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Highlights of Natural Products in Prostate Cancer Drug Discovery

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1. Introduction

The remarkable impact of natural products (NPs) in the quest for new agents and new directions in medicinal discovery is well established. The exploration of Nature as a source of novel active agents that may serve as leads and scaffolds for drugs targeting a myriad of diseases and the use of synthetic organic chemistry to modify them have been a driving force for drug discovery. Worldwide, prostate cancer (PC) is the second leading cause of death after lung cancer on both USA and Australia, and the third after lung and colo-rectal cancers in Europe. The heavy burden of PC is further exemplified by the fact that it accounts for about 1 in 4 newly diagnosed cancers each year among USA men, and in 2010, approximately 32,050 men are expected to die from this disease in the USA alone whereas in Europe 2.5 million cases of PC are freshly diagnosed every year, 9% of which prove fatal. PC is a slow progressing disease found to be primarily dependent on androgens which are involved in its development, growth and progression. Transition into a hormone-refractory state typically occurs in less than 2 years following the onset of the common androgen deprivation therapies available. Thus, a relevant issue on PC drug discovery is the ability to target both androgen-dependent and –independent cells in order to avoid recurrence phenomena which could be accomplished by multi-target agents. NPs from various sources have been tested on PC-related targets with promising results. Recent research has brought into light compounds such as iejimalide B, spisulosine, pristimerin, celastrol, withaferin A, and several other pentacyclic triterpenoids such as betulinic, ursolic, and boswellic acids which show promise for future drug development. Other examples include the synthetic epothilone ixabepilone A, the gossypol-derived AT-101, the triptolide derivative PG490-88Na, irofulven, trabectedin, the rapamycin derivative temsirolimus, and docetaxel which is currently first-line therapy for castration-resistant PC combined with prednisone. This

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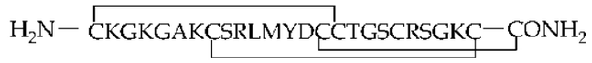
chapter will highlight significant contributions of NPs and NP-derived agents on PC drug discovery starting from their action on PC-related targets and focusing on molecules which have proceeded into clinical trials.

2. Natural products and cancer

Over the course of millennia, natural compounds have evolved into specific scaffolds that interact with cellular macromolecules (Clardy & Walsh, 2004). Such scaffolds can be used as templates and fine-tuned by medicinal chemists to produce novel compounds with therapeutic applications. Indeed, about 40% of drugs used today are derived from natural plant, animal or microbial sources (Carlson, 2010). A total of 13 NPs and NP-derived drugs were approved for marketing worldwide from 2005 to 2007, out of which ziconotide (Prialt®, Elan), exanetide (Byetta®, Eli Lilly and Amylin Pharmaceuticals), retapamulin (Altabax® or Altargo®, GSK), trabectedin (Yondelis®, ET-743, J&J), and ixabepilone (Ixempra®, BMS-247750, Bristol-Meyers Squibb) were members of new human drug classes (Butler, 2008). These compounds are depicted on Figure 1.

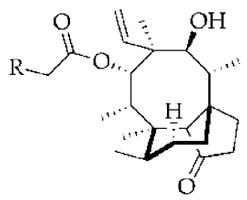
Historically, the development of a NP lead has been limited by availability and structural complexity of the parent natural compounds (Cragg *et al.*, 2009). NPs are often produced in trace quantities, and biomass is limited or, in the case of microbial sources, unculturable. To circumvent such difficulties as extraction, assay-based functional fractionation, isolation, characterization, and target validation, classical drug-discovery has been gradually replaced by molecular target-based drug discovery (Ojima, 2008). This approach uses high-throughput screening of large libraries of compounds, lead identification from hits, and lead optimization, computational and structural biology, and has become a main stream in the past two decades. Nonetheless, sorafenib mesylate remains the only *de novo* combinatorial drug approved by the Food and Drug Administration (FDA) to date and is used for the treatment of advanced renal cancer (Newman & Cragg, 2007).

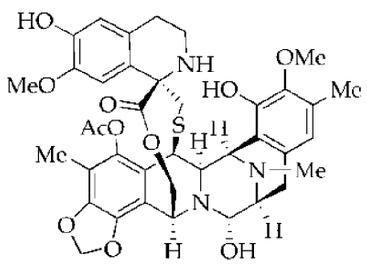
It is therefore clear that Nature will continue to be a major source of new drug leads, including anticancer agents. Newman & Cragg have recently reported that in the period of 1981 to 2006, out of 100 new chemical anticancer entities only 22.2% were totally synthetic (Newman & Cragg, 2007). Expressed as a proportion of the nonbiologicals/vaccines, 77.8% were either NPs *per se* or were based thereon, or mimicked NPs in one form or another. Recent success examples of NP-derived anticancer agents approved for marketing worldwide include temsirolimus (Torisel®, CCI-779, Fig.1), a semi-synthetic derivative of sirolimus (rapamycin, rapamune) which is an immunosuppressant first isolated from the bacterium *Streptomyces hygroscopicus* (Butler, 2008). It was approved in the US in May 2007 and Europe in November 2007 for the treatment of advanced renal cell carcinoma. Temsirolimus is the first mammalian target of rapamycin (mTOR) inhibitor approved for use in oncology. Trabectedin (Fig.1), a tetrahydroisoquinoline alkaloid produced by the ascidian *Ecteinascidia turbinata* was approved by the European Medicines Agency (EMA) in September 2007 for the treatment of advanced soft tissue sarcoma. Trabectedin is in Phase III clinical trials for the treatment of ovarian cancer and other ongoing Phase II trials include paediatric sarcomas, breast and prostate cancers (Butler, 2008). Also, ixabepilone (Fig. 1), a semi-synthetic derivative of epothilone B (Fig. 1) was approved in October 2007 by the FDA for the treatment of breast cancer, either as monotherapy or in combination with capecitabine (Butler, 2008, Toppmeyer & Goodin, 2010).

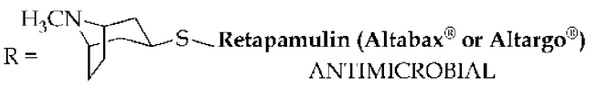


Ziconotide (Prialt®)
Synthetic analogue of ω-conotoxin MVIIA isolated from Cognus Magnus
PAIN

Exanatide (Byetta®)
Heloderma suspectum
TYPE II DIABETES



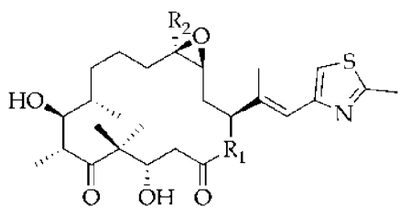


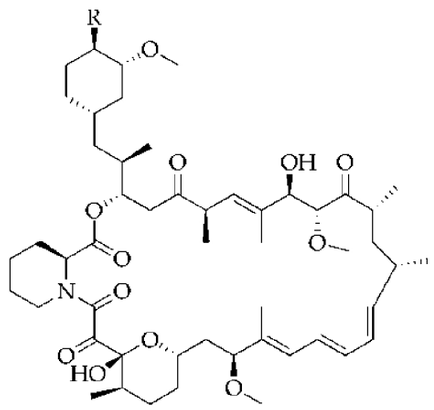


Retapamulin (Altabax® or Altargo®)
ANTIMICROBIAL

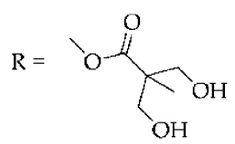
R = OH **Pleuromutilin**
Pleurotus mutilus

Trabectedin (Yondelis®)
Ecteinascidia turbinata
CANCER





R_1 = O; R_2 = Me **Epothilone B (patupilone)**
R_1 = NH; R_2 = Me **Ixabepilone (Ixempra®)**
Sorangium cellulosum
CANCER



Temsirolimus (Torisel®)
CANCER

R = OH **Sirolimus (Rapamycin)**
Streptomyces hygroscopicus

Fig. 1. NPs approved for marketing which constitute new human drug classes (2005-2007).

3. Prostate cancer worldwide

PC is a common disease worldwide. Apart from skin cancer, PC is one of the most common cancers in men in developed countries such as the USA and Australia, as well as in the European Union (Black *et al.*, 1997, Greenlee *et al.*, 2000, Jemal *et al.*, 2011, Jemal *et al.*, 2010). It is also a leading cause of mortality and the second most common cause of cancer-related death in both the USA and Australia, and the third most common cause of cancer-related death in the European Union (Jemal *et al.*, 2011, Jemal *et al.*, 2010).

