodon grandiflorus (Jacq.) A.DC. | PC-3 | In vitro | Antiproliferation | Not investigated | Li (2020) |
osteoblastogenesis, which explains the usual condensing aspect of PCa-derived bone metastases. Src activity specifically affects ruffled borders of osteoclasts (essential for bone resorption), through dynamic regulating the interactions of actin cytoskeleton and formation of podosomes (Horne et al., 2005; Destaing et al., 2011). Src and other SFKs also play important roles in the antiapoptotic signal transduction of RANKL and other tumor necrosis factor family members in osteoclasts (Xing et al., 2001). One essential role for Src in osteoblasts has also been demonstrated that reduction of Src expression decreases osteoblast (responsible for bone formation) proliferation and increases differentiation (Marilena et al., 2000).

Recently, a large number of studies have shown that the activation of SRC is an important mediator of AR signaling. (Asim et al., 2008). AR can form a tertiary complex with the scaffold protein modulator of non-genomic actions of the estrogen receptor (MNAR/PELP1) and Src (Unni et al., 2004). Initially, Src is inactive within this complex. However, when AR binds to Src, this results in the activation of Src in this complex (AR/MNAR/Src) and the subsequent activation of a downstream effector, MEK (Unni et al., 2004). Subsequent studies have shown that AR-induced Src activation can promote cell proliferation through cell cycle progression from G1 phase to S phase (Migliaccio et al., 2002).

**MAPKs Signaling Pathway**

The MAPKs signaling cascade play important roles in regulating diverse biological functions including cell proliferation, motility and survival, which are essential to prostate carcinogenesis (Rossomando et al., 1989; Armenia et al., 2018; Abida et al., 2019). Studies of DHT-responsiveness in prostate cancer cells show that DHT treatment induces phosphorylation of ERK-1/2 within 1–2 min and peak levels of phosphorylation within 5–10 min (Liao et al., 2013). Activated ERK-1/2 then translocate to the nucleus and directly interact with and phosphorylate transcription factors (TFs), such as nuclear ETS domain-containing Elk1 (Marais et al., 1993; Gille et al., 1995; Yang et al., 1998). Elk1 transcriptionally regulates immediate early genes (IEGs) such as c-fos (Gille et al., 1995; Unni et al., 2004), and regulates the expression of several genes related to cell proliferation (Marais et al., 1993; Unni et al., 2004). In addition, recent studies showed that other molecules induce prostate cancer via MAPK signaling. Jason et al. reported that ADP-ribosylation factor 1 (ARF1), a crucial regulator in vesicle-mediated membrane trafficking and involved in the activation of signaling molecules, promotes the occurrence of prostate cancer via targeting oncogenic MAPK signaling (Davis et al., 2016). Gonzalo et al. reported that epidermal growth factor (EGF) could stimulate G0/G1-S transition via p38 MAPK to overcome the growth restriction of androgen deprivation in prostate cancer cells (Rodriguez-Berriguete et al., 2016).

**JAK-STAT3 Signaling Pathway**

Janus kinases (JAK) signal transducers and activator of transcription (STAT) pathway play an important role in differentiation, hematopoiesis, immune function and cell growth (Bolli et al., 2003). Recently, accumulating evidence indicated that IL-6 is indispensable for activation of JAK/STAT3.
TABLE 8 | Extracts obtained from plants with anti-prostate cancer activities.

