Introduction

Prostate cancer (PCa) is one of the most common malignancies in men and a leading cause of death worldwide for men. Taking into consideration that chemotherapy has severe side effects and usually a poor outcome, there is an intensive need for the development of safer and more effective agents. Since plants have been used by traditional medicine for the treatment of various diseases, in the last decades, many natural products have been isolated from plants and tested for their tumor selectivity and cytotoxic efficacy. Several of these naturally occurring compounds have been found to inhibit PCa growth and metastasis and are thus a promising approach for the treatment of this malignancy. Laboratory studies in different in vitro and in vivo systems have shown that these natural products modulate cellular processes, exhibit chemopreventive and/or chemotherapeutic effects, and induce apoptosis and autophagy. Accordingly, the antiproliferative and autophagic effects of nontoxic dietary agents could be of additional significance for the prevention, control, and management of PCa, specifically for the advanced and androgen-independent stage of the malignancy [1–3]. As there is increasing data on how natural compounds interfere with diverse molecular pathways in cancer cells, this review discusses the mechanism of action of bioactive natural products in the field of PCa and emphasizes the implicated molecular pathways of apoptosis and autophagy as important processes that control cellular homeostasis and that have been highlighted as promising targets for novel cancer therapies.

Apigenin

Apigenin (4’,5,7-trihydroxyflavone) is a flavone found in plants of the Asteraceae family, such as Anthemis sp., and many fruits and vegetables [4]. Apigenin has been tested in various types of cancer cell lines (breast, colon, liver, lung) showing promising results [5]. In prostate cancer in particular, apigenin administered in various concentrations (1–20 μM) for 24, 48, and 72 h not only causes G1 cell cycle arrest both in androgen-dependent (LNCaP) and -independent (DU145 and PC-3) PC cell lines through the decreased expression of cyclins D1, D2, and E, but also induces apoptosis through a shift in the Bax/Bcl-2 ratio [6,7]. Further studies in PC-3 cells have also demonstrated that apigenin (5–40 μM), delivered for 24 h, suppresses cell proliferation and induces apoptosis by inhibiting IGF-IGF-IR signaling and inactivating the PI3K/Akt pathway [8]. Apigenin...
treatment of PC-3M cells (25 µM for 16 h) also prevents cell motility and invasion through a disruption of the actin cytoskeleton organization and inhibition of FAK/scr signaling [9]. Apigenin is also a mediator of epigenetic events, when administered at similar concentrations (20–40 µM), as it inhibits class I HDACs both in PC-3 and 22Rv1 cells [10]. In 22Rv1 cells, induction of apoptosis is attributed to ROS generation, which subsequently triggers transcriptional, p53-dependent and -independent, pathways [11]. The antiangiogenic potential of apigenin is also demonstrated in PC-3, LNCaP, and C4-2B cells and is attributed to a decreased production of vascular endothelial growth factor (VEGF) leading to the inhibition of cancer progression and metastasis [12]. Finally, in vivo studies have shown that apigenin causes growth inhibition of 22Rv1 and PC-3 tumor xenografts in athymic nude mice [13], whereas in TRAMP mice, apigenin suppresses cancer progression [14].

**Artemisinin and Derivatives**

Artemisinin (3R,5aS,6R,8aS,9R,12S,12aR)-octahydro-3,6,9-trimethyl-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepin-10 (3H)-one is a sesquiterpene lactone and a naturally occurring component of *Artemisia annua* (Asteraceae) [15]. It is a potent antimarial compound that was shown to have antiproliferative effects on a number of human cancer cell lines. Artemisinin treatment (300 µM for 48 h) triggers G1 cell cycle arrest of LNCaP human prostate cancer cells due to the transcriptional downregulation of CDK4 expression caused by a disruption of Sp1 interactions with the CDK4 promoter [16]. Furthermore, artesunate (ART), a semisynthetic derivative of artemisinin, is found to cause G2/M cell cycle arrest in PC-3 cancer cells [17]. Other studies demonstrated that dihydroartemisinin (DHA), another derivative of artemisinin, reduces cell viability in a time- (30–40 µM for 24, 48, and 72 h) and dose-dependent (10–50 µM for 24 h) manner in androgen-dependent (LNCaP) and -independent (DU145 and PC-3) cells by the activation of caspases 8 and 9, suggesting that DHA is involved both in the extrinsic and intrinsic pathways of apoptosis. Finally, DHA and the artemisin dimers ON-2Py and 2Py cause a dose-dependent decrease in the proliferation of LNCaP and PC-3 cells through growth arrest [18,19].

**Baicalin–Baicalein**

7-D-glucuronic acid-5,6-dihydroxyflavone is a flavone isolated from *Scutellaria baicalensis* (Lamiaceae) which is converted to baicalein, in vivo [20]. Baicalein inhibits cell proliferation of various cancer cell lines (bladder, bone, breast, colon, liver) and exerts its cytotoxic/cytostatic effect through the induction of apoptosis in DU145, PC-3, LNCaP, and CA-HPV-10 prostate cancer cell lines when administered at concentrations of 150 µM or above for 2–4 days [21]. A study in LNCaP cells revealed that baicalein increases the expression of cyclin-dependent kinase inhibitor [p27 (kip1)] and causes G1 cell cycle arrest. Similar results are found for baicalein [22]. Baicalein at doses of 50 µM and 125 µM also induces G1 arrest and apoptosis in DU145 cells through the inhibition of bcl-2, loss of Bax, and upregulation of Fas [23]. In PC-3 cells, baicalein overcomes TRAIL resistance by upregulating DR5. Finally, both baicalein and baicalein prevent angiogenesis and reduce tumor volume in xenograft models receiving different doses of baicalein (10–40 mg/kg per day) for 28 days.

**Berberine**

Berberine (5,6-dihydro-9,10-dimethoxybenzo[g]-1,3-benzodioxolo[5,6-a]quinolinizinium) is an isoquinoline alkaloid derived from the plants of the genus *Berberis* (*Berberidaceae*) [24]. Treatment of DU145, PC-3, and LNCaP cells with berberine leads to inhibition of cell proliferation combined with G1 cell cycle arrest in a dose- (10–100 µM) and time-dependent (24–72 h) manner, without affecting normal human prostate epithelial cells. The suggested molecular mechanisms refer to the inhibition of the expression of cyclins D1, D2, and E and cyclin-dependent kinase (Cdk) 2, Cdk4, and Cdk6 proteins, the increased expression of the Cdk inhibitory proteins (Cip1/p21 and Kip1/p27), and the enhanced binding of Cdk inhibitors to Cdns. Berberine induces cell death of cancer cells via modulations of the Bax/Bcl-2 ratio, disruption of the mitochondrial membrane potential, and activation of poly(ADP-ribose) polymerase and caspases [25]. Low concentrations of berberine (less than 50 µM) in RM-1 cells trigger G1 arrest associated with the activation of the p53-p21 cascade, whereas higher concentrations (over 50 µM) of berberine cause G2/M arrest. Studies in LNCaP xenografts in nude mice revealed that berberine delivered at 5 mg/kg/day inhibits tumor growth due to a reduction in AR expression [26]. Finally, berberine (at doses of 30 µM and 50 µM) enhances the radiosensitivity of human prostate cancer cells as it interferes with MAPK/caspase-3 and ROS pathways and inhibits the expression of HIF-1alpha and VEGF [27].