PC is a hormone-sensitive cancer that is influenced by androgens such as testosterone, produced from cholesterol mainly in the testis but also in the adrenal glands as well as in other tissues including prostate tissue (Moreira *et al.*, 2008, Schrijvers *et al.*, 2010). Dihydrotestosterone, the main metabolite of testosterone, is the principal ligand for the androgen receptor (AR). After transfer from the cytoplasm to the nucleus, this ligand-receptor complex activates different pathways involved in cell cycle progression and cell division. Huggins & Hodges introduced androgen deprivation as therapy (ADT) for advanced and metastatic PC in 1941 (Huggins & Hodges, 1941, Huggins *et al.*, 1941) and ever since this strategy has been applied for advanced PC treatment. Thus, in patients with metastatic PC which are symptomatic and have rapidly increasing levels of prostate-specific antigen (PSA), standard first-line treatment is castration either by bilateral orchietomy or by biochemical methods using luteinizing hormone-releasing hormone (LHRH) agonists (Antonarakis & Carducci, 2010, Harzstark & Small, 2010). This procedure is effective in about 80 to 90% of patients. However, transition into a hormone-refractory state will typically occur in less than 2 years following the onset of the common ADTs. There is evidence that AR-mediated signaling and gene expression can persist in metastatic castrate-resistant PC (mCRPC), even in the face of castrate levels of androgen (Chatterjee, 2003, Debes & Tindall, 2004, Sartor, 2011). This may be due in part to the upregulation of enzymes involved in androgen synthesis, the overexpression of AR, or the emergence of mutant ARs with promiscuous recognition of various steroidal ligands. Patients with castrate-resistant PC (CRPC) can be offered antiandrogens in addition to castration which results in response in 33% of individuals (Harzstark & Small, 2010). In case of progression, antiandrogen withdrawal results in response in about 5 to 20% of patients (Harzstark & Small, 2010). Other options include secondary hormonal therapy using mainly ketoconazole due to its ability to inhibit cytochrome P450 17α-hydroxylase $C_{17,20}$-lyase (CYP17), one of the enzymes responsible for the biosynthesis of androgen precursors in the human body (Moreira *et al.*, 2008). Despite its efficacy and ease of administration, ketoconazole bears several side effects (De Felice *et al.*, 1981, Lake-Bakaar *et al.*, 1987). Patients with CRPC are currently treated with docetaxel (Fig. 5) chemotherapy and prednisone which improves survival time in about 18 months (Mancuso *et al.*, 2007, Harzstark & Small, 2010). Nonetheless, patients with CRPC will die of their cancer and thus new treatments are required (Lassi & Dawson, 2010, Sartor, 2011). Two additional treatment options for mCRPC patients have been recently established in the "post-docetaxel space." Therapy with cabazitaxel (Fig. 5) and prednisone or treatment with the CYP17 inhibitor and antiandrogen abiraterone (also combined with prednisone) has been shown to improve survival in patients with mCRPC following docetaxel therapy (Sartor, 2011). Compared with mitoxantrone/prednisone, cabazitaxel/prednisone significantly improved overall survival, with a 30% reduction in rate of death, in patients

with progression of mCRPC. Similarly, abiraterone acetate plus prednisone significantly decreased the rate of death by 35% compared with placebo plus prednisone in mCRPC patients progressing after prior docetaxel therapy (Sartor, 2011).

A relevant issue on PC drug discovery is the ability to target both androgen-sensitive and androgen-insensitive cells in order to avoid recurrence phenomena, which could be accomplished by multi-target drugs. In addition, androgen-insensitive PC cells have a very low rate of proliferation (Nemoto *et al.*, 1990). Less than 10% of such cells proliferate during a given day thus leaving an extremely small therapeutic index for anti-proliferation drugs. The development of new drugs that can delay the onset and/or progression of human PC is therefore bound to have a significant impact on disease-related cost, morbidity and mortality for a large fraction of the world population.

4. Natural products and prostate cancer

4.1 Marine compounds

The preclinical pipeline continues to supply several hundred novel marine compounds every year and those continue to feed the clinical pipeline with potentially valuable compounds (Singh *et al.*, 2008, Mayer *et al.*, 2010). Thus, in the US there are three FDA approved marine-derived drugs, namely cytarabine (Cytosar-U®, Depocyt®, Fig. 2), vidarabine (Vira-A®, Fig. 2) and ziconotide (Fig. 1). The current clinical pipeline includes 13 marine-derived compounds that are either in Phase I, Phase II or Phase III clinical trials. Several key Phase III studies are ongoing and there are seven marine-derived compounds now in Phase II trials (Mayer *et al.*, 2010).

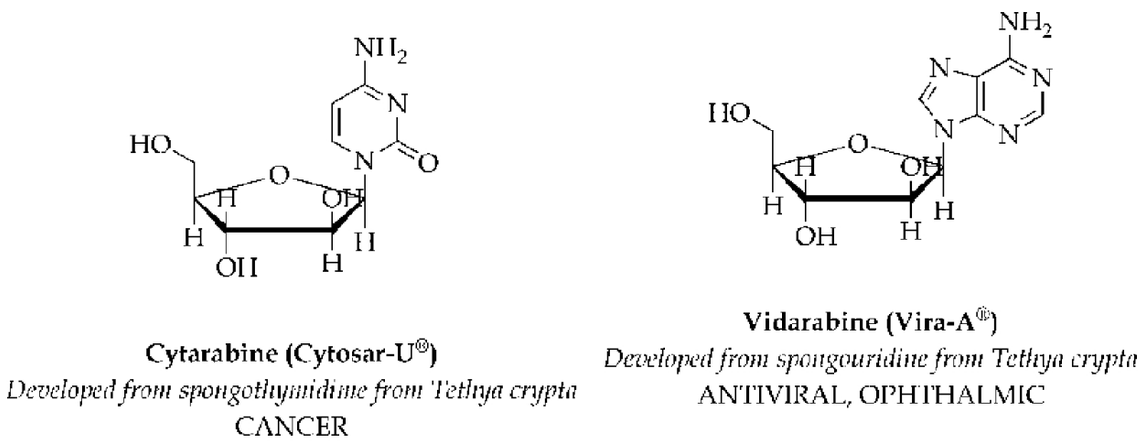


Fig. 2. FDA-approved marine-derived products

Several marine-derived products have been tested on PC targets. Iejimalides A-D (Fig. 3), 24-membered ring lactones bearing an *N*-formyl serine terminated side chain, are a class of marine macrolides found in the tunicate *Eudistoma cf. rigida*, a species of marine tunicate native to coral reefs in the vicinity of Ie Island (Iejima) near Okinawa in Japan, which have been found to be cytotoxic against a wide range of cancer cells at low nanomolar concentrations (Schweitzer *et al.*, 2007, McHenry *et al.*, 2010). The effects of iejimalide B were

studied on LNCaP and PC-3 cells (Wang *et al.*, 2008). On LNCaP cells, the compound induced a dose-dependent G0/G1 arrest and apoptosis, after 48 hours of treatment. Iejimalide B was found to modulate the steady-state levels of many gene products associated with the cell cycle and death, however, the same concentrations of compound initially induced a G0/G1 arrest followed by S phase arrest on PC-3 cells, without triggering apoptosis (Wang *et al.*, 2008). Increased expression of the cyclin kinase inhibitor $p21^{WAF1/CIP1}$ and downregulation of cyclin A expression were also observed with no modulation of the genes associated with cell death. Comparison of the effects of iejimalide B on the two cell lines suggested that the compound induced cell cycle arrest by two different mechanisms and that the induction of apoptosis on LNCaP cells was p53-dependent (Wang *et al.*, 2008).

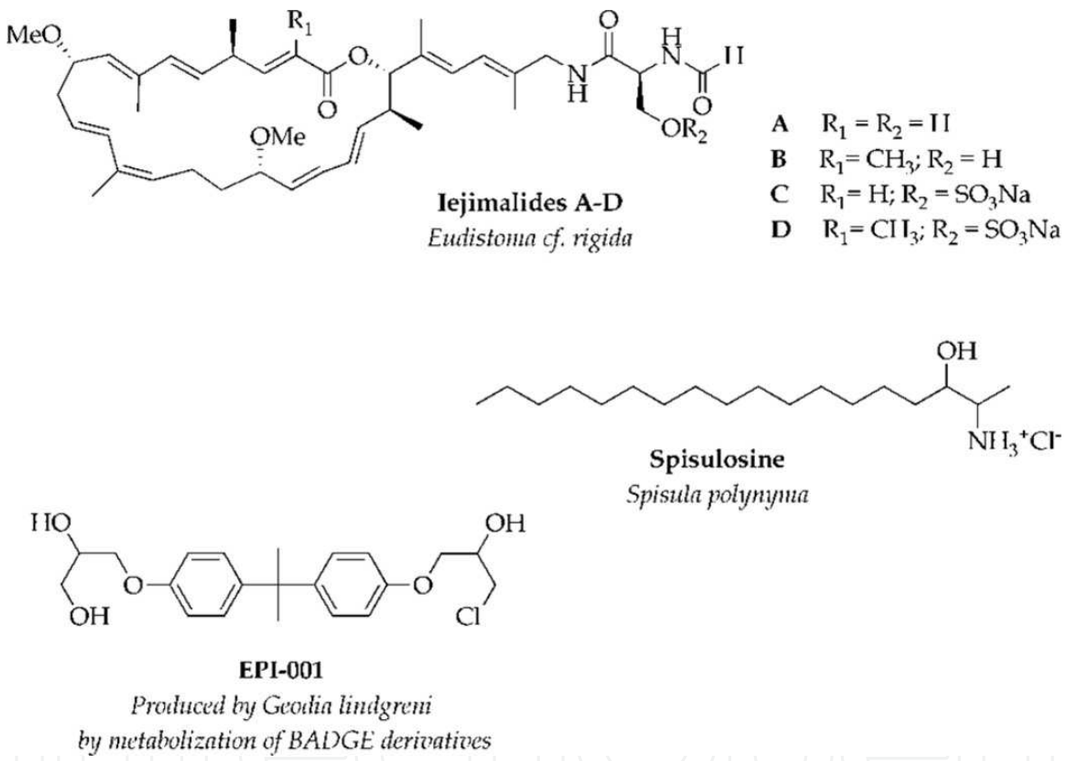


Fig. 3. Marine-derived compounds with impact on PC

Spisulosine (PharmaMar, ES-285, Fig. 3) is a novel anti-cancer agent recently isolated from the sea mollusc *Spisula polynyma* which inhibits the growth of several solid tumor cell lines (Padron & Peters, 2006) including human prostate PC-3 and LNCaP cells with an IC_{50} of 1-10 μM, through intracellular accumulation of ceramide and activation of the atypical protein kinase isoform PKCζ (Sanchez *et al.*, 2008). Thus, intracellular ceramide levels were increased after 48 hours of treatment with spisulosine. Both fumonisin B1, a mycotoxin produced by *Fusarium verticillioides* and a reported inhibitor of ceramide synthase, and myriocin, a potent fungal inhibitor of serine palmitoyltransferase, prevented this effect