| Extract                              | Botanical name                                      | Medicinal part | Cell type | Observation | Activity | Mechanism of action                                                                 | Refs               |
|-------------------------------------|-----------------------------------------------------|----------------|-----------|-------------|----------|--------------------------------------------------------------------------------------|--------------------|
| Ethanol extract                     | Vitex negundo L.                                    | Seed           | PC3       | In vitro    | Antiproliferation                      | Induction of cleavage in poly ADP ribose polymerase protein; upregulation of Bax and downregulation of Bcl-2; increase of caspase-3 and -9. | Zhou et al. (2009) |
| Methanolic extract                  | Aloe perryi Baker                                   | Fruit          | HTB-81    | In vitro    | Induction of apoptosis                 | Not investigated.                                          | Al-Oqail et al. (2016) |
| Ethanol extract                     | Arumna muricata L.                                  | Leaf           | PC3       | In vitro    | Antiproliferation                      | Not investigated.                                          | Yang et al. (2015)  |
| Aqueous extract                     | Camellia sinensis (L.) Kuntze                       | Leaf           | PC3       | In vitro    | Antiproliferation                      | Increase of Bax/Bcl-2 ratio and decrease of Ki67 protein expression; decrease of blood concentrations of tumor growth factors and tumor concentrations of VEGF and EGF expressions. | Wang et al. (2016b) |
| Methanolic extract                  | Artocarpus altiss (Parkinson) Fosberg               | Leaf and stem  | DU145     | In vitro    | Antiproliferation                      | Inhibition of STAT3 Ty705 phosphorylation and STAT3 activation. | Jeon et al. (2015a) |
| Hexane extract                      | Juglans regia L.                                    | Leaf           | PC3       | In vitro    | Antiproliferation                      | Not investigated.                                          | Li et al. (2015b)   |
| Ammonia dichloromethane extract     | Berberis Ianonica                                   | Root           | DU145     | In vitro    | Antiproliferation                      | Induction of G0/G1 cell cycle arrest; eradication of self-renewal ability of highly resistant prostate cancer stem cells. | Wu et al. (2014)    |
| Supercritical extract               | Azadirachta indica A.Juss.                          | Leaf           | LNCap PC3 | In vitro    | Antiproliferation                      | Inhibition of caleptucin, integrin b1, and focal adhesion kinase activation; increase of the AKR1C2 level. | Lewandowska et al. (2013) |
| Acetone extract                     | Chaenomeles japonica (Thunb.) Lindl. ex Spach       | Fruit          | PNT1A PC3 | In vitro    | Antiproliferation                      | Increase of Bax/Bcl-2 ration.                              | Baron et al. (2009)  |
| Hexanic lipidosterolic extract      | Senna repens (W.Bartram) Small                      | Whole plant    | LNCap PC3 | In vitro    | Antiproliferation                      | Increase of caspase 9 activation and poly (ADP-ribose) polymerase 1 cleavage, and mitochondrial PTP activation. | Sigstedt et al. (2008) |
| Aqueous extract                     | Taraxacum officinale F.H.Wigg.                     | Root           | C4-2B     | In vitro    | Inhibition of metastasis               | Decrease of phosphorylation levels of FAK and SRC, and activities of matrix metalloproteinases (MMP-2 and MMP-9). Decrease of Bax expression; suppression of JNK activation. | Xiao et al. (2011)  |
| Ethyl acetate extract               | Commiphora mukul (Hook, ex Stocks) Engl.            | Bark           | LNCap    | In vitro    | Antiproliferation                      | Not investigated.                                          | Vitali et al. (2011) |
| Aqueous extract                     | Cistus creticus L.; Cistus monspeliensis L.; Morus nigra L. | Whole plant | PZ-HPV-7/PNT1A | In vitro   | Antiproliferation                      | Induction of G1 cell cycle arrest; decrease mitochondrial membrane potential. | Turan et al. (2017) |