**Betulinic Acid**

Betulinic acid [(3beta-hydroxy-20(29)-lupene-28-oic acid] (BA) is a pentacyclic triterpepe derived from the bark of *Betula populifera* (*Betulaceae*) [28]. BA (1–5 µM) was firstly shown to trigger apoptosis and antiangiogenic responses in LNCaP cells and then in xenograft models when delivered at doses of 10 and 20 mg/kg/day every second day for 14 days by decreasing the expression of the anti-apoptotic proteins, survivin and VEGF, caused by degradation of the transcription factors specificity proteins Sp1, Sp3, and Sp4 [29]. Treatment of PC-3 cells with BA (10 µM and 20 µM) inhibits TNFα-induced activation of NF-κB, which shifts the Bax/Bcl-2 ratio and leads to cleavage of poly(ADP)ribose polymerase and thus induces apoptosis [30]. Recently, BA was found to inhibit multiple ubiquitininasases (DUBs), which results in poly-ubiquinated protein accumulation, decreased levels of oncoproteins, and increased apoptotic cell death in LNCaP, DU145, and PC-3 cells. BA treatment (10 mg/kg for 15 days) of TRAMP mice results in inhibition of proliferation, tumor growth, and angiogenesis, and lowers the levels of the androgen receptor and cyclin D expression and the induction of apoptosis [31].

**Capsaicin**

Capsaicin (8-methyl-N-vanillyl-6-nonenamide) is a vanilloid isolated from the plants of the genus *Capsicum* (*Solanaceae*) [32]. Capsaicin inhibits the growth of PC-3 cells, both in vitro (IC50 of 20 µM) and in xenograft models (5 mg/kg), and stimulates apoptosis through reactive oxygen species generation, dissipation of the mitochondrial inner transmembrane potential, and activation of caspase 3 [33]. Further studies in PC-3 cells reveal that apoptosis is also induced by ceramide accumulation and activation...
of JNK and ERK [34]. Likewise, capsaicin at varying concentrations (100–500 µM) triggers apoptosis both in androgen-dependent (LNCaP) and refractory (DU-145) prostate cancer cell lines and is associated with an increase of p53, p21, and Bax, a down-regulation of both the prostate-specific antigen (PSA) and AR, and inhibition of proteasome activity [35].

**Curcumin**

Curcumin (diferuloylmethane), a diphenylethanoïd isolated from *Curcuma longa* (turmeric; *Zingiberaceae*) [36], was firstly described to induce apoptosis at doses of 5–50 µM in both androgen-dependent and refractory prostate cancers by interfering with the EGF-R signaling pathway [37]. Apoptosis is also prompted by curcumin’s interference with Bcl proteins, ROS generation, and the activation of mitochondrial related pathways. In PC-3 cells, the induction of apoptosis is attributed to apoptosis-inducing factor (AIF) and caspase-independent mechanisms [38]. Further studies revealed that curcumin decreases the proliferation of prostate cancer cells through the downregulation of the androgen receptor, whereas the activation of caspase-dependent apoptosis is a result of the downregulation of AP-1, NF-κB, cAMP response element-binding protein (CREB), PSA, and cyclin D [39]. In addition, prostate cancer cells are accumulated in the G1 phase by the proteasome-mediated downregulation of cyclin E and the upregulation of CDKs. In early-stage prostate cancer, curcumin acts as a chemopreventive agent affecting Wnt/β-catenin pathways, leading to autophagy [40]. Furthermore, curcumin suppresses glycolases, and thus modulates metabolic cellular pathways and acts as a histone acetyltransferase inhibitor [41]. Other studies have shown that curcumin prevents PC angiogenesis and metastasis by interfering with the cell cytoskeleton organization and the VEGF expression, respectively. Studies in DU145 xenografts, when curcumin is administered at doses of 5 mg/kg thrice a week for four weeks, show that invasion and me- ganization and the VEGF expression, respectively. Studies in Other studies have shown that curcumin prevents PC angiogene-

**Ellagic Acid**

Ellagic acid (2,3,7,8-tetrahydroxy-chromeno[5,4,3-cde]chromene-5,10-dione) (EA) is a polyphenolic compound [51] found in various fruits such as blackberries (*Rubus* sp., *Rosaceae*), cranberries (*Vaccinium sp., *Ericaceae*), pecans, pomegranates, raspberries and strawberries. Studies in LNCaP cells show that EA can cause DNA damage while it downregulates antiapoptotic proteins, such as silent information regulator 1 (SIRT1), upregulates the tumor suppressor protein p21, and modulates the expression of AIF thus resulting in ROS-mediated and caspase-mediated apoptosis [52]. Recent studies in LNCaP cells also depict the antiangiogenic effects of EA (at concentrations of 25 and 50 µM) as it decreases the eicosanoid biosynthesis levels and suppresses the HO system. In androgen-independent PC cells, DU145 and PC-3, EA is found to induce cell cycle arrest in the S phase and apoptosis in a dose- (15–60 µmol/L) and time-dependent (24–120 h) manner, which is associated with a decrease in cyclin B1 and cyclin D1 levels and caspase-dependent pathways. Finally, EA is shown to confine the invasive potential of PC-3 and rat PC cell lines by interfering with protease activity and decreasing the secretion of matrix metalloproteinase MMP-2 [53].

**Epigallocatechin-3-Gallate**

Epigallocatechin-3-gallate (EGCG) is a catechin derived mainly from tea (*Camellia sinensis, Thea-

**Delphinidin**

Delphinidin [2-(3,4,5-trihydroxyphenyl)chromenyl-3,5,7-triol] is an anthocyanin (coumaroyl glucoside) mostly isolated from *Viola sp. (Violaceae*) and *Delphinium sp. (Ranunculaceae*) and from many pigmented fruits and vegetables [48]. Delphinidin has been shown to induce a dose-dependent (30–180 µM) inhibition of cell growth and apoptosis in LNCaP, C4-2, 22Rv1, and PC-3 cells via the inhibition of NFκB signaling and the subsequent activation of caspases. Other studies propose that delphinidin induces cell growth inhibition and apoptosis of human PC-3 cells by inhibition of Notch-1 and/or NF-κB/P34K pathways and Wnt/β-catenin signaling [49]. In PC-3 xenografts in athymic nude mice, delphinidin administration (2 mg/animal thrice a week) resulted in a significant inhibition of tumor growth [50].
via an MEK-independent, PI3-K-dependent signaling pathway in PC-3 cells [58, 59]. In addition, EGCG (10–60 µM) antagonizes androgen action at multiple levels, as it suppresses the activation of the agonist-dependent androgen receptor through Sp1-protein and AR-regulated gene transcription, thus resulting in the inhibition of PCa growth. Invasion and migration are also inhibited after EGCG treatment via modulations in VEGF, uPA, angiopoietin 1 and 2, MMP-2, and MMP-9 [60].