pointing to a *de novo* synthesis of ceramide in the mechanism of action of spisulosine on PC cells. The same effect was not observed with specific inhibitors of the stress-related mitogen activated protein (MAP) kinases as well as of the peroxisome proliferator-activated receptor (PPARγ), phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt), and classical protein kinases C (PKCs) pathways, rulling out interference of these pathways in the mechanism of action of spisulosine (Sanchez *et al.*, 2008). Spisulosine entered Phase I clinical trials in patients with solid tumors. A dose-escalation study evaluated the safety, pharmacokinetics, pharmacogenomics, and efficacy of ES-285 in adult cancer patients (Baird *et al.*, 2009). ES-285 showed an acceptable safety profile at doses up to 128 mg/m^2. At this dose level, pharmacokinetic data indicated that pharmacologically relevant concentrations had been achieved, and pharmacogenomic studies indicated consistent, dose-responsive changes in expression of genes of potential biological relevance. This study identified transaminitis and neurotoxicity as the dose-limiting toxicities associated with a 24-hour infusion of ES-285 given once every 3 weeks (Baird *et al.*, 2009). These schedule independent hepato- and neuro-toxicity events caused the discontinuation of the clinical development of ES-285 (Vilar *et al.*, 2010, Schoffski *et al.*, 2011).

As previously mentioned, trabectedin (Fig. 1) is currently under phase II/III development in breast cancer, hormone-resistant PC (HRPC), sarcomas, and ovarian cancer (Bayes *et al.*, 2004, Michaelson *et al.*, 2005, Zelek *et al.*, 2006, Carter & Keam, 2007). Trabectedin binds to the minor groove of DNA and forms covalent bonds at the N2 position of guanidine (Marco *et al.*, 2006). Two of the tetrahydroisoquinoline rings recognize and bind to the minor groove of the DNA double helix whereas the other ring protrudes out of the minor groove and interacts directly with transcription factors. Trabectedin bends DNA towards the major groove rather than towards the site of interaction, unlike other compounds that bind to the minor groove (Carter & Keam, 2007). The cytotoxicity of this compound towards cancer cells has been explained mostly by its interference with the transcription-coupled nucleotide excision repair (TC-NER) pathway (Carter & Keam, 2007). Sensitization of the death receptor pathway has been recently reported to be essential in amplifying the cytotoxic properties of trabectedin and to account for the hepatotoxicity observed in patients treated with this drug (Martinez-Serra *et al.*, 2011). Both *in vitro* and *in vivo* activities have been found for trabectedin against a range of tumor cells lines, human xenografts, and human tumor explants, including STS, ovarian, breast, prostate and renal cancers, melanoma, and non-small cell lung cancer (NSCLC) (Li *et al.*, 2001, Carter & Keam, 2007). Unlike most anticancer drugs, the mechanism of resistance to trabectedin does not appear to involve P-glycoprotein (Carter & Keam, 2007).

Recently, a specific inhibitor of AR-dependent tumour growth that does not exhibit toxicity at a therapeutic dose range has been identified (Skinner, 2010, Thompson, 2010). EPI-001 (Fig. 3) has a new mode of action, as it targets the transactivation of AR regardless of the presence of androgen, and is a promising therapy to delay the progression of CRPC. This compound was first isolated from the marine sponge *Geodia lindgreni* by Sadar *et al.* which immediately identified its similarity to BADGE (bisphenol A diglycidic ether) and realized that it must be of industrial origin (Andersen *et al.*, 2010). The collected sponge presumably bioaccumulated the BADGE derivatives from contaminated seawater. EPI-001 was first isolated and purified and afterwards synthesized in order to be tested on PC targets. Thus, EPI-001 blocked transactivation of the amino-terminal domain of the AR and was specific for its inhibition without attenuating transcriptional activities of related steroid receptors

(Andersen *et al.*, 2010). EPI-001 interacted with the AF-1 region, inhibited protein-protein interactions with AR, and reduced AR interaction with androgen-response elements on target genes. Importantly, EPI-001 blocked androgen-induced proliferation and caused cytoreduction of CRPC in xenografts dependent on AR for growth and survival without causing toxicity (Andersen *et al.*, 2010).

4.2 Microbial compounds

Due to the current ability to cultivate only a vanishingly small number of naturally occurring microorganisms, the study of either terrestrial or marine natural microbial ecosystems has been severely limited (Cragg *et al.*, 2009). Nonetheless, a most impressive number of highly effective microbially derived chemotherapeutic agents has been discovered and developed (Cragg *et al.*, 2009, Newman & Cragg, 2009), examples of which are temsirolimus and ixabepilone (Fig. 1) (Butler, 2008, Toppmeyer & Goodin, 2010). The microbial universe thus presents a vast untapped resource for drug discovery and the advent of genetic techniques that permit the isolation and expression of biosynthetic cassettes will most likely place microbes at the frontier for NPs lead discovery.

4.2.1 Epothilones

Ixabepilone or aza-epothilone B (BMS-247550, Bristol-Myers-Squibb Co., Fig. 1) is a semi-synthetic analogue of patupilone (epothilone B, EPO906, Fig. 1) which is FDA-approved for the treatment of breast cancer (Butler, 2008, Toppmeyer & Goodin, 2010). The epothilones are 16-membered macrolides isolated from the myxobacterium *Sorangium cellulosum* (Hofle *et al.*, 1996, Gerth *et al.*, 1996) which bind to tubulin heterodimers and prevent the depolymerization of microtubules with subsequent mitotic arrest and apoptotic cell death, in a fashion analogous to plant-derived taxanes such as paclitaxel (Fig. 5) (Wartmann & Altmann, 2002, Cheng *et al.*, 2008). The main difference resides in the fact that taxanes are substrates for P-glycoprotein and epothilones are not, and this ability together with ease of formulation have been considered advantages for overcoming taxane resistance of tumor cells (Wartmann & Altmann, 2002, Cheng *et al.*, 2008). Moreover, whereas the synthesis of paclitaxel relies on 10-deacetylbaccatin III which is available from the needles of various *Taxus* species (Cragg *et al.*, 2009), total synthesis of patupilone B has been accomplished (Su *et al.*, 1997). The progress of epothilones in the PC setting has been extensively reviewed (Lee & Kelly, 2009, Lassi & Dawson, 2010, Cheng *et al.*, 2008, Bystricky & Chau, 2011).