(Continued on following page)
| Extract                | Botanical name                             | Medicinal part | Cell type | Observation | Activity | Mechanism of action                                                                 | Refs                                      |
|------------------------|--------------------------------------------|----------------|-----------|-------------|----------|--------------------------------------------------------------------------------------|------------------------------------------|
| Dichloromethane extract| Strobilanthes crispa (L.) Blume            | Leaf DU145 PC3 | In vitro  | Induction of apoptosis | Increase of caspase 3 and/or 7 activity; Upregulation of p21 and p27; increase of JNK phosphorylation; suppression of AKT/mTOR signaling; modulation of the IGF-IGFBP axis. | Visweswaran et al. (2010) Deng et al. (2017) |
| Punica granatum extract| Punica granatum L. Seed                    | Seed LNCaP PC3 | In vitro  | Induction of apoptosis; Inhibition of metastasis | Upregulation of p21 and p27; increase of JNK phosphorylation; suppression of AKT/mTOR signaling; moduation of the IGF-IGFBP axis. | Deng et al. (2017)                        |
| Hydroalcoholic extract | Justicia spicigera Schltdl. stems; leaves | LNCaP PC3      | In vitro  | Antiproliferation | cytostatic mechanism                                                             | Fernández-Pomares et al. (2017) Mirza et al. (2018) |
| Ethyl acetate fraction | Phoenix dactylifera L. (Aiwa dates) Fruit  | PC3            | In vitro  | Induction of apoptosis | Arrest of the cell cycle in S phase Phosphatidylserine translocation; overproduction of reactive oxygen species; release of Cytochrome C at mitochondrial level; activation of caspase-3 and -9; downregulation of apoptosis-related proteins Bcl-2, XIAP, and PKCε and DNA fragmentation and cell cycle arrest | Arias-González et al. (2018) |
| Ethyl acetate extract  | Kalanchoe fl ammea Stapf (Crassulaceae) leaves | PC-3; LNCaP; PrEC | In vivo  | Induction of apoptosis | Not investigated                                                                       | Asadi-Samani et al. (2018) Ju et al. (2018) Pradhana et al. (2019) |
| Hydroalcoholic extract | Euphorbia szovitsai Fisch. & C.A.Mey., U. dioica and Medicago sativa L. aerial parts | PC-3; DU145; HDF | In vitro  | Antiproliferation | Downregulation of AKT Pathway Modulating chromatin modification enzymes and altering pro-inflammatory cytokine gene expression | Abou-Hashem et al. (2019) Abou-Hashem et al. (2019) |
| Ethanol extract        | Moringa oleifera flower                    | flower         | PC-3      | Induction of apoptosis | Cell cycle arrest at sub-G0 phase and DNA fragmentation. | Abou-Hashem et al. (2019) Abou-Hashem et al. (2019) |
| Methanolic extract     | Paederia foetida L. leaves                 | PC-3; DU-145; HaCaT | In vitro  | Inhibition of cell growth, migration; induction of apoptosis | Not investigated                                                                       | Asadi-Samani et al. (2018) Ju et al. (2018) Pradhana et al. (2019) |
| Ethanol extract        | Moringa peregrina (Forssk.) Fiori         | seed           | PC-3      | Induction of apoptosis | Both apoptosis and autophagy mechanisms                                               | Gioti et al. (2020)                       |
| Ethanol extract        | dandelion (Taraxacum officinale) root and lemongrass (Cymbopogon citratus) | Root           | In vivo   | Induction of apoptosis | Inhibition of Jak-1/STAT-3 activity Downregulation of Notch signaling; downregulation of Hedgehog Signaling Pathway β-galactosidase overexpression Via the caspase-8-mediated extrinsic pathway | Wang et al. (2020) Khan et al., 2020a; Khan et al., 2020b Rosa et al. (2020) Lee et al. (2020) |
| Methanolic extract     | Glycyrrhiza glabra (Fabaceae family) roots | PC-3           | In vitro  | Antiproliferation | Not investigated                                                                       | Asadi-Samani et al. (2018) Ju et al. (2018) Pradhana et al. (2019) |
| Dimethyl sulfoxide extract| Ganoderma lucidum whole plant              | PC3            | In vitro  | Induction of apoptosis | Not investigated                                                                       | Wang et al. (2020) Khan et al., 2020a; Khan et al., 2020b Rosa et al. (2020) Lee et al. (2020) |
| Methanolic extract     | Moringa oleifera Lam. leaf                 | leaf           | PC-3      | Induction of apoptosis; Senescence induction of apoptosis; 50/51 cell cycle arrest | Not investigated                                                                       | Asadi-Samani et al. (2018) Ju et al. (2018) Pradhana et al. (2019) |
| Dichloromethane and methanol extract | Cecropia pachystachya Trécul Draccophalum palmatum Stephan leaves | PC-3           | In vitro  | Senescence induction of apoptosis | Not investigated                                                                       | Asadi-Samani et al. (2018) Ju et al. (2018) Pradhana et al. (2019) |
| Methanolic extract     | Glycyrrhiza glabra (Fabaceae family) roots | PC-3           | In vitro  | Antiproliferation | Both apoptosis and autophagy mechanisms                                               | Gioti et al. (2020)                       |
| Ethanol extract        | Moringa peregrina (Forssk.) Fiori         | seed           | PC-3      | Induction of apoptosis | Cell cycle arrest at sub-G0 phase and DNA fragmentation. | Abou-Hashem et al. (2019) Abou-Hashem et al. (2019) |
| Methanolic extract     | dandelion (Taraxacum officinale) root and lemongrass (Cymbopogon citratus) | Root           | In vivo   | Induction of apoptosis | Not investigated                                                                       | Asadi-Samani et al. (2018) Ju et al. (2018) Pradhana et al. (2019) |
| Methanolic extract     | Glycyrrhiza glabra (Fabaceae family) roots | PC-3           | In vitro  | Antiproliferation | Both apoptosis and autophagy mechanisms                                               | Gioti et al. (2020)                       |
| Dimethyl sulfoxide extract| Ganoderma lucidum whole plant              | PC3            | In vitro  | Induction of apoptosis | Not investigated                                                                       | Wang et al. (2020) Khan et al., 2020a; Khan et al., 2020b Rosa et al. (2020) Lee et al. (2020) |
| Methanolic extract     | Moringa oleifera Lam. leaf                 | leaf           | PC-3      | Induction of apoptosis; Senescence induction of apoptosis; 50/51 cell cycle arrest | Not investigated                                                                       | Asadi-Samani et al. (2018) Ju et al. (2018) Pradhana et al. (2019) |
| Dichloromethane and methanol extract | Cecropia pachystachya Trécul Draccophalum palmatum Stephan leaves | PC-3           | In vitro  | Senescence induction of apoptosis | Not investigated                                                                       | Asadi-Samani et al. (2018) Ju et al. (2018) Pradhana et al. (2019) |
| Methanolic extract     | Glycyrrhiza glabra (Fabaceae family) roots | PC-3           | In vitro  | Antiproliferation | Both apoptosis and autophagy mechanisms                                               | Gioti et al. (2020)                       |
TABLE 8 | (Continued) Extracts obtained from plants with anti-prostate cancer activities.