Administration of 0.06% EGCG in TRAMP mice demonstrated that EGCG leads to attenuation of AR and the IGF-1 expression and decreases the MAPK signaling, thus inducing apoptosis without toxicity. Combinational treatment with 1 µM EGCG and cisplatin (2.5 or 5 µM) promotes the expression of the proapoptotic splice isoform of caspase 9 in PC-3 cells. Furthermore, oral administration of encapsulated EGCG reduces cell viability and induces apoptosis of DU145 PC cells. Finally, chitosan nanoparticles encapsulating epigallocatechin-3-gallate cause tumor growth inhibition and a reduction of secreted PSA levels [61, 62].

**Fisetin**

Fisetin (3,3′,4′,7-tetrahydroxyflavone) is a flavonol derived from many plants, such as *Acacia greggii* (*Fabaceae*) [63], which has been shown to have cytotoxic and cytostatic effects in numerous cancer cell lines (breast, blood, liver, lung, melanoma, ovary, pancreas) [5]. Studies in prostate LNCaP cells revealed that fisetin, when administered at 10–60 µM for 24 and 48 h, causes G1 cycle arrest by downregulating cyclins and cyclin-dependent kinases and triggers both caspase-dependent and -independent apoptotic pathways. Fisetin also decreases AR levels and competes with the AR ligand [64]. In highly metastatic PC-3 cells, fisetin inhibits adhesion, migration, and metastasis by interfering with the NF-κB pathway and by downregulating MMP-2 and MMP-9 [65]. The downregulation of NF-κB is accompanied with an increased TRAIL-induced apoptosis in LNCaP, DU145, and PC-3 cells [66]. It is noteworthy that fisetin also induces autophagic cell death through the inhibition of mTOR and PI3K/Akt signaling [67]. In a CWR22Rv1 xenograft human xenograft model, a fisetin injection (1 mg/animal) twice weekly was found to suppress tumor growth and reduce PSA levels [64].

**Gallic Acid**

Gallic acid (3,4,5-trihydroxybenzoic acid) (GA) is a polyphenolic constituent of grape (*Vitis vinifera, Vitaceae*) seed extract [72]. GA prompts a dose- (10–50 µmol/L) and time-dependent (6–24 h) growth inhibition and G2/M cell cycle arrest in DU145 cells through DNA damage and an increase of cdc25A/C-cdc2 phosphorylation. GA also results in apoptotic death of PCa cells by triggering the cleavage of caspase-9, caspase-3, and poly(ADP-ribose) polymerase (PARP) as well as by inducing ROS and mitochondria-mediated mechanisms [73]. GA has been shown to cause DNA damage and inhibit the invasion and migration of PC-3 cells in a dose- (50–200 µM) and time-dependent (12–48 h) manner by blocking the p38, JNK, PKC, and PI3K/Akt signaling pathways while it reduces the levels of the NF-κB protein, resulting in the repression of MMP-2 and –9 [74]. In addition, GA exerts a synergistic effect with doxorubicin in suppressing the growth of DU145 cells [73].

It is noteworthy that oral feeding with drinking water supplemented with 0.3% and 1% (w/v) GA until 24 weeks of age inhibits PCa growth and progression to advanced-stage adenocarcinoma in TRAMP mice by decreasing the expression levels of Cdk2, Cdk4, Cdk6, cyclin B1, and E proteins [75]. In DU145 and 22Rv1 PC xenografts in nude mice being fed water with 0.3%, 1% (w/v) of GA for 5 days/week for six weeks, GA was shown to suppress tumor cell proliferation, reduce the microvessel density of tumor xenografts, and induce apoptosis [76].

**Gambogic Acid**

Gambogic acid is a xanthone isolated from *Carcinia hanburyi* (*Clusiaceae*) [77] that suppresses the viability of PC-3 cells at doses of 1–5 µmol/L, and downregulates TNF-α-induced invasion of PC-3 cells at doses of 0.125–0.5 µmol/L via inactivation of the PI3K/Akt and NF-κB signaling pathways [78]. Gambogic acid, when injected in a xenograft prostate tumor model at 3 mg/kg, was shown to suppress tumor growth and angiogenesis by inhibiting the activation of vascular endothelial growth factor receptor 2 (VEGF-2R) and its downstream protein kinases, such as c-Src and AKT [79].

**Formononetin**

Formononetin (7-hydroxy-4′-methoxyisoflavone) (FN) is an O-methylated isoflavone acting as a phytoestrogen, which is found in red clover plants (*Trifolium pretense, Fabaceae*) [45]. FN has been shown to provoke apoptosis in LNCaP and PC-3 cells through the ERK1/2 MAPK-Bax pathway [68]. Further studies in PC-3 cells show that FN-induced apoptosis is associated with the inhibition of the IGF-1/IGF-1R pathway, alterations in the Bax/Bcl-2 ratio, and modulations of the p38/Akt pathway when delivered at 25, 50, and 100 µM for 48 h [69, 70]. FN triggers apoptosis in DU145 cells as well through the activation of the mitochondrial apoptotic pathway, which follows the upregulation of RASD1 [71].

**Genistein**

Genistein (4′,5,7-trihydroxyisoflavone) is a flavanone isolated from *Glycine max* (*Fabaceae*) [80]. Genistein acts as a tyrosine protein kinase inhibitor, thus causing a dose-dependent growth inhibition of DU145, PC-3, and LNCaP PCa cell lines via the suppression of protein phosphorylation [81]. Another study conducted in LNCaP and PC-3 cells concluded that genistein-mediating growth inhibition is caused by the downregulation of survivin, DNA topoisomerase II, cell division cycle 6 (CDC6), and mitogen-activated protein kinase 6, and the augmented regulation of glutathione peroxidase. In PC-3 cells, suppression of cell growth is also attributed to the downregulation of the IGF-1/IGF-1R signaling pathway [82, 83].

Recent studies have shown that genistein exerts its apoptotic and antiproliferative effects by regulating microRNAs. Thus, genistein is found to cause apoptosis through the downregulation of miR-1260b and its target genes sRRP1 and Smad4 [84]. Furthermore,
studies in PC-3 and DU145 cells show that genistein inhibits cell growth by modulating miR-34a and HOTAIR expression [85]. Apoptosis is also attributed to various mechanisms such as inhibition of proteasomal chymotrypsin-like activity, inactivation of NF-κB, and inhibition of Akt [86]. Genistein in high doses has inhibitory effects due to modulating the expression of the AR function, but its growth inhibitory effect is independent of PSA expression [87]. However, genistein at physiological concentrations (0.5–5 µM) activates mutant types of AR present in advanced PC [88]. Moreover, numerous genes involved in cell adhesion and migration (MMP-9, protease M, uPAR, VEGF) are downregulated in PC-3 cells after genistein treatment [89]. A recent study showed that genistein also targets cancer stem cells (CSC) and can contribute to an anti-CSC effect, which is important for inhibiting PC relapse and metastasis [90]. Epigenetics effects of genistein administered at 40 µM are also found in DU-145 and PC-3 cells, as it reverses DNA hypermethylation of tumor suppression genes leading to their activation and subsequent inhibition of cancer progression [91].