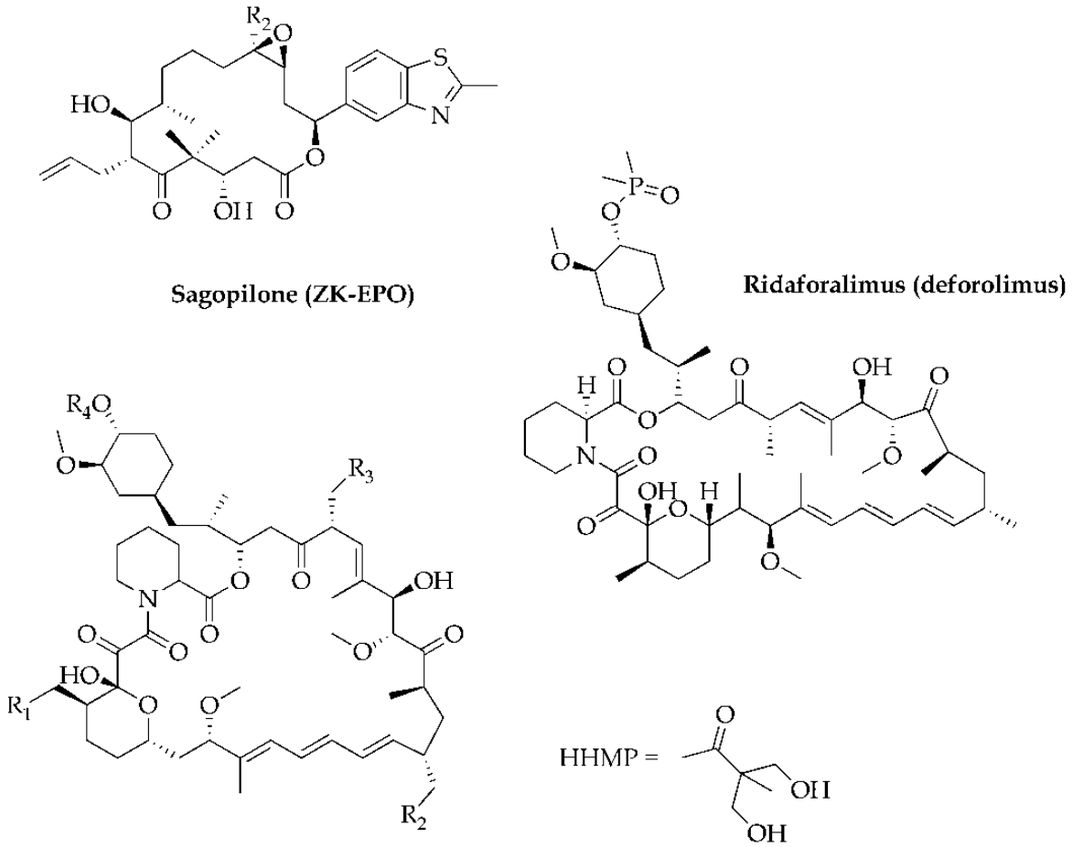
Patupilone inhibits the proliferation of DU145 and TSU-Pr1 PC cells in the low nanomolar range causing mitotic arrest (Sepp-Lorenzino *et al.*, 1999). Inhibition of proliferation appears to be dependent on the p53 status of the tumor cells (Ioffe *et al.*, 2004). Patupilone is active *in vivo* against human PC xenografts (O'Reilly *et al.*, 2005). It produced transient to long-lasting tumor regressions, including apparent cures, in s.c. transplanted DU145 and PC-3M PC xenografts in mice, with the 2.5 mg/kg regimen twice every 7 days being superior to a single dose of 4 mg/kg patupilone (O'Reilly *et al.*, 2005). The anti-tumor activity was superior to that of paclitaxel, which failed to produce tumor regressions, although displaying a better tolerability profile. Despite the enthusiastic *in vivo* results, an objective tumor response rate of only 20% has been reported for patupilone on HRPC in which 78% of patients had received one (unspecified) prior line of chemotherapy, a number comparable to

the 12% objective tumor response obtained with docetaxel (Fig. 5) and prednisone combined treatment, in the phase III TAX 327 study (Larkin, 2007). In phase I trials, patupilone has been considered generally safe and well tolerated, with patients experiencing no severe neuropathy or hematologic toxicity (Rubin *et al.*, 2005). Therefore, the safety and efficacy of weekly patupilone 2.5 mg/m^2 were investigated in patients with CRPC in a multicenter phase II trial (Hussain *et al.*, 2009). Modest response rates were observed with 2.5 mg/m^2 of patupilone weekly for 3 weeks of a 4-week cycle and therefore development of patupilone in advanced PC at the dose and schedule tested was not warranted. A once every 3 weeks schedule with proactive antidiarrhea management appeared to be the most promising schedule (Hussain *et al.*, 2009).

Ixabepilone has demonstrated activity in patients with chemotherapy-naive metastatic HRPC (Hussain *et al.*, 2005). Phase I clinical trials of ixabepilone administered i.v. as a 1 hour infusion daily, for 5 consecutive days every 21 days, at doses of 1.5 mg/m^2/day, displayed antitumor responses in patients with prior taxane treatment against solid tumors (Mancuso *et al.*, 2007). Major adverse effects were neutropenia and neuropathy. Ixabepilone was also evaluated as a single agent in two first line studies. PSA response was observed in 30-35% of cases with an objective clinical response rate of over 15% in patients with measurable disease (Mancuso *et al.*, 2007). When combined with estramustine phosphate (ixabepilone 35 mg/m^2 i.v. on day 2 with a 280 mg oral dose of estramustine, 3 times/day, on days 1-5, every 3 weeks), it was found to be well tolerated and have antitumor activity in patients with castrate-metastatic PC (Rosenberg *et al.*, 2006, Rivera *et al.*, 2008). Second-line taxane chemotherapy after ixabepilone resulted in a substantial frequency of PSA declines. Although patients with ixabepilone-refractory disease were less likely to respond to second-line taxane chemotherapy, 36% did achieve a PSA response. For patients with taxane-resistant HRPC, a randomized phase II study compared ixabepilone to mitoxantrone/ prednisone (Mancuso *et al.*, 2007). A PSA decline of over 50% was seen in 20% of patients and median survival of 13 months was found for patients on the mitoxantrone arm, as compared to a PSA decline of over 50% in 17% and median survival of 12 months for ixabepilone treatment (Mancuso *et al.*, 2007, Rivera *et al.*, 2008). A recent phase II clinical trial concluded that the combination of ixabepilone and mitoxantrone with prednisone appears to have greater activity than either mitoxantrone or ixabepilone alone in the second-line setting for CRPC, and suggests at least additive if not synergistic activity (Harzstark *et al.*, 2011). The combination is well tolerated, although some hematologic toxicity is present and dosing with pegfilgrastim is required. The results of this study suggest that it is appropriate to study further the ixabepilone and mitoxantrone with prednisone regimen in patients with docetaxel resistant CRPC (Harzstark *et al.*, 2011).

The fully synthetic epothilone sagopilone (Fig.4) (ZK-EPO, Bayer Schering Pharma AG) is undergoing initial testing in PC with promising results (Galmarini, 2009). In preclinical studies, sagopilone inhibited cell growth in a wide range of human cancer cell lines. Moreover, sagopilone was not recognized by multidrug-resistant (MDR) cellular efflux mechanisms, and maintained its activity in MDR tumor models. Phase I clinical trials established that the sagopilone side-effect profile was similar to that reported for taxanes, with neuropathy and neutropenia being the most commonly reported toxicities (Arnold *et al.*, 2009, Schmid *et al.*, 2010). A recommended dose for phase II studies was established at 16.53 mg/m^2, once every 3 weeks (Schmid *et al.*, 2010). Proof-of-concept has already been

established in patients with platinum-resistant ovarian cancer and androgen-independent PC, and clinical responses have been shown in patients with melanoma and small-cell lung cancer. Results are awaited from other ongoing trials (Schmid *et al.*, 2010).



$R_1 = R_2 = R_3 = H$; $R_4 = CH_2CH_2OH$ **Everolimus (Zortress®)**
$R_1 = CH_3$; $R_2 = R_3 = H$, R_4 = HHMP **Homotemsirolimus A**
$R_1 = R_3 = H$; $R_2 = CH_3$; R_4 = HHMP **Homotemsirolimus B**
$R_1 = R_2 = H$; $R_3 = CH_3$; R_4 = HHMP **Homotemsirolimus C**

Fig. 4. Microbial-derived compounds with impact on PC.

4.2.2 mTOR inhibitors

The protein kinase mTOR regulates protein translation, cell growth, and apoptosis (Garcia & Danielpour, 2008, Seeliger *et al.*, 2007). Alterations in the pathway regulating this kinase occur in many solid malignancies including prostate, bladder, and kidney cancer. *In vitro* and *in vivo* models of prostate and bladder cancer have established the importance of the mTOR pathway in control of cancer progression and metastasis (Garcia & Danielpour, 2008, Opdenaker & Farach-Carson, 2009). The mTOR inhibitors temsirolimus (Fig. 1) and everolimus (RAD001, Zortress®, Novartis, Fig.4), two ester analogues of sirolimus (rapamycin, Fig. 1), as well as rapamycin itself have clear antitumor activity in *in vitro* and *in vivo* models and are under clinical trial investigations for prostate and bladder cancers (Seeliger *et al.*, 2007, Armstrong *et al.*, 2010). Ridaforulimus (deforolimus, AP23573, MK-

8669, Merck and ARID Pharmaceuticals, Fig. 4), yet another mTOR inhibitor and a derivative of rapamycin is also undergoing clinical trials for PC (Gross *et al.*, 2006, Squillace *et al.*, 2008).

Genetic alterations, including loss of phosphatase and tensin homolg (PTEN), mutation of the PI3K, and amplification of AKT1 and AKT2 leading to activation of Akt kinase activity have been linked with the development of castrate progressive PC (Seeliger *et al.*, 2007, Majumder *et al.*, 2004). It is also known that alterations of the Akt signaling cascade (mTOR dependent) can lead to the development of prostate intraepithelial neoplasia (Majumder *et al.*, 2004). Repopulation of PTEN-negative cancer cells between courses of chemotherapy has been reported to be inhibited by temsirolimus on PC-3 and DU145 PC xenografts with only mild myelosuppression, thus suggesting its role on minimization of drug resistance in patients (Wu *et al.*, 2005). In addition, the effects of concurrent and sequential administration of docetaxel and temsirolimus on PC-3 and LnCaP tumor cells and xenografts were studied (Fung *et al.*, 2009). Temsirolimus originated greater growth delay of PC-3 xenografts than docetaxel alone. This effect was greater than that expected from the *in vitro* sensitivity, and differed from the general experience in treatment of human PC, where chemotherapy has shown greater activity than molecular-targeted agents. In contrast, for LnCaP cells, temsirolimus had similar inhibitory effects to those observed with PC-3 cells in culture, but no significant effect on LnCaP xenografts (Fung *et al.*, 2009). Despite similar cell cycle effects between concurrent and sequential treatments in *in vitro* experiments, *in vivo* growth delay studies showed better delay of tumor regrowth with concurrent temsirolimus and docetaxel treatment compared to sequential treatment in the prostate xenografts (Fung *et al.*, 2009). As previously mentioned, temsirolimus is the first mTOR inhibitor approved for use in oncology (Butler, 2008). Further results from ongoing clinical trials should help to establish whether a role exits for this drug on the PC setting.