| Extract | Botanical name | Medicinal part | Cell type | Observation | Activity | Mechanism of action | Refs |
|---------|----------------|----------------|-----------|-------------|----------|----------------------|------|
| Extract of multi-solvent systems (Cyclohexane, Hexane, Diethyl Ether, Ethyl Acetate, Methanol, Water) | Hippophae rhamnoides L. and Hippophae tibetana Schltdl. | leaves | LNCaP; C4-2 | In vitro | Antiproliferation | Downregulation of androgen responsive genes, PSA, ELL2, EAF2 and CALR | Masoodi et al. (2020) |
| Ethanol extract | Salvia miltiorrhiza Bunge. | roots | DU-145 | In vitro; In vivo | Antiproliferation; induction of apoptosis; | Increase of the expression of p53 and reduction of the expression of Bcl-2 proteins | Bae et al. (2020) |
| Methanol extract | Spirogyra neglecta (Hassall) Kutzing | whole plant | PC3 | In vitro | Antimetastasis activity | Inhibiting the Akt signaling pathway | Arjsi et al. (2021) |
| Methanol extract | Artemisia krueliana subsp. alaskana (Rydberg) D.F. Murray & Elven | stems and leaves | PC-3 | In vitro | Induction of autophagy; | Inhibitions of phosphor (p)-AKT, p-mTOR, Bcl-2, and Bax, activating beclin 1 and LC3 ratio in PC-3 cells | Lee et al. (2021) |
| Ethanol extracts | Treculia africana Decne. (Moraceae) and Entandrophragma angolense Welw. (Meliaceae) | whole plants | LNCaP, DU145 and PC3 | In vitro | Antiproliferation; induction of apoptosis; anti-metastatic effects | Overexpression of caspase-3; low expression of Akt, pAkt and Bcl-2 proteins; decrease of chemotaxis and cell migration | Zingue et al. (2021) |
| Ethanol extracts | Moringa oleifera Lam. | Flower | PC-3 | In vitro | Induction of apoptosis | Downregulation of AKT Pathway | Ju et al. (2018) |

STAT pathway, which is involved in the oncogenesis of prostate cancer (Liu X. et al., 2012). Compared with men with normal prostates, benign prostatic hyperplasia, prostatitis and localized disease, approximately 50% of patients with advanced prostate cancer have increased levels of serum IL-6 (Twillie et al., 1995). Upon the binding of IL-6 to the IL-6 receptor, JAK-1 and STAT-3 become activated in sequence (C Schindler and Jr, 1995). L Tam et al. reported that cytoplasmic expression of IL-6 receptor and pSTAT3 Tyr705 are associated with the shortened biochemical recurrence time and death time from hormone relapse, respectively. Therefore, it is reasonable to target this pathway in hormone-refractory prostate cancer treatments (Tam et al., 2007).

Ca²⁺ Signaling Pathway
Ca²⁺ signaling is also involved in prostate cancer progression (Figiel et al., 2019; Chalmers and Monteith et al., 2018). Increased calcium intake from dairy products has been considered as a risk factor for prostate cancer (Foradori et al., 2007; Flourakis and Prevarskaya, 2009). As a primary signaling molecule, extracellular Ca²⁺ works through the Ca²⁺-sensing receptor (CaR, a G protein coupled receptor) which directly regulates cell signal transduction and the Ca²⁺ channels (Vaz et al., 2015). Depletion of intracellular Ca²⁺ stores serves as a signal for the activation of Ca²⁺ influx across the plasma membrane. The proteins STIM1 and ORAI1 were identified as the key components of store-operated Ca²⁺ entry (SOCE). When Ca²⁺ is released from intracellular Ca²⁺ pool, Ca²⁺ dissociates from a luminal EF hand motif of STIM1. As a consequence, STIM1 proteins aggregate and recruit Orai1 Ca²⁺ channels, which then mediate SOCE (Kilch et al., 2016).

Recently, Huang et al. found that Ca²⁺ via CaR-mediated signaling induces filamin A cleavage, which is an actin-binding protein, and promotes the migration of AR-deficient and highly metastatic prostate cancer cells (Huang et al., 2016). In one additional study, Christian demonstrated that transient receptor potential melastatin 4 channel (TRPM4) is activated by a rise in intracellular Ca²⁺ in prostate cancer cells. Upon activation, a Na⁺ influx via TRPM4 depolarizes the membrane potential, which reduces the driving force for Ca²⁺ and limits SOCE, and thus promotes migration of androgen-insensitive prostate cancer cells (Christian et al., 2015).