In vivo studies reveal a chemopreventive activity of genistein. Lobund-Wistar (L-W) rats that are susceptible to spontaneous and induced metastasizing adenocarcinomas in the prostate-seminal vesicle complex were found to exert a reduced incidence of induced prostate-related cancer after genistein feeding [92]. TRAMP mice fed with a phytoestrogen-rich diet containing 100, 250, or 500 mg of genistein per kg showed a low percentage of PD (poorly differentiating) developed cancer [93].

Oral administration of genistein in PCa patients does not affect PSA levels, yet a more recent study showed that 30 mg of synthetic genistein, given daily for three to six weeks, reduces serum PSA levels [94]. In addition, combinational treatment of metastatic-castration-resistant PCa with Cabazitaxel and genistein was found to have an enhanced apoptotic effect [95]. Clinical use of genistein against cancer is limited by its extremely low aqueous solubility, poor bioavailability, and pharmacokinetics. Based on structural analogy with steroidal compounds, liposomal vehicle compositions are designed and optimized for maximum incorporation of genistein’s flavonoid structure. The pharmaceutical design of genistein-loaded liposomes seems to improve cellular delivery and specific proapoptotic effectiveness of the incorporated drug against various cancers [96]. Finally, a meta-analysis of studies that investigated soy food consumption and risk of PCa was reported. The results of this meta-analysis suggested that high consumption of non-fermented soy foods (e.g., tofu and soybean milk) might significantly decrease the risk of PC [97].

Glycyrrhiza Compounds

The hexane/ethanol extract of *Glycyrrhiza uralensis* (Fabaceae) (HEGU), comprising the two active compounds isoungustone A and licoricidin, has been shown to exert anticarcinogenic effects [107].

HEGU and its active flavonoid compound isoungustone A (5,7,3’-4’-tetrahydroroxyl-6,5’-diprenylisoflavone) were found to induce apoptosis of androgen-insensitive DU145 cells by augmenting the levels of cleaved caspase-9, caspase-7, caspase-3, and poly (ADP-ribose) polymerase (PARP) in combination with mitochondrial membrane depolarization and cytochrome C release to the cytosol [107]. Additionally, HEGU and its active component, isoungustone A, diminish DNA synthesis in a dose-dependent manner, reduce the levels of CDK2, CDK4, cyclin A, and cyclin D proteins and decrease the CDK2 activity causing G1 phase arrest in DU145 cells [108]. HEGU also contains licoricidin, which has been shown to act as a potent antitumor agent. Licoricidin inhibits the metastatic and invasive capacity of malignant PCa cells by suppressing the expression of adhesion molecules and restricting the secretion and activation of the matrix metalloproteinases (MMP-2, MMP-9, TIMP-1, urokinase-type plasminogen activator, and VEGF [109].

Licochalcone (LA) (3-dimethylallyl-4,4’-dihydroxy-6-methoxy-chalcone) is an estrogenic flavonoid isolated from licorice root (*Glycyrrhiza glabra*) [110]. LA is found to cause G2/M cell cycle arrest of PC-3 prostate cells, accompanied with the suppression of cyclin B1 and cdc2 [111]. LA can also induce caspase-dependent and autophagy-related cell death in LNCaP cells [112].

Glycyrrhetinic acid (18β-glycyrrhetinic acid) is an active triterpenoid metabolite abundantly present in licorice roots, which inhibits proliferation and growth of DU-145 cells (10–500 µM) by the induction of apoptosis. It also reduces HUVEC tube formation and prevents the invasion of DU-145 PC cells on matrigel-coated
wells via the downregulation of NF-κB (p65), VEGF, and MMP-9 expression [113]. In LNCaP androgen-dependent PC cells, glycyrrhetinic acid was shown to reduce the proliferation rate as well as the production of prostate-specific antigen [114].

**Gossypol**

Gossypol [2,2-bis-(formyl-1,6,7-trihydroxy-5-isopropyl-3-methylpynaphthalene) is a polyphenolic aldehyde present in cottonseed (Gossypium hirsutum, Malvaceae) [115], which has been shown to exert antiproliferative and cytotoxic effects in PC cell lines and implanted MAT-LyLu cells in Copenhagen rats. In MAT-LyLu cells, gossypol modulates TGFβ1 and Akt signaling, altering the expression of regulatory proteins such as cyclin D1, Cdk4, and phospho-Rb and finally causing G0/G1 cell cycle arrest when delivered at 0.5–4.0 µM for 24, 48, and 72 h [116]. Gossypol has also been found to induce G0/G1 cell cycle arrest in PC-3 cells and prostatic cells from human benign prostatic hyperplasia (BPH) patients as it evokes alterations in TGF-β1 expression levels. In addition, gossypol at doses of 5–20 µM downregulates Bcl-xL resulting in the inhibition of the heterodimerization of Bcl-xL/Bcl-2 with proapoptosis molecules, which is followed by caspase-dependent and -independent apoptotic processes [117]. Recently, gossypol was shown to induce autophagy in androgen-independent PCa cells that have high levels of Bcl-2 and are resistant to apoptosis, both in vitro and in vivo (PC xenografts), by interrupting the interactions between Beclin 1 and Bcl-2/Bcl-xL at the endoplasmic reticulum, thus releasing the BH3-only pro-autophagic protein Beclin 1, which in turn triggers the autophagic cascade [118].

Gossypol also inhibits metastatic behaviors (adhesion, migration, and invasion) and angiogenesis. In PC-3 cells, GP suppresses AP-1 and NF-κB activity, resulting in the inhibited secretion of the urokinase plasminogen activator and VEGF in combination with the downregulation of chemokine receptor 4 [119]. In human prostate tumor PC-3 xenografts in mice, gossypol at a dosage of 15 mg/kg/day prompts the suppression of angiogenesis in the solid tumors as it blocks the activation of VEGF receptor 2 kinase causing the subsequent suppression of phosphorylation of focal adhesion kinase, extracellular signal-related kinase, Akt kinase, and key intracellular proangiogenic kinases such as Src family kinase [120].

Combination treatment of docetaxel and gossypol was found to be cytotoxic and apoptotic in PC-3 cells in a dose- and time-dependent manner [121]. Gossypol (0.5–10 µM) and sorafenib (2–20 µM) were found to induce cell death via apoptotic pathways in DU145 cells and via autophagic pathways in PC-3 cells, respectively [122]. Finally, administration of AT-101 (gossypol), at 20 mg/day for 21 days, was found to decline PSA levels in some men with chemotherapy-naïve, castrate-resistant PCa [123].