Deforolimus alone was shown to inhibit proliferation of several prostate cell lines by 20−60% (maximal inhibition) and as expected, sensitivity was associated with loss of PTEN (Squillace *et al.*, 2008). The anti-proliferative activity of deforolimus and bicalutamide, alone and in combination, was determined in three cell lines representing different stages of PC progression. The combination was strongly synergistic in both androgen-dependent LNCaP and androgen-independent C4−2 cells but only additive in RWPE-1 (normal prostate epithelium) cells. The data provided support for the clinical testing of deforolimus in combination with bicalutamide to treat androgen-dependent and -independent PC (Squillace *et al.*, 2008). Also, a phase II clinical trial of deforolimus in patients with taxane-resistant HRPC concluded that the compound is well tolerated and promotes disease stabilization (Gross *et al.*, 2006).

The ability of everolimus to enhance the cytotoxic effects of radiation on PC-3 and DU145 cells has been reported (Cao *et al.*, 2006). Both cell lines became more vulnerable to irradiation after treatment with everolimus, with the PTEN-deficient PC-3 cell line showing the greater sensitivity. This increased susceptibility to radiation was found to be associated with induction of autophagy (Cao *et al.*, 2006). Treatment with everolimus resulted in growth inhibition of C4-2 cells in bone, an effect augmented by addition of docetaxel and zoledronic acid (Morgan *et al.*, 2008). Moreover it had a significant impact on maintenance of body weight. A single phase II study evaluated the effect of everolimus in patients with newly diagnosed, localized PC (Lerut *et al.*, 2005). The most frequently observed adverse events are common toxicity criteria grade 1 to 2 stomatitis and rash. Recently, three

temsirolimus analogues, homotemsirolimuses A-C (Fig. 4), were isolated from a temsirolimus preparation made from rapamycin and found to inhibit mTOR as well as the proliferation of LNCaP cells with potency comparable to that of rapamycin and temsirolimus (Kong *et al.*, 2011).

4.3 Plant compounds

Plant-derived NPs have been an important source of several clinically useful anti-cancer agents (Grothaus *et al.*, 2010, Cragg *et al.*, 2009, Butler, 2008, Ojima, 2008). Plants continue to play a major role in drug discovery as evidenced by the number of promising new agents in clinical development based on selective activity against cancer-related molecular targets. One of the most noteworthy contributions of plants to this field has been the isolation of tubulin interactive agents such as the *Vinca* alkaloids and the taxanes which are the basis of the majority of the currently available anticancer therapies.

4.3.1 Taxanes

Paclitaxel (Taxol®, Bristol-Myers Squibb, Fig. 5) was first isolated from the bark of the Western yew tree in 1971 and found to possess unique pharmacological actions as an inhibitor of mitosis, differing from the *Vinca* alkaloids and colchicine derivatives in that it promotes rather than inhibits microtubule formation (Hardman & Limbird, 2001). It binds specifically to the β-tubulin subunit of microtubules and antagonizes the disassembly of this key cytoskeletal protein causing mitotic arrest. Resistance to paclitaxel is associated to high levels of P-glycoprotein expressed by tumor cells (Hardman & Limbird, 2001). Paclitaxel is currently used to treat multiple cancers such as lung, ovarian, head and neck, breast, and advanced stages of Kaposi's sarcoma. Modification of the side chain of paclitaxel resulted in the more potent analogue docetaxel (Taxotere®, Sanofi-Aventis, Fig. 5) which has clinical activity against breast, ovarian and NSCLC (Hardman & Limbird, 2001). The present status and perspectives of taxane-based regimens for cancer treatment have been thoroughly reviewed (Mancuso *et al.*, 2007, Sartor, 2011).

In 2004, the results of the two major phase III clinical trials TAX 327 and SWOG 9916 established docetaxel as a primary chemotherapeutic option for patients with mCRPC (Berthold *et al.*, 2008, Tannock *et al.*, 2004). Outcomes of TAX 327 demonstrated that chemotherapy with docetaxel was a viable option that prolonged survival for patients with mCRPC and in addition with an extended follow-up, the survival benefit of docetaxel in the TAX 327 trial has persisted. In SWOG 9916, a regimen of docetaxel and estramustine was compared with mitoxantrone and prednisone (Petrylak *et al.*, 2004). In this study, the docetaxel regimen also conferred a significant survival benefit and increased median survival. At present, docetaxel/prednisone remains the first-line chemotherapy of choice for patients with CRPC (Sartor, 2011). Combinations of docetaxel and different drug classes, including tyrosine kinase inhibitors, antiangiogenesis agents, and immunologic agents, have been the object of several studies for CRPC. Nonetheless, phase III data for combination therapy with docetaxel has not produced any viable therapeutic options (Sartor, 2011).

Cabazitaxel (XRP-6258, Jevtana®, Sanofi-Aventis, Fig. 5) is a novel taxane-class cytotoxic agent in which two hydroxyl groups have been replaced by methoxy groups, that has shown efficacy in model system tumors that are resistant to paclitaxel and docetaxel (Kumar *et al.*, 2010, Sartor, 2011). Multiple cases of complete regression were observed with cabazitaxel in studies using human tumor xenografts. Notably, long-term tumor-free

survival (exceeding 133 days) and complete tumor regression were seen in pancreatic xenografts (MIA PaCa-2), head and neck xenografts (SR475), and prostate DU145 xenografts (Kumar *et al.*, 2010). In a recently published, randomized, multicenter, phase III trial (TROPIC), the efficacy and safety of cabazitaxel and prednisone were compared with those of mitoxantrone and prednisone for the treatment of mCRPC that had progressed following docetaxel-based chemotherapy (De Bono *et al.*, 2010). Tumor response and PSA response significantly favored cabazitaxel, as did median time to tumor progression and median time to PSA progression. Pain response and time to pain progression were similar between the treatment groups (De Bono *et al.*, 2010). Neutropenia, leukopenia, and anemia were the predominant toxicities associated with cabazitaxel in the study. The findings of TROPIC study established cabazitaxel as the first agent to prolong survival after docetaxel treatment, with a 30% reduction in death over mitoxantrone (De Bono *et al.*, 2010). On the basis of these data, cabazitaxel has been approved by the FDA for use in patients with mCRPC who have progressed after docetaxel (Galsky *et al.*, 2010, Sartor, 2011).

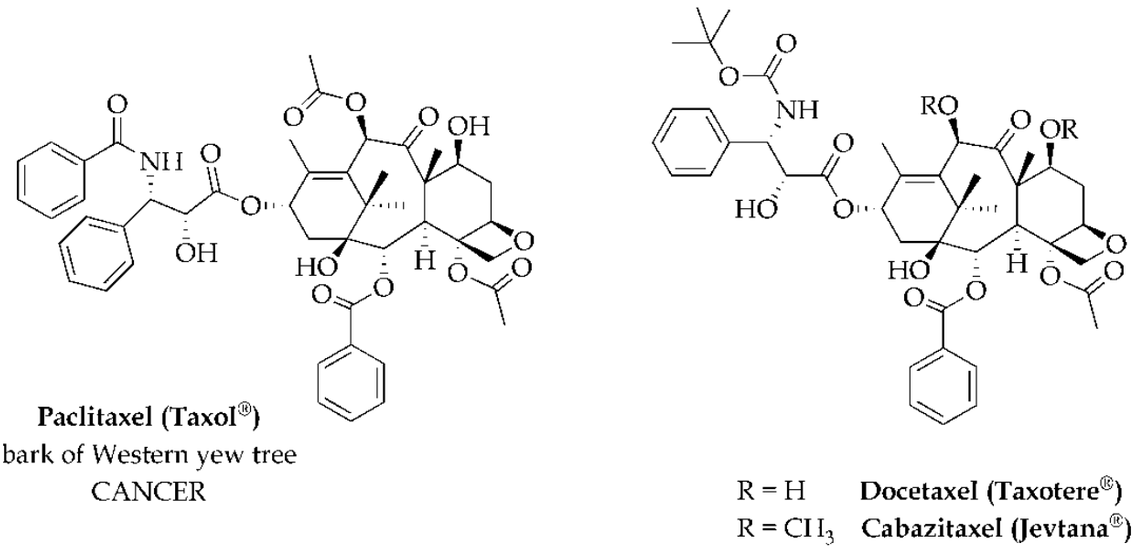


Fig. 5. Taxanes.