Other Genomic Alterations in Castration-Resistant Prostate Cancer
Prostate cancer is characterized by a high genetic heterogeneity due to genomic alterations and instabilities associated with diverse PCa risk factors (Squire et al., 2011; Yap et al., 2016; Ciccarese et al., 2017; Rodrigues et al., 2017), which was evidenced by extensive genomic profiling analysis conducted on primary tumors (Network T. C. G. A., 2015) and on metastatic samples (Dan et al., 2015).

Speckle-type POZ protein (SPOP) is the substrate-binding subunit of a cullin-3 (CUL3)-based E3 ubiquitin ligase complex, which mediates the ubiquitylation and degradation of many target proteins. SPOP binds to the substrates through its N-terminal meprin and traf homology (MATH) domain, whereas it interacts with cullin-3 via BTB domain on its C terminal (Pintard et al., 2003; Xu et al., 2003; Zhuang et al., 2003).
Recent cancer whole-genome and exome sequencing studies have shown that \textit{SPOP} is the most frequently mutated gene (in up to 15% of cases) in primary prostate cancer (Barbieri et al., 2012; Network T. C. G. A., 2015). Interestingly, all \textit{SPOP} somatic mutations identified in prostate cancer are clustered in its substrate binding MATH domain, thus having a dominant-negative effect on substrate binding and degradation (Theurillat et al., 2014). Recent studies have unanimously reported that \textit{SPOP} interacts with bromodomain and extraterminal (BET) proteins that largely act as transcriptional coactivators and play vital roles in cell cycle, apoptosis, migration and invasion in physiological conditions. In addition, \textit{SPOP} also promotes the ubiquitylation and proteasomal degradation of bromodomain-containing protein 2 (BRD2), BRD3 and BRD4, (Dai et al., 2017; Janouskova et al., 2017; Zhang et al., 2017). Pathologically, BET proteins are frequently overexpressed and are clinically linked to various types of human cancer (French et al., 2003; Crawford et al., 2008; Belkina and Denis, 2012). Recently, Janouskova et al. reported prostate cancer–associated \textit{SPOP} mutants impaired its binding to BET proteins, leading to the reduced proteasomal degradation and accumulation of these proteins in prostate cancer cell lines and patient specimens, which subsequently causes resistance to BET inhibitors (Janouskova et al., 2017). Similar study has also demonstrated that \textit{SPOP}-mutated prostate cancer cell lines and patient-derived organoids were intrinsically resistant to BET inhibitor-induced growth arrest and apoptosis (Dai et al., 2017). Furthermore, Dai et al. provided that stabilization of BRD4 may be a molecular mechanism for resistance to BET inhibitors in patients with prostate cancer bearing \textit{SPOP} mutations (Dai et al., 2017). Taken together, these findings offer mechanistic insights into how \textit{SPOP} mutations influence prostate cancer.

The \textit{TMPRSS2-ERG} fusion gene arising from genetic rearrangement (fusion of encoding transmembrane protease
serine 2, TMPRSS2 gene, and EST-related gene, ERG) has also been a central focus in prostate cancer, which leads to aberrant expression of the ETS transcription factor ERG (Tomlins et al., 2005; Kandoth, 2013). TMPRSS2-ERG is the most common gene rearrangement in prostate cancer and is present in approximately 50% of prostate cancer tissues in Western countries (Cary and...
Previous studies indicated that ERG overexpression was driven by hijacking of androgen-responsive elements within the TMPRSS2 promoter (Tomlins et al., 2005; Wang et al., 2007; Thangapazham et al., 2014). However, Kron et al. found that the molecular process is more complex. Their study indicated that overexpressed ERG co-opts prostate-specific master regulatory transcription factors, including AR, HOXB13 and FOXA1, in a process facilitated by their physical interaction with ERG and activates NOTCH signaling in primary prostate cancer (Kron et al., 2017). ERG overexpression is now an instrumental indicator in the diagnosis of prostate cancer. In addition, Graff et al. recently found that obesity and height might be correlated with the development of TMPRSS2-ERG-positive prostate cancer (Graff et al., 2018). Collectively, the functions and mechanisms of TMPRSS2-ERG increase the opportunities for finding new therapeutic targets for prostate cancer (Wang et al., 2017; Kong et al., 2020).

NATURAL COMPOUNDS THAT EXERT ANTI-PROSTATE EFFECTS

Natural compounds that have been found to inhibit prostate cancer cells proliferation/tumor growth, promote prostate cancer cells apoptosis, or modulate specific signaling pathways involved in prostate cancer in vivo and in vitro are categorized and presented according to their source of isolation (marine organisms, microorganisms and plants) and the structural scaffolds. Besides the effects on prostate cancer cells growth or apoptosis, special emphasis was given to the mechanism of action of a compound interfering specific signaling pathways involved in prostate cancer.