**Lycopene**

Lycopene (γ,γ-carotene) is a carotenoid mostly isolated from Solanum lycopersicum (tomato; Solanaceae) [129]. Extensive research has been conducted both in vitro and in clinical trials in order to identify the mechanisms of lycopene's cytotoxic and chemopreventive effects against PCa. More specifically, lycopene is found to induce cell cycle arrest and apoptosis in PC-3, LNCaP, DU145 cells, and DU145 xenografts. In LNCaP cells, lycopene induces mitochondrial-related apoptosis when delivered in physiologic concentrations (0.3–3.0 µM), whereas in high concentrations (> 5 µM), it leads to DNA damage [130]. A lycopene-mediated reduction in cholesterol synthesis was also shown through the activation of the PPAR-α-LXR-α pathway both in LNCaP and DU145 cells [131]. In PC-3 cells and xenograft models, high concentrations of lycopene (16 mg/kg twice a week for seven weeks) induced apoptosis through alterations in IGF-1, IGF-1R, and IGFBP-3 expression levels [132]. Both in LNCaP and PC-3 cells, G0/G1 cell cycle arrest is caused by lycopene via its interference with phosphatidylinositol 3-kinase signaling, which leads to a decrease in Cdk4, cyclins D1 and E, and RB phosphorylation. Cell cycle arrest and apoptosis are also attributed to a reduced activation of NF-κB in combination with an increased expression of p21, p27, and p53, shifting the Bax:Bcl-2 ratio. Migration and invasion of LNCaP and PC-3 cells are also suppressed by lycopene via a reduction in the expression levels of integrins [133, 134].

Moreover, lycopene acts also as a chemopreventive agent, delaying or preventing the establishment of PCa. In LNCaP cells, lycopene exerts its chemopreventive effect through an increase in detoxification proteins and subsequent prevention of DNA damage, and suppresses ROS generation and oxidative stress as well [135]. Chemopreventive activity of lycopene was also found in TRAMP mice fed 28 mg lycopene per kg for 20 weeks [136]. In clinical trials, lycopene was found to be more of a chemopreventive agent than a cytostatic agent of established tumors. Lycopene given to patients at a dose of 4 mg twice a day for one year was shown to delay or prevent high-grade prostate intraepithelial neoplasia from developing into PC [137], whereas whole tomato lycopene administration in men with established PCa at a dose of 10 mg per day for one year resulted in a reduced PSA velocity [138]. Finally, recent epidemiologic studies have suggested a potential benefit of lycopene against the risk of PCa. Five studies support a 30 to 40% reduction in risk associated with high tomato or lycopene consumption, three are consistent with a 30% reduction in risk, but the results were not statistically significant, and seven were not supportive of an association [139].
Compounds Derived from *Magnolia* sp.

Honokiol (2-(4-hydroxy-3-prop-2-enyl-phenyl)-4-prop-2-enyl-phenol), a lignan isolated from *Magnolia officinalis* (*Magnoliaceae*) [140], has been found to decrease the viability of PC-3 and LNCaP human PCA cells in a dose- and time-dependent manner through G0–G1 phase cell cycle arrest. Honokiol also triggers apoptotic DNA fragmentation in a dose- (20–60 µM) and time-dependent (24–72 h) manner both in androgen-dependent and -independent prostate cell lines (PC-3, LNCaP, and C4-2), which is correlated with the induction of Bax, Bak, and Bad in addition to a decrease in Bcl-xL and Mcl-1 protein levels [141,142]. Likewise, honokiol treatment exhibits growth inhibitory, apoptotic, and antiangiogenic effects on PC xenografts fed with 1–3 mg honokiol thrice a week [141].

Magnolol (4-allyl-2-(5-allyl-2-hydroxy-phenyl)phenol) is a hydroxylated biphenyl (lignan) isolated from the root and stem bark of *Magnolia officinalis* [140]. Magnolol was shown to induce apoptotic cell death in a dose-dependent (10–60 µM) manner in PC-3 cancer cells through epidermal growth factor receptor (EGFR)-mediated signaling transduction pathways and also inhibits the adhesion, invasion, and migration of PC-3 human prostate [143].

Obovatol (5-prop-2-enyl-3-(4-prop-2-enylphenoxy)benzene-1,2-diol), a biphenyl ether lignan isolated from *Magnolia obovata* [144], engages LNCaP and PC-3 cells to apoptotic cell death through the inhibition of NF-κB activity and also enhances the cell growth inhibition of chemotherapeutics (docetaxel, paclitaxel, cisplatin, and doxorubicin) [145].

Oridonin

Oridonin (7a,20-epoxy-1α,6β,7,14-tetrahydroxy-Kaur-16-en-15-one) is an isoprenoid (kaur-type diterpenoid) isolated from *Rabdosia rubescens* (*Labiateae*) [146]. Oridonin has been found to elicit G0/G1 cell cycle arrest and apoptosis of LNCaP cells through the upregulation of p53 and Bax and the downregulation of Bcl-2 expression in a dose-dependent manner [147]. Oridonin has also been shown to trigger G2/M cell cycle arrest, autophagy, and apoptosis in LNCaP and PC-3 cells by upregulating the expression of p21 in a time- (12–72 h) and dose-dependent (10, 25–100 µM) manner [148].

Quercetin

Quercetin (2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromen-4-one) is a polyphenol (flavonol) isolated from grapes (*V. vinifera, Vitaceae*) [63]. Quercetin was found to reduce cell growth and cause apoptosis in various cell lines (bladder, blood, bone, breast, colon, liver, lung, mouth, esophagus) [5]. Quercetin reduces cell growth of PC-3, LNCaP, and DU145 PC cells in a dose-dependent manner by interfering with the expression levels of numerous oncoproteins and tumor suppressor genes. In LNCaP, quercetin causes G2/M cycle arrest due to p21 upregulation and cyclin B suppression [161]. Studies in PC-3 cells suggest that growth inhibition is caused by a decreased phosphorylation of ErbB-2, ErbB-3, c-Raf, MAPK kinase 1/2 (MEK1/2), and MAPK, Akt-1 and is combined with a reduced metastatic rate and drug resistance. In addition, quercetin has been described as interfering with c-Jun and SP1, causing AR reduction [162]. Quercetin at doses of 5–100 µM was also shown to provoke apoptosis in PCA cell lines through inhibition of fatty acid synthase and downregulation of heat shock protein 90 [163]. More studies showed that quercetin induces G2/M cycle arrest and apoptosis of PC-3 cells via a decrease in Cdc2/Cdk-1, cyclin B1, phosphorylated pRb, IGF-I, and IGF-II and an increase in p21, Bax, and caspase-3, and modulations of the Bcl-2/Bax ratio [164]. In addition, quercetin augments TRAIL-induced cytotoxicity through caspase-8 oxygen species generation and protein degradation [151]. Other studies show that PEITC represses the androgen receptor’s expression through the inhibition of Sp1 transcription, thus mediating growth arrest both in androgen-dependent and -independent PC cells [152].

In LNCaP and PC-3 cells, PEITC (2.5 and 5 µM) triggers apoptotic mechanisms via the activation of Bax and ROS production, whereas it downregulates survivin and X-linked inhibitors of apoptosis [153]. It is noteworthy that PEITC induces both apoptotic and autophagic cell death in PC-3 and LNCaP cells regulated by Atg5 protein [154].

Furthermore, PEITC (2.5 and 5 µM) was shown to restrain migration of PC-3 and LNCaP cells. The suggested mechanisms propose that PEITC treatment leads to inactivation of Akt with a subsequent suppression of VEGF and interference with the Notch pathway [155].