4.3.2 Irofulven

Irofulven (MGI 114, NSC 683863, Pharma, Inc., Fig. 6), an anticancer agent derived from the mushroom natural product illudin S has been found to inhibit DU145, PC-3, and LNCaP cell proliferation with IC_{50} values of 100, 200, and 700 nM, respectively (Poindessous *et al.*, 2003). The cytotoxicity of irofulven is not affected by loss of p53 or mismatch repair function, and the drug is not a substrate for multidrug transporters such as P-glycoprotein and MDR-1. Irofulven acts by alkylating cellular macromolecular targets (Liang *et al.*, 2004). The drug is a potent inducer of apoptosis in various types of tumor cells, whereas it is nonapoptotic in normal cells. Irofulven-induced signaling was studied on LnCaP-Pro5 cells and was found to be integrated at the level of mitochondrial dysfunction. The induction of both caspase-dependent and caspase-independent death pathways was consistent with pleiotropic effects, which include targeting of cellular DNA and proteins (Liang *et al.*, 2004). The effect of irofulven on apoptosis was also reported to be largely Bcl-2 independent, a highly desirable

property seeing that elevated levels of this protein correlate with an increased metastatic potencial of cancer cells (Herzig *et al.*, 2003). Irofulven has demonstrated activity against PC-3 and DU145 cells as monotherapy and enhanced efficacy was displayed in combination with mitoxantrone or docetaxel (Van Laar *et al.*, 2004) and these results highlighted its potential to be used in combination regimens in clinical trials. Thus a phase I and pharmacokinetic study of irofulven (0.4 mg/kg) and cisplatin (30 mg/m^2) in patients with solid tumors concluded that the regimen was adequately tolerated with substantial evidence of antitumor activity observed (Hilgers *et al.*, 2006). Combination regiments of the same dosage of irofulven with capecitabine (2,000mg/m^2/day) were also found safe on phase I clinical trials in patients with solid tumors (Alexandre *et al.*, 2007). Other combination regimens with oxaliplatin were reported to be effective on docetaxel-resistant HRPC patients (Tchen *et al.*, 2005). Irofulven was also reported to be active as a single agent against HPRC on a phase II trial (Senzer *et al.*, 2005). Based on evidence of irofulven activity in HRPC observed in these prior Phase I/II studies, a randomized Phase II study in docetaxel-refractory HRPC patients was initiated using irofulven/prednisone or irofulven/capecitabine/predisone versus mitoxantrone/prednisone (Hart *et al.*, 2006). Preliminary results suggested a longer survival and time to progression, a higher PSA response, and an acceptable safety profile for irofulven/prednisone and irofulven/capecitabine/predisone compared to mitoxantrone/ prednisone. Based on these data, irofulven may have a role in treating docetaxel-resistant HRPC patients (Hart *et al.*, 2006).

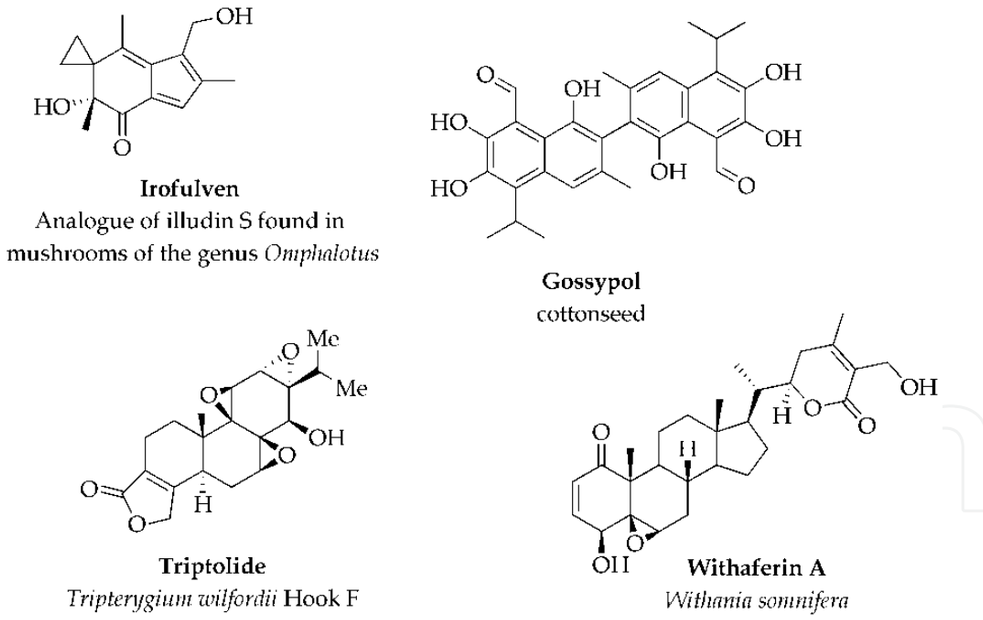


Fig. 6. Plant-derived compounds with impact on PC

4.3.3 Gossypol

Gossypol (Fig. 6), a polyphenolic compound present in cottonseed (Huang *et al.*, 2006), was originally identified as a male antifertility agent. Gossypol treatment resulted in a marked reduction of the prostate weight of guinea-pigs and adult rats as well as induction of structural and functional changes of the gland somewhat similar to the ones observed after

castration (Moh *et al.*, 1992, Wong & Tam, 1989). Antiproliferative and antimetastatic activities in androgen-independent Dunning R3327-MAT-LyLu PC cell-bearing Copenhagen rats have been reported with gossypol (Chang *et al.*, 1993). The compound has also been reported to potently inhibit both isoforms of 5α-reductase (Chang *et al.*, 1993). Gossypol inhibited the proliferation without affecting the viability of PC-3 cells with an IC_{50} value of lower than 1 μM, and induced a dose- and time-dependent accumulation of cells at the G0/G1 phase of the cell cycle (Shidaifat *et al.*, 1996). On DU145 cells gossypol significantly enhanced apoptosis through downregulation of Bcl-2 and Bcl-xL and upregulation of Bax at the mRNA and protein levels (Huang *et al.*, 2006). Activation of caspases 3, 8, and 9 was also found to occur as well as increased PARP cleavage. Thus, gossypol is a natural BH3 mimetic and small molecule inhibitor of Bcl-2/Bcl-xL/Mcl-1 that potently induces apoptosis in various cancer cell lines (Meng *et al.*, 2008). It also significantly enhances the antitumor activity of docetaxel in human PC both *in vitro* and *in vivo*. Gossypol effectively reduced the viability of LAPC4, PC-3, and DU145 PC cells and inhibited tumor growth in a NOD/SCID xenograft model (Volate *et al.*, 2010). The growth of prostate tumor initiating cells (pTICs) isolated from DU145 (CD44+/hi) were also inhibited. The inhibitory effects of gossypol have been attributed to the induction of DNA damage, which consequently leads to the stabilization of p53 and the activation of the mitochondrial pathway of apoptosis (Volate *et al.*, 2010). In addition, gossypol was recently reported to induce autophagy in human androgen-independent PC with a high level of Bcl-2 both *in vitro* and *in vivo* (Lian *et al.*, 2011).

A derivative of gossypol, *R*-(–)-gossypol acetic acid (AT-101, Ascenta Therapeutics, Inc.) has been evaluated on a phase I/II trial as a single-agent in men with chemotherapy-naive castrate-resistant PC (Liu *et al.*, 2009). The compound was well tolerated when administered at 20 mg/day for 21 of 28 days. Evidence of single-agent clinical activity was observed with PSA declines in some patients. Further investigation of AT-101 in PC thus is warranted and trials combining AT-101 with androgen deprivation, as well as with docetaxel chemotherapy are ongoing (Liu *et al.*, 2009).

4.3.4 Triptolide

Triptolide (PG 490, Fig. 6) is a diterpene triepoxide purified from *Tripterygium wilfordii* Hook F (Kupchan *et al.*, 1972) that was found to attenuate activation of p53 in response to γ-irradiation or other stresses such as hypoxia or DNA damaging drugs, in primary cultures of normal and malignant PC epithelial cells, despite the presence of the wild-type p53 gene (Girinsky *et al.*, 1995). Moreover, triptolide inhibited LNCaP growth with an IC_{50} value of 10 ng/ml (Shamona *et al.*, 1997). Half-maximal growth inhibition of five PC cell strains, E-PZ-10 and four cell lines derived from prostatic adenocarcinomas of Gleason grade 3/3 (E-CA-11), 30% intraductal carcinoma / 70% Gleason grade 4 (E-CA-12) and 3/4 (E-CA-13 and E-CA-14), was observed with 0.1 ng/ml triptolide (Kiviharju *et al.*, 2002). Whereas low concentrations of triptolide induced senescence of cells with G1 arrest, higher concentrations (50-100 ng/ml) triggered apoptosis. However, in contrast with the previous findings, protein levels of p53 were significantly increased and predominantly accumulated in the nuclei of prostatic epithelial cells (Kiviharju *et al.*, 2002). Nonetheless, downregulation of p53 target gene products such as Hdm-2 and p21WAF1/CIP1 and Bcl-2 was also found to occur. It was suggested that triptolide may use multiple signaling pathways, some of which involve p53 in cells with wild-type p53, growth arrest and induction of apoptosis (Kiviharju *et al.*, 2002). Clinical and experimental studies have demonstrated that triptolide has anti-

inflammatory and immunosuppressive activities, and effectively prolongs allograft survival in organ transplantation including bone marrow, cardiac, renal and skin transplantation (Liu, 2011).