Natural Compounds Obtained From Marine Organisms or Microorganisms

As is well known, marine organisms or microorganisms possess the capacity to produce a large amount of diverse secondary metabolites with unique structural features and biological properties. Thus, marine and microbial organisms represent interesting and important sources of single molecules with promising skeletons and significant anti-prostate cancer activity. Up to now, a total of 24 natural compounds (Figures 3) isolated from marine organisms have been found to exhibit significant anti-prostate cancer activity either in vivo or in vitro. Detailed information about the compounds origin, activity and mechanism of action is listed in Table 1. Most of them exhibit antiproliferative, apoptosis inducing or metastasis inhibitory activities, with various acting mechanisms such as induction of autophagy, inhibition of AR activation, PI-3K/AKT/mTOR or JAK/STAT signaling pathways (Senderowicz et al., 1995; Liu et al., 2006; Wang WL et al., 2008; Hellsten et al., 2008; Gantar et al., 2012; Meimetis et al., 2012; Shin et al., 2013; Liberio et al., 2015; Liu et al., 2016). Especially, frondoside A not only caused cell type
specific cell cycle arrest and induction of caspase-dependent or -independent apoptosis in vivo but also significantly inhibited the cell growth of PC-3 and DU145 with a notable reduction of lung metastasis and decrease of circulating tumor cells in the peripheral blood (Dyshlovoy et al., 2016). In addition, gliotoxin, chaetocin and chetomin exhibited antiangiogenic effects in vitro and attenuated tumor growth mainly by disrupting the HIF-1α/p300 complex, which makes them attractive molecules for the design of future chemotherapeutic agents (Cook et al., 2009).

Natural Compounds Isolated From Plants
Medicinal plants have always been a very good source of drugs, which could produce plenty of secondary metabolites with high structural diversity and versatile bioactivities. Many candidates with promising anti-prostate activity have been reported, including 7 alkaloids, 23 flavonoids, 25 terpenoids, 13 polyphenols, 10 lignans and 48 other compounds (Figures 4–9). Almost all these candidates show anti-prostate cancer activities via anti-proliferation, apoptosis induction or metastasis and invasion inhibition, involved in canonical AR signaling and non-AR signaling like caspase cascades, AKT/mTOR pathway, MAPKs pathway, NF-κB pathway, Ca2+ pathway and JAK/STATs pathway. Additionally, there exist other acting mechanisms, for example, anibamine exhibited anti-prostate cancer activity by binding to the chemokine receptor CCR5; fisetin inhibited tumor growth by downregulating the expression of NudC protein, MMP-2 and MMP-9; lycopene showed anti-prostate cancer effects by inhibiting androgen receptor element and signaling of insulin-like growth factor-1 (Afaq et al., 2008; Khan et al., 2008; Bureyko et al., 2009; Wertz, 2009; Zhang et al., 2010b; Chien et al., 2010; Suh et al., 2010; Tang et al., 2011; Holzapfel et al., 2013; Mukhtar et al., 2015). Detailed information is provided in Tables 2–7.

EXTRACTS WITH ANTI-PROSTATE CANCER ACTIVITY
Extracts consist of a group of bioactive natural compounds, which may exert and possess the advantages of synergistic effects against diseases. Recently, nutraceuticals have also received increasing attention as the agents or dietary supplements for cancer prevention and treatment, as well as some extracts derived from edible sources. Thus in this section we will respectively review those extracts and nutraceuticals that have the potential effects against prostate cancer either in vitro or in prostate cancer mice models. Chinese herbal compound preparations of more than one medicinal plants that have been reported to inhibit prostate cancer are also presented in this review.

Herbal Extracts
Traditional and folk herbal medicines from medicinal plants offer great potential for the discovery of novel anti-prostate cancer drugs. The plant extracts listed in Table 8 are complex mixtures, which need further investigations to reveal their bioactive constituents through bioguided isolation and to clarify the roles of these different compounds in against prostate cancer when used alone or in combination. Also, the synergistic effect of the individual active components of these extracts and molecular mechanisms involved need further elucidation in order to evaluate the potential of these compounds as antineoplastic agents.

Chinese Herbal Compound Preparations
There are four traditional Chinese medical formulations reported to display significant anti-prostate cancer properties, that is, Zyflamend, PC-SPEs and LCS101, which are composed of different medicinal plants (Table 9; Bemis et al., 2005; Hsieh et al., 1997; Cohen et al., 2015). Especially, PC-SPEs significantly inhibited prostate tumor growth in tumor-bearing mouse model,