PEITC was found to cease angiogenesis both in human umbilical vein endothelial cells (HUVEC) and in ex vivo experiments (chicken egg chorioallantoic membrane assay) [156]. In xenograft models, similar results were observed. When administered orally at a dose of 12 µM/day for five days per week, PEITC delays growth of PC-3 xenografts in athymic mice [157]. In an LNCaP xenograft model, PEITC regulates tumor growth by suspending the expression of the platelet/endothelial cell adhesion molecule (PECAM1-CD31) and by the suppression of angiogenesis [158]. Studies in transgenic adenocarcinoma of the mouse prostate, in mice fed with 3 µmol PEITC/g for 19 weeks, also revealed inhibition of prostate carcinogenesis induced by the overexpression of E-cadherin and autophagy-regulated pathways [159]. Finally, the combination treatment of PEITC (2 µM) with docetaxel (1 nM) increased the rate of apoptosis in PC-3 and DU145 cells by the suppression of Bcl2 and the induction of Bax and Bak proteins, while combinational treatment of PEITC with adriamycin and etoposide led to PC-3 cell death through the downregulation of protein kinase C and inhibition of telomerase [160].
activation, inhibition of surviving, and Akt phosphorylation [165]. Moreover, in vitro and in vivo studies in prostate xenograft mouse models depict quercetin’s antiangiogenic effects as it interacts with the VEGF-R2-regulated autophagic (AKT/mTOR/PI3K/Akt) pathway when administered at a dose of 20 mg/kg/day [166].

Sanguinarine ▼
Sanguinarine (13-methyl-1,3-benzodioxolo[5,6-c]-1,3-dioxolo [4,5-]<i>l</i>phenanthridinium) is a benzophenanthridine alkaloid derived from <i>Sanguinaria canadensis</i> (Papaveraceae) (the bloodroot plant) [167]. In LNCaP and DU145, sanguinarine causes G0/G1 cell cycle arrest in a dose-dependent manner (0.1–2 μM) by interfering with the expression of cyclin kinase inhibitors p21/WAF1 and p27/KIP1, cyclin E, D1, and D2 and cyclin-dependent kinases 2, 4, and 6 [168]. Sanguinarine has also been shown to confer PCa cells growth and induce apoptosis at concentrations of 0.1–8 μM. This has been attributed to the suppressed expression of survivin and protein degradation via the ubiquitin-proteasome system [169]. Treatment of DU145, C4-2B, and LNCaP cells with sanguinarine (2 μM and 4 μM, for 1–12 h) revealed that it restricts PCa growth, migration, and invasion through Stat3 inactivation [170]. In DU145 cell xenografts, the administration of sanguinarine (0.25 mg/kg and 0.5 mg/kg) reduced tumor weight and volume after 31 days [169].

Silibinin ▼
Silibinin or silybin (3,5,7-trihydroxy-2-(3-(4-hydroxy-3-methoxyphenyl)-2-(hydroxymethyl)-1,4-benzodioxan-6-yl)-4-chromanone) is a flavolignan isolated from the fruits of <i>Silybum marianum</i> (Asteraceae) [171]. Silibinin has been described as causing G1 cell cycle arrest and decreasing both intracellular and secreted forms of PSA in LNCaP cells in a dose- (<50–200 μM) and time-dependent (12–48 h) manner, which has been attributed tomodulations of retinoblastoma (Rb) levels and its phosphorylation status combined with a decreased activity of cyclin-dependent kinases (CDKs) [172]. Further studies in LNCaP cells revealed that the decrease of PSA was caused by the downregulation of the androgen receptor’s coactivator and the epithelium-derived Ets transcription factor [PDEF] [173]. Silibinin was not only found to suppress global protein translation, thus inhibiting HIF-1 alpha expression and telomerase activity [174], but also, as a lipophilic compound, was found to compete in the EGF-erbB1 interaction and to interfere with the mitogenic signaling and DNA synthesis in LNCaP and DU145 cells [175].

In DU145 cells, silibinin treatment (50–200 μM, for 24 and 48 h) caused G1 cell cycle arrest mediated by a decrease in p21 and p27 expression [176]. Silibinin also restrains Wnt/LRP6 signaling and induces apoptosis through the inhibition of active Stat3 while it sensitizes cells to TNFα-induced apoptosis through constitutive NF-κB inactivation [177].

Silibinin at pharmacologically achievable concentrations (0.02–20 μM) causes G1 and G2/M cycle arrest in PC-3 cells by interfering with the expression levels of cyclins and CDKs [178] and the insulin-like growth factor I receptor-mediated signaling pathway [179].

Silibinin has also been found to prevent migratory and invasive potential of PC-3, PC-3MM2, C4-2B LNCaP, and DU145 cells [180]. In general, silibinin inhibits the epithelial to mesenchymal transition of PC cells through interference with the NF-κB pathway and subsequent downregulation of ZEB1 and SLUG transcription factors and by downregulating vimentin and MMP2 [181]. Silibinin also exerts inhibitory effects in high bone metastatic prostate models and prevents PC cells-induced osteoclastogenesis [182].

In xenograft models, silibinin is described as having anti proliferative, proapoptotic, and antiangiogenic effects. Studies in PC-3 tumor xenografts in athymic mice revealed that silibinin effects are attributed to an increase in IGFBP-3, Cip1/p21, and Kip1/p27 levels, activation of ERK1/2, and a decrease in Bcl-2 and VEGF levels. In TRAMP mice fed 0.5% and 1% w/w silybin-phyto diets for 11 weeks, silibinin blocked PCa growth and progression through IGF-IGFBP-3 axis modulation, whereas it suppressed tumor microvessel density via a decrease in VEGF, VEGFR-2, MMPs, and vimentin [183]. Finally, in patients receiving a silybin-phyto- some (13 g/day) for 14–31 days, high blood concentrations were found transiently, but low levels of silibinin were detected in prostate tissue. Silibinin’s lack of tissue penetration may be explained by its short half-life, the brief duration of therapy in this study, or an active process of removing silibinin from the prostate [184].

Sulforaphane ▼
Sulforaphane (1-isothiocyanato-4-methylsulfinylbutane) (SFN) is a natural isothiocyanate found in many cruciferous vegetables, firstly isolated from <i>Brassica oleracea</i> (broccoli; Brassicaceae) [185]. Many studies have shown that SFN can provoke cell cycle arrest and apoptosis in androgen-dependent and androgen-refractory PC cell lines. SFN (IC50 of 10 μM) causes G2/M phase arrest in DU145 cells [186] and G1 cell cycle arrest in LNCaP and PC-3 cells. The antiproliferative effects of SFN at doses of 10–40 μM involve mechanisms such as the modulation of methyltransferases expression, which leads to an increase in cyclin D2 in LNCaP cells, and protein synthesis inhibition through decreased phosphorylation of mTOR substrates in PC-3 cells [187]. Apoptosis is induced through caspase activation in LNCaP cells, ROS generation that triggers intrinsic and extrinsic caspase cascades in PC-3 and DU145 cells [186], and inhibition of histone deacetylase 6 in BPH-1, LNCaP, and PC-3 cells [188,189]. SFN has also been reported to inhibit HIF-1α with a subsequent decrease in VEGF expression, thus preventing prostate cell angiogenesis [190]. Cell migration of PC-3 and LNCaP cells is also restricted by SFN when delivered at 20 μM for 8 and/or 24 h due to modulations of the Notch pathway [191].