PG490-88Na (Pharmagenesis Inc.), a water-soluble prodrug of triptolide (14-succinyl sodium salt) that is converted into triptolide in the serum, has been elucidated as a new immunosuppressant (Fidler *et al.*, 2003). It effectively prevents acute and chronic rejection in organ transplantation and shows potent antitumor activity. The compound has been approved for phase I clinical trials for PC (Fidler *et al.*, 2003, Kiviharju *et al.*, 2002). However, the safety and side effects of triptolide for PC therapy need to be further elucidated. Further development of triptolide derivatives may produce promising anticancer drug candidate (Liu, 2011).

4.3.5 Withaferin A

Withaferin A (Fig. 6), a steroidal lactone purified from the medicinal plant "Indian Winter Cherry" or *Withania somnifera*, has been widely studied for its antitumor effects (Glotter *et al.*, 1966). Withaferin A was inhibits the chymotrypsin-like activity of purified rabbit 20S proteasome (IC_{50} of 4.5 μM) and of 26S proteasome in cultured PC-3 cells, with an IC_{50} value of 10-20 μM, and tumors (Yang *et al.*, 2007). Inhibition of PC tumor cellular proteasome both *in vitro* and *in vivo* by withaferin A was accompanied by accumulation of Bax, IκB-α and p27, and induction of apoptosis (Yang *et al.*, 2007). Proteasome inhibition occurred before the apoptotic events of caspase-3 activation with PARP cleavage and the expected morphological changes (rounding and condensation), on PC-3 cells, at 10 μM of withaferin A. On LNCaP cells, AR protein levels were decreased by withaferin A and apoptosis triggered by the same mechanisms seen on PC-3 cells (Yang *et al.*, 2007). Treatment of human PC-3 xenografts with withaferin A at 4.0 and 8.0 mg/kg/day for 24 days caused 54 to 70% inhibition of tumor growth, as compared to control, that was associated with a 28 to 56% inhibition of proteasomal chymotrypsin-like activity. Induction of apoptosis by withaferin A on PC cells bears additional interest because it has been shown to be mediated by the cancer specific target protein (Par-4) (El-Guendy *et al.*, 2003). Moreover, treatment of androgen-responsive PC cells with antiandrogens such as flutamide or bicalutamide which do not induce apoptosis on their own, rendered these cells amenable to apoptosis triggered by withaferin A. Apoptosis by withaferin A required upregulation of Par-4 expression for inhibition of NF-κB activity and activation of the caspase cascade (Srinivasan *et al.*, 2007). Therefore, withaferin A shows promise for HRPC treatment seeing that it not only seems to suppress the growth of metastatic cells but can also be exploited in combination regimens with antiandrogens to target resistant clones.

4.3.6 Pentacyclic triterpenoids

Terpenoids, among which are pentacyclic triterpenoids such as betulinic, ursolic, oleanolic, and boswellic acids as well as pristimerin and celastrol (Fig. 7), are extensively found in fruits, vegetables and medicinal plants (Salvador, 2010). This category of compounds exhibits multiple properties including antioxidation, anti-inflammation, anti-HIV, and anticancer activities (Shah *et al.*, 2009, Petronelli *et al.*, 2009).

In vitro and *in vivo* studies indicate that pentacyclic triterpenoids caused inhibition on cell proliferation and tumor growth in a variety of human cancers (Salvador, 2010). Structurally some of the terpenoids are similar to human hormones and thus bear interest in the

development of drugs that target hormone-dependent cancers such as breast and prostate cancers (Yang & Dou, 2010). The mechanisms by which these compounds exhibit their anticancer activity include inhibition of the proteasome, NF-κB, and the antiapoptotic protein Bcl-2 (Yang & Dou, 2010, Wang & Fang, 2009).

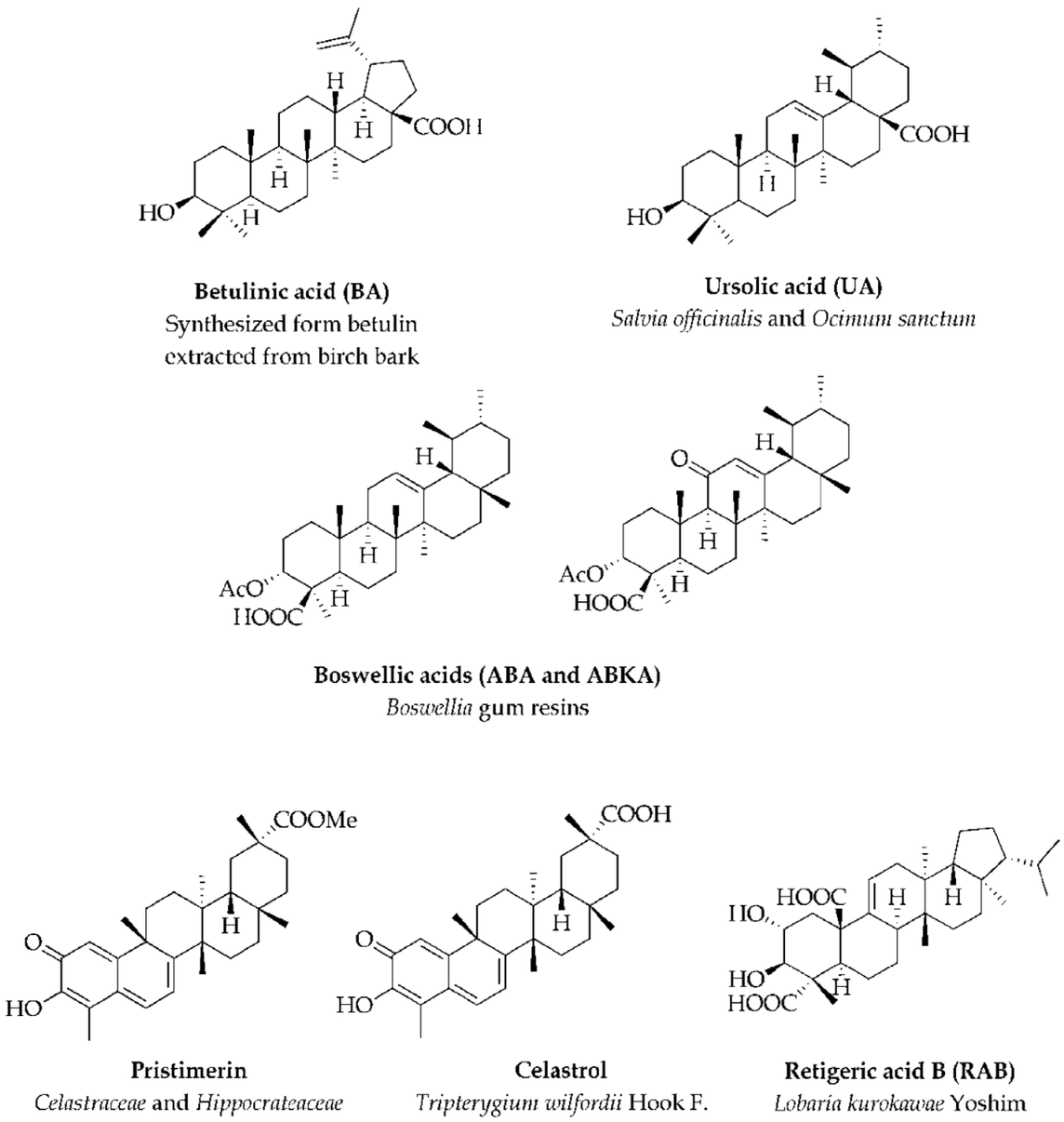


Fig. 7. Pentacyclic triterpenoids

Betulinic acid (BA, Fig. 7) is a NP identified in various bark extracts and is readily synthesized from betulin, a major constituent of the bark of birch trees (Aggarwal & Shishodia, 2006). It is currently undergoing development as a therapeutic agent against melanoma (Tan *et al.*, 2003). BA inhibited the proliferation of several PC cells and triggered apoptosis probably due to AR downregulation that led to decreased expression

of vascular endothelial growth factor (VEGF) and survivin, and caspase-dependent PARP cleavage (Chintharlapalli *et al.*, 2007, Kessler *et al.*, 2007). BA was shown to induce proteasome-dependent degradation of Sp proteins in LNCaP cells (Chintharlapalli *et al.*, 2007, Yao *et al.*, 2004, Wang *et al.*, 2003). *In vivo*, BA (10 and 20 mg/kg/day) inhibited tumor growth in athymic nude mice bearing LNCaP cell xenografts, which was accompanied by decreased expression of Sp1, Sp3 and Sp4 proteins and VEGF, and increased apoptosis in tumors from BA-treated mice (Chintharlapalli *et al.*, 2007). In androgen-refractory PC-3 cells, BA effectively inhibited NF-κB binding to DNA and its translocation to the nucleus, IκBα phosphorylation, and IκB kinase complex (IKK) activation, and in addition sensitized cells to TNFα-induced apoptosis through suppression of NF-κB (Rabi *et al.*, 2008). A major advantage in using BA for cancer therapy is its low toxicity. Doses as high as 500 mg/kg, administered every 4th day for 6 weeks to athymic mice carrying human melanomas have been shown to have no detectable toxic side effects (Pisha *et al.*, 1995). However, a study demonstrated that BA cannot be used to potentiate cell death in combination with most anticancer drugs that induce apoptosis via formation of topoisomerase I-DNA cleavable complexes such as camptothecin, staurosporine and etoposide (Ganguly *et al.*, 2007). Thus, the compound inhibits all types of topoisomerase-I DNA cleavable complexes formation irrespective of the process of initiation, therefore disrupting the series of events that leads to cell death.