| TABLE 9 | Chinese herbal compound preparations obtained from plants with anti-prostate cancer activities. |
| --- | --- | --- | --- | --- | --- |
| Medical formulation | Composition | Cell type | Observation | Activity | Mechanism of action | Refs |
| Zyflamend | Rosemary; Ginger; Turmeric; Green tea; Holy basil; Hu zhang; Chinese goldthread; Oregano; Barberry; Scutellaria baikalensis. | LNCaP | In vitro | Antiproliferation | Inhibition of COX-1 and COX-2 enzyme activities; upregulation of p21 expression; downregulation of AR expression; induction of phosphorylation of Stat3 and PKCa. | Bemis et al. (2005) |
| PC-SPES | Ganoderma lucidium; Dendranthema montifolium; itsatis indigotica; Glycyrrhiza glabra; Rabdosia rubescens; Panax pseudoginseng; Senecio repens; Scutellaria baikalensis. | DU145 | In vitro | Induction of apoptosis | Induction of G0/G1 and G2/M cell cycle arrest; upregulation of p21/waf1 expression and downregulation of Bcl-2 expression. | Hsieh et al. (1997) |
| LCS101 | Atractylodes macrocephala; Astragalus membranaceus; Glehnia littoralis; Citrus reticulata; Lycium chinense; Ligustrum lucidum; Oldenlandia diffusa; Millettia reticulata; Ophiopogon japonicus; Paeonia obovata; Paeonia lactiflora; Prunella vulgaris; Poriae cocos; Scutellaria barbata. | PC3 | In vitro | Induction of apoptosis | Not investigated | Cohen et al. (2016) |
mainly through cell cycle arrest and apoptosis induction, which is already clinically utilized for the treatment of clinical patients with prostate cancer (Hsieh et al., 1997).

Nutraceuticals and Extracts Derived From Edible Sources
Nowadays, dietary factors play an increasingly important role in the chemopreventive and/or therapeutic management of cancer (Table 10). The study of dietary agents (nutraceuticals or extracts derived from edible sources) in prostate cancer prevention is an important area of research since about 43–80% patients with prostate cancer are on alternative therapy based on dietary modification (Lippert et al., 1999; Nam et al., 1999). There are strong evidences that nutraceuticals and extracts derived from edible spices, vegetables or fruits such as vitamin D, pomegranate and tea polyphenols have demonstrated significant anti-prostate cancer activity when tested either in vitro and/or in vivo (Kasimsetty et al., 2009; Gregory et al., 2010; Koyama et al., 2010; Mordanmccombs et al., 2010; Hsu et al., 2011; Xiao et al., 2011; Turan et al., 2017). Especially, dietary phytochemicals that can selectively interfere cellular pathways involved in prostate


TABLE 10 | Nutraceuticals and extracts obtained from plants with anti-prostate cancer activities.

| Dietary agents | Cell type | Observation | Activity | Mechanism of action | Refs |
|----------------|-----------|-------------|----------|---------------------|------|
| Epigallocatechin-3-Gallate (Green Tea) | Du145 | In vitro | Antiproliferation; Induction of apoptosis | Downregulation of ID2; increase of Bax/Bcl-2; inducing cell death via an ID2-related mechanism; Antiproliferation by increasing the activity of ERK 1/2 through a MEK-independent and PI3K-dependent mechanism. | Xiao et al. (2011), Turan et al. (2017) |
| | LNCaP | In vitro | Antiproliferation | Decrease of nail and pSTAT3 expression; inhibition of Snail-mediated CatL activity. | Burton et al. (2015) |
| | C4-2B | In vitro | Induction of apoptosis | Cell growth inhibition and apoptosis induction via inhibiting MAPK/ERK signaling pathway and activating caspase 3. | Azémé et al. (2007), Yan and Katz (2010) |
| | LNCaP | In vitro | Inhibition of migration invasion | Downregulation of expression CCND1, CDK4, E2F1,and MAPK6; upregulation of CDKN1A expression; downregulation of CAV1, IGF2, NR2F1, and PLAU genes expression; suppression of the urokinase plasminogen activator (uPA) secretion. | Li et al. (2005), Hong et al. (2008), Kasimsetty et al., (2009), Koyama et al. (2010) |
| | ARCaP-E | In vivo | Induction of apoptosis | Inhibition of enzyme (cytochrome P450) expression and activity; inhibition of mTOR phosphorylation at Ser2448 and Ser2481 and IGF1 expression. | Pinto et al. (2007), Xiang et al. (2009), Sarveswaran et al. (2010) |
| | LNCaP | In vitro | Induction of apoptosis | Increase of p53 expression; apoptosis induction by superoxide generation through the mitochondrial-dependent pathway. | Huang et al. (2004), Svami et al. (2009), Rabiau et al. (2010) |
| | PC3 | In vitro | Inhibition of tumour growth | Decreased of COX-2 RNA and protein expression; inhibition of the synthesis of prostaglandins; downregulation growth factors involved in angiogenesis (EGF and IGF-1) and the IL-8 gene; inhibition of ERK-1 and ERK-2 expression. | Wang et al. (2004), Svami et al. (2009), Rabiau et al. (2010) |
| | 22Rv1 | In vivo | Induction of apoptosis | Increase of E-cadherin expression; decrease of urokinase plasminogen activator receptor levels. | Gregory et al. (2010), Mordanmccombs et al. (2010), Hsu et al. (2011) |
| | | | | Downregulation of the expression of androgen receptor, BIP, survivin, while activating caspase-3 and -7, PARP-1 cleavage, p21 and DNA damage response marker, phospho-H2AX. | Dasari et al. (2018) |
| | | | | Blocking the cell cycle at G0/G1 phase. | Zabaou et al. (2019) |

Cancer cells have attracted research interest of scientists in prostate cancer therapies in recent years.