In vivo studies have deduced that oral administration of a daily dose of 7.5 mmol per animal for 21 days in PC-3 xenografts in nude mice causes a >50% reduction in tumor volume due to a decrease in HDAC activity. Finally, TRAMP mice that were fed broccoli sprouts exhibited a decrease in prostate tumor growth [192].

Thymoquinone ▼
Thymoquinone (2-isopropyl-5-methylbenzo-1,4-quinone) (TQ) is a phytochemical isolated from the plant <i>Nigella sativa</i> (Ranunculaceae) [193]. TQ (40–100 μM) has been found to reduce cell
growth both in androgen-dependent (LNCaP, C4-B) and androgen-refractory (DU145, PC-3) PC cell lines. Cell growth reduction is attributed to a decrease in AR and E2F-1 as well as the E2F-1 regulated proteins [194]. In PC-3 and C4-B cells, TQ (IC50 values of approximately 50 and 80 mM) was shown to induce apoptosis through increased ROS generation and decreased GSH levels [195]. Other studies in PC-3 cells also demonstrated that TQ inhibits cell proliferation through suppression of AKT and prevents tumor angiogenesis via the repressed activation of induced extracellular signal-regulated kinase by VEGF [196].

Ursolic Acid

Ursolic acid ((3β)-3-hydroxyurs-12-en-28-oic acid) (UA) is a pentacyclic triterpenoid compound derived from Cornus officinalis (Cornaceae) [197]. In PC-3 cells, UA evokes apoptosis via extrinsic and intrinsic apoptotic pathways while it confines cell invasion by inhibiting Akt and downregulating matrix metalloproteinase-9 [198]. UA was also shown to induce apoptosis through JNK activation, which results in Bcl-2 phosphorylation and degradation causing the activation of caspase 9, both in androgen-dependent (LNCaP) and androgen-independent PCa cell lines (LNCaP-AI and DU145 cells) [199]. In addition, UA displays a role in the suppressed activation of NF-κB and STAT3 by downregulating the expression of various NF-κB and STAT3 gene products involved in proliferation, survival, and angiogenesis, and thus induces apoptosis in PCa cell lines (LNCaP, DU145) and TRAMP mice [200]. UA was also found to restrict metastasis through the suppression of CXCR4 expression in PC both in vitro (PC-3, LNCaP, DU145 cells) and in vivo (TRAMP mice fed 1% w/w UA for 6 to 8 weeks) [201]. Finally, in DU145 cells, UA and its cis- and trans-3-O-p-hydroxycinnamoyl esters derived from American cranberries, such as Vaccinium macrocarpon, were shown to limit tumor cell growth at micromolar concentrations through matrix metalloproteinase (MMP-2 and MMP-9) inhibition [202].

Conclusion

In this review article, the most promising bioactive natural products and their respective mechanisms of action for the treatment of PCa are presented, as they affect the processes of cell proliferation, cell cycle control, apoptosis, autophagy, tumor angiogenesis, invasion, and metastasis (Fig. 1, Table 1). Indeed, a variety of natural products have gained widespread use in the clinical treatment of a number of malignancies, such as carcinomas of the colon, breast, ovary, lung, and prostate. Unlike conventional chemotherapy, targeted agents have a relatively wide therapeutic window and have nonoverlapping toxicity profiles. Natural compounds that interfere with essential carcinogenic pathways, without demonstrating severe side effects, could exert a significant role as chemotherapeutic or chemopreventive agents, thus offering an alternative or complementary approach to the treatment of cancer. However, further in vivo studies should be con-

Fig. 1 Mechanism of action of bioactive natural products in prostate cancer cells. Natural compounds provoke apoptosis of PCa cells by triggering caspases (berberine, gallic acid) and mitochondrial-dependent cascades (honokiol) or by inhibiting oncopgenes (baicalein), and by suppressing the NFκB signaling pathway (curcumin). Other compounds trigger autophagy via inhibition of the PI3K signaling pathway (apigenin), suppression of the mTOR complex (fisetin), or activation of the phagophore formation-related proteins (PEITC, gossypol).
### Table 1  Bioactive natural products against prostate cancer.

<table>
<thead>
<tr>
<th>Compound</th>
<th>In vitro</th>
<th>In vivo</th>
<th>Mechanism</th>
<th>Molecular pathway</th>
<th>Plant</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apigenin (flavonoid)</td>
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<td>HDACs</td>
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<td>CDK4</td>
<td>Artemisia annua (Asteraceae)</td>
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<td></td>
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<td>PC-3</td>
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<td>C4-2, LNCaP</td>
<td>Cell cycle arrest</td>
<td></td>
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<td></td>
<td></td>
</tr>
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<td>DU145, PC-3, LNCaP, CA-HPV-10</td>
<td>G1 cycle arrest, Apoptosis</td>
<td>P27kip1, Bcl-2, Bax, Fas</td>
<td>Scutellaria baicalensis (Lamiaceae)</td>
<td>[20–23]</td>
<td></td>
</tr>
<tr>
<td></td>
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<td>Xenografts</td>
<td>Antiangiogenesis</td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>Berberine (alkaloid)</td>
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<td>Cyclins, CDKs, CDKs inhibitors</td>
<td>Berberis sp. (Berberidaceae)</td>
<td>[24–27]</td>
<td></td>
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<td>Apoptosis, antiangiogenesis</td>
<td>NF-κB, survivin, VEGF</td>
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<td>Apoptosis</td>
<td>ROS, JNK, ERK, ↑ p53, p21, Bax, ↑ PSA, AR</td>
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</table>

cont.
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<th>Compound</th>
<th>In vitro</th>
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<tbody>
<tr>
<td>Curcumin (diphenylheptanoid)</td>
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<td>VEGF, MMPs</td>
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<td>CDKs, IGF, EGF, VEGF</td>
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</tr>
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<td>Caspases, NF-αB/Pi3K, Notch-1, Wnt/β-catenin</td>
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<td>[48–50]</td>
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<td>Rubus sp. (Rosaceae)</td>
<td>[51–53]</td>
</tr>
<tr>
<td></td>
<td>DU145, PC-3</td>
<td></td>
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<td>Cycin D1, B1, Bcl2/Bax, caspases</td>
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<td>Go/G1 cycle arrest</td>
<td></td>
<td>↑ WAF1/p21, KIP1/p27, INK4, I-cyclins, CDks</td>
<td>Camellia sinensis (Theaceae)</td>
<td>[54–62]</td>
</tr>
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<td>Apoptosis</td>
<td>PS3, NF-αB, Bcl-B ratio, caspases, COX-2, PI3K, AR antagonist</td>
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<td>i Invasion-metastasis</td>
<td>VEGF, MMPs, uPA, angiopoietins</td>
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<td>Apoptosis</td>
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<td>NF-αB, MMP2, MMP9, mTOR, PI3K/Ark</td>
<td>Acacia gregii (Fabaceae)</td>
<td>[63–67]</td>
</tr>
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<td>Tumor growth</td>
<td>i PSA</td>
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</table>

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<table>
<thead>
<tr>
<th>Compound</th>
<th>In vitro</th>
<th>In vivo</th>
<th>Mechanism</th>
<th>Molecular pathway</th>
<th>Plant</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formononetin (isoflavone)</td>
<td>DU145</td>
<td>DU145, LNCaP</td>
<td>Apoptosis, no invasion</td>
<td>No migration</td>
<td>Vicia villosa (Vicieae)</td>
<td>[88–91]</td>
</tr>
<tr>
<td>Gallic acid (polyphenol)</td>
<td>PC-3</td>
<td>PC-3</td>
<td>Apoptosis, cycle arrest, growth inhibition</td>
<td>p21WAF1, IGF-1, cyclins, survivin, DNA topoisomerase II, IGF-1, VEGF</td>
<td>Vitis vinifera (Viticaceae)</td>
<td>[72–76]</td>
</tr>
<tr>
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<td>PC-3</td>
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<td>No migration</td>
<td>Carcinia hanburyi (Clusiaceae)</td>
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References:

- Gioti K, Tenta R. Bioactive Natural Products... Planta Med 2015; 81: 543–562
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Table 1 Continued
hibits glyoxalase 1: a possible link to its anti-inflammatory and anti-
42 Hong JH, Ahn KS, Bae E, Jeon SS, Choi HY. The effects of curcumin on the 
invasiveness of prostate cancer in vitro and in vivo. Prostate Cancer 
Prostatic Dis 2006; 9: 147–152
43 Killian PH, Kroski E, Michalik KM, Barbieri O, Astigiano S, Sommerhoff 
CP, Pfeffer U, Nerlich AG, Bachmeier BE. Curcumin inhibits prostate can-
cer metastasis in vivo by targeting the inflammatory cytokines CXCL1 and 
–2. Carcinogenesis 2012; 33: 2507–2519
44 Thangapazham RL, Puri A, Tele S, Blumenthal RK. Evaluation of a nano-
technology-based carrier for delivery of curcumin in prostate cancer 
45 Labow RS, Layne DS. The formation of glucosides of isoflavonones and 
of some other phenols by rabbit liver microsomal fractions. Biochem J 
1972; 128: 491–497
46 Rahbari N, Kosasih M, Braud M, Chalabi N, Sithi S, Bignon YJ, Bernard-Gal-
lon DJ. Genistein and daidzein act on a panel of genes implicated in cell 
cycle and angiogenesis by polymerase chain reaction arrays in human 
prostate cancer cell lines. Cancer Epidemiol 2010; 34: 200–206
47 Vardi A, Bosvriel R, Rahbari N, Adjikly A, Sithi S, Dechelotte P, Boiteux JP, 
Fontana L, Bignon YJ, Guy L, Bernard-Gallon DJ. Soy phytoestrogens modify 
DNA methylation of GSTP1, RASSF1A, EPH2 and BRCAl promoter in 
prostate cancer cells. In Vivo 2010; 24: 393–400
48 Ribereau-Gayon J, Ribereau-Gayon P. The Anthocyanins and Leuco-
49 Syed DN, Sah Y, Afqar F, Mukhtar H. Dietary agents for chemoprevention 
50 Hafeez BB, Siddiqui IA, Asim M, Malik A, Afqar F, Adhami VM, Saleem M, 
Din M, Mukhtar H. A dietary anthocyanidin delphinidin inhibits apop-
tosis of human prostate cancer PC3 cells in vitro and in vivo: involve-
8572
51 Nierenstein M. The formation of ellagic acid from galloyl-glycine by 
Penicillium. Biochem J 1915; 9: 240–244
52 Valenla I, Di Giacomo C, Acquaavira R, Barbagallo I, Cardile V, Kim DH, 
Growth inhibition, cell-cycle dysregulation, and induction of apoptosis by green tea constitu-
tive-insensitive human prostate carcinoma cells. Toxicol Appl Pharma-
68: 1843–1850
64 Khan N, Asim M, Afqar F, Abu Zaid M, Mukhtar H. A novel dietary flavo-
65 Chien CS, Shen KH, Huang JS, Ko SC, Shih YW. Antimetastatic potential of 
 fisetin involves inactivation of the PI3K/Akt and JNK signaling path-
ways with downregulation of MMP-2/9 expressions in prostate cancer 
PC-3 cells. Mol Cell Biochem 2010; 333: 169–180
66 Szlizska E, Helewski KJ, Mignola E, Krol W. The dietary flavonol fisetin 
67 Adhami VM, Syed DN, Khan N, Mukhtar H. Dietary flavonoid fisetin: a 
new dual inhibitor of PI3K/Akt and mTOR for prostate cancer manage-
ment. Biochem Pharmacol 2012; 84: 1277–1281
68 Ye Y, Hou R, Chen J, Mo L, Zhang J, Huang Y, Mo Z. Formononetin-in-
duced apoptosis of human prostate cancer cells through ERK1/2 mito-
gen-activated protein kinase inactivation. Horm Metab Res 2012; 44: 
263–267
69 Huang WJ, Bi LY, Li ZZ, Zhang X, Ye Y. Formononetin induces the mito-
chondrial apoptosis pathway in prostate cancer cells via downregulation of the 
IGF-1/IGF-1R signaling pathway. Pharm Biol 2014; 52: 
466–470
70 Zhang X, Bi L, Ye Y, Chen J. Formononetin induces apoptosis in PC-3 prostate cancer cells through enhancing the Bax/Bcl-2 ratios and regu-
71 Liu XJ, Li YQ, Chen YQ, Xiao SJ, Zeng SE. Up-regulating of RASD1 and 
apoptosis of DU-145 human prostate cancer cells induced by formonone-
72 Henri B. Observations sur la préparation et la purification de l’acide 
galique, et sur l’existence d’un acide nouveau dans la noix de galle. 
Ann Chim Physique 1818; 9: 181–184
73 Chen HM, Wu YC, Chia YC, Chang FR, Hsu HK, Hsieh YC, Chen CC, Yuan SS. 
Gallic acid, a major component of Toona sinensis leaf extracts, contains a 
ROS-mediated anti-cancer activity in human prostate cancer cells. 
74 Liu KC, Huang AC, Wu PP, Lin HY, Chueh FS, Yang JS, Lu CC, Chiang JH, 
Meng M, Chung JC. Gallic acid suppresses the migration and invasion of 
PC-3 human prostate cancer cells via inhibition of matrix metallo-
protease-2 and –9 signaling pathways. Oncol Rep 2011; 26: 177–184
75 Raina K, Rajamanickam S, Deep G, Singh M, Agarwal R, Agarwal C. Che-
mo preventive effects of oral gallic acid feeding on tumor growth and 
progression in TRAMP mice. Mol Cancer Ther 2008; 7: 1258–1267
76 Kaur M, Velmurugan B, Rajamanickam S, Agarwal R, Agarwal C. Gallic acid, 
an active constituent of grape seed extract, exhibits anti-proliferative, 
pro-apoptotic and anti-tumorigenic