Ursolic acid (UA, Fig. 7) is present in many plants such as *Salvia officinalis* and Basil (*Ocimum sanctum*) and also a constituent of several herbal medicines marketed in Asia and worlwide for inflammatory conditions (Aggarwal & Shishodia, 2006, Kondo *et al.*, 2011, Kwon *et al.*, 2010). UA inhibits the proliferation of PC-3 and LNCaP cells with IC_{50} values of 32.6 and 15.7 μM, respectively (Kassi *et al.*, 2007). At 55 μM, induction of apoptosis is seen on PC-3 cells with a decrease on bcl-2 gene levels. UA-induced apoptosis on human prostate epithelial cells has been suggested to involve caspase activation through downregulation of cellular inhibitor of apoptosis proteins (c-IAPs) family proteins and without mitochondrial dysfunction (Choi *et al.*, 2000). On DU145 cells UA-induced apoptosis was reported to occur via JNK-mediated Bcl-2 phosphorylation and degradation (Zhang *et al.*, 2009). Also, UA was found to overcome Bcl-2-mediated resistance to apoptosis in LNCaP androgen-independent cells (Zhang, Kong, Wang *et al.*, 2010). UA inhibits cell invasion by downregulating matrix metalloproteinase-9 via inhibition of Akt in PC-3 cells (Zhang, Kong, Zeng *et al.*, 2010).

Boswellic acids, particularly acetyl-boswellic acids such as acetyl-β-boswellic acid (ABA) and acetyl-11-keto-β-boswellic acid (ABKA, Fig. 7), can be isolated to chemical homogeneity from the gum resins of various *Boswellia* species and are well-known for their anti-inflammatory and antitumor activities (Aggarwal & Shishodia, 2006, Moussaieff & Mechoulam, 2009, Shah *et al.*, 2009). It has been reported that acetyl-boswellic acids promote apoptosis of PC-3 cells both *in vitro* and *in vivo* by intercepting IKK activity (Syrovets *et al.*, 2005). In particular, AKBA has the ability to induce cell growth arrest and reduce the AR expression and transcriptional activity in LNCaP cells via inhibition of the Sp1 binding activity (Yuan *et al.*, 2008). Both PC-3 and LNCaP cells were sensitive to AKBA-induced apoptosis that correlated with the activation of caspase-8 and the upregulation of death-receptor 5 (DR5) protein most likely by induced expression of CCAAT/enhancer binding protein homologous protein (CHOP) protein (Lu *et al.*, 2008). In addition, AKBA potently inhibits human prostate tumor growth through inhibition of angiogenesis induced by VEGFR2 signaling pathways (Pang *et al.*, 2009).

Pristimerin (Fig. 7) is a natural compound found in the *Celastraceae* and *Hippocrateaceae* families that are rich in quinone-methide triterpenes (Filho *et al.*, 2002). Pristimerin targets the proteasome to induce apoptosis in human PC-3 and AR-positive C4-2B cells (Yang, Landis-Piwowar *et al.*, 2008). Proliferation of PC-3 cells was inhibited by pristimerin (Chang *et al.*, 2003) with induction of apoptosis that correlated with inhibition proteasome activity (Yang, Landis-Piwowar *et al.*, 2008). The IC_{50} value for the inhibition of purified rabbit 20S proteasome with pristimerin was 2.2 μM. Similarly, pristimerin also potently inhibited 26S proteasome chymotrypsin-like activity in a extract prepared from exponentially grown PC-3 cells, with an IC_{50} of 3.0 μM (Yang, Landis-Piwowar *et al.*, 2008). About 40% inhibition of cellular proteasome activity occurred in C4-2B cells with 5 μM of pristimerin and was accompanied by AR suppression with consequent apoptosis induction. Computational modeling showed that pristimerin interacts with the catalytically active amino acid *N*-Thr of the proteasome β5 subunit (Yang, Landis-Piwowar *et al.*, 2008). Celastrol (Fig. 7), an active compound extracted from the root bark of the Chinese medicine ''Thunder of God Vine'' (*Tripterygium wilfordii Hook F.*), has been used for years as a natural remedy for inflammatory conditions (Kannaiyan *et al.*, 2011). The anti-inflammatory effects of this triterpene have been demonstrated in animal models of different inflammatory diseases, including arthritis, Alzheimer's disease, asthma, and systemic lupus erythematosus. Celastrol has also been found to inhibit the proliferation of a variety of tumor cells and suppress tumor initiation, promotion and metastasis in various cancer models *in vivo* (Salminen *et al.*, 2010, Kannaiyan *et al.*, 2011). Celastrol potently and preferentially inhibits the chymotrypsin-like activity of human PC cellular 26S proteasome at 1-5 μM (Yang *et al.*, 2006). Inhibition of the proteasome activity by celastrol is accompanied by suppression of AR protein expression and induction of apoptosis. The involvement of calpain in AR breakdown during celastrol-induced apoptosis in PC cells has been demonstrated (Yang, Murthy *et al.*, 2008). By inhibiting proteasomal activity, celastrol suppresses proliferation, invasion and angiogenesis by inducing the apoptotic machinery and attenuating constitutive NF-kB activity, both *in vitro* and *in vivo*, in androgen-independent PC cell lines (Dai *et al.*, 2010). Angiogenesis-mediated tumor growth is also suppressed by celastrol by targeting the AKT/mTOR/P70S6K pathway, (Pang *et al.*, 2010). Celastrol sensitizes PC-3 cells to radiation both *in vitro* and *in vivo* by impairing DNA damage processing and augmenting apoptosis (Dai *et al.*, 2009). It also potentiated the apoptotic effects of TRAIL through down-regulation of cell survival proteins and up-regulation of death receptors via the ROS-mediated up-regulation of CHOP pathway on several tumor cell lines including PC (Sung *et al.*, 2010).
Recent research has brought into light the effects of retigeric acid B (RAB, Fig. 7), a NP isolated from the lichen *Lobaria kurokawae* Yoshim and previously exploited for its antifungal activity, on PC cells (Liu *et al.*, 2010). Thus, RB was able to suppress AR expression and transcriptional activity in LNCaP cells, and inhibition of PC-3 cell growth was accompanied by induction of the S-phase cell cycle arrest as well as apoptosis.

5. Conclusion

Outstanding contributions from Nature have paved the way in drug discovery and allowed the establishment of conventional therapies for the treatment of the majority of human diseases, including cancer. Whereas plants have been the most common source of active molecules throughout the centuries, the now unraveling potential of marine and microbial sources is bound to provide highly active compounds with a myriad of biological activities which may improve the therapeutic options available for many human diseases in a nearby

future. Many compounds from plant, marine and microbial sources have been studied on PC targets. Therapies which target both androgen-dependent and –independent PC cells and can thus circumvent the mechanisms of PC recurrence have been exhaustively investigated. In this setting, molecules such as AT-101, EPI-001, trabectedin, temsirolimus and everolimus, ixabepilone A and sagupilone, docetaxel and cabazitaxel, irofulven, PG490-88Na, as well as several pentacyclic triterpenoids, which have been discussed herein, are excellent examples of NPs with an impact on PC.

6. Acknowledgment

Jorge A. R. Salvador thanks Universidade de Coimbra for financial support. Vânia M. Moreira acknowledges Fundação para a Ciência e a Tecnologia for financial support (SFRH/BPD/45037/2008).

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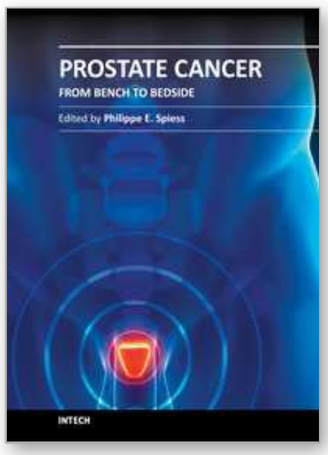

Prostate Cancer - From Bench to Bedside

Edited by Dr. Philippe E. Spiess

ISBN 978-953-307-331-6
Hard cover, 528 pages
Publisher InTech
Published online 25, November, 2011
Published in print edition November, 2011

The present textbook highlights many of the exciting discoveries made in the diagnosis and treatment of prostate cancer over the past decade. International thought leaders have contributed to this effort providing a comprehensive and state-of-the art review of the signaling pathways and genetic alterations essential in prostate cancer. This work provides an essential resource for healthcare professionals and scientists dedicated to this field. This textbook is dedicated to the efforts and advances made by our scientific community, realizing we have much to learn in striving to some day in the not too distant future cure this disease particularly among those with an aggressive tumor biology.

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