CONCLUSION AND PERSPECTIVES

Prostate cancer is the second most frequently diagnosed tumor and the fifth leading cause of cancer-related deaths in men in the worldwide (McEleny et al., 2002). And the mortality of prostate cancer mainly occurs as a result of the castrate resistant ones. Up to date, different kinds of drugs have been employed to improve the treatment condition, mainly including LHRH antagonists, antiandrogen (androgen receptor antagonists and androgen synthesis inhibitors), tyrosine kinase inhibitors, angiogenesis inhibitors, endothelin antagonists, matrix metalloproteinase inhibitors, antioxidants, and cell cycle inhibitors. However, as mentioned above, there is no effective therapy for CRPC at present, except for docetaxel, which is the only chemotherapeutic agent that has been proven to prolong the overall survival in CRPC patient population though with many adverse effects reported (Eyben et al., 2015). Hence, it is urgent for us to explore an effective treatment for prostate cancer, especially for CRPC. In recent years, many natural products and extracts have been scientifically investigated in vitro and/or in vivo and proved as potential anti-prostate cancer agents, which are currently scattered across various publications. So a systematic summary and knowledge of future prospects are necessary to facilitate further chemical and pharmacological studies for anti-prostate cancer agents.

In our review, we provided a comprehensive overview of the molecular basis of the incidence and development of prostate cancer, especially for castration-resistant prostate cancer (CRPC), which mainly including canonical AR signaling (AR
amplification, over-expression, mutation, and unconventional activation), and non-nuclear AR signaling (PI3K/AKT, Src, MAPKs, JAK-STAT3, and Ca$^{2+}$ signaling pathways). So most components involved in above-mentioned pathways represent potential targets for screening natural compounds and/or extracts with anti-prostate cancer activity. And natural compounds or

FIGURE 8 | Lignans obtained from plants with anti-prostate cancer activities.
So far, a great amount of natural products isolated from diverse sources have been found to significantly inhibit prostate cancer cell proliferation/tumor growth or affected cellular signaling pathways in prostate cancer. As shown in our paper, the majority of natural compounds with direct relevance to prostate cancer are primarily derived from plants, with comparatively few molecules from marine and microbial sources. For these reported bioactive constituents, there is still plenty of room for improvement regarding the studies focused on efficacy enhancement and side effects amelioration by semi-synthetic modifications based on quantitative structural activity relationship elucidation. Since marine and microbial organisms represent important sources for single molecules exploit, more available and improved approaches should be included in finding novel natural products with significant anti-prostate cancer activity from these resource. Especially, engineering bacteria or fungus with novel gene clusters, currently used mainly for the identification of antibiotics or anti-tumor drugs, would be another promising approach for discovering natural compounds with anti-prostate activity. Extracts are another applicable option for anti-prostate purposes, in which case the chemical profile should be further elucidated, possibly affording a pure bioactive compound with precise mechanism of action. Also clinically used Chinese herb preparations should be profiled using techniques such as HPLC–MS to standardize the complex system to make it more controllable, stable, and reproducible in prostate cancer treatment. Furthermore, drug combination of these reported natural compounds with conventional chemotherapeutic agents may also be a promising way in finding solution for prostate cancer treatment. Finally, safety large-scale studies are needed to evaluate promising compounds or extracts and determining non-toxic doses for treating prostate cancer in mammals.

In conclusion, tackling prostate cancer (especially CRPC) is a much needed task that requires not only the great progress in understanding the genetic basis of prostate cancer, but also the significant technological improvements in tracking of bioactive natural compounds and structural characterization, which will facilitate the identification of novel natural compounds with significant anti-prostate cancer properties for drug development and therefore can be translated into significant health benefits for humans.

**AUTHOR CONTRIBUTIONS**

CZ, WX, and QY conceived and designed the outline of the manuscript; BB, QC, and RJ collated and summarized the literatures; XQ, HW and YB analyzed the data; RJ, BB, and CZ wrote the manuscript, QC, WX, and QY revised the manuscript and provided technical assistance to RJ and BB.

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extracts that could function as modulators of canonical AR or non-nuclear AR signalling pathways thus can be regarded as promising candidates for anti-prostate interventions.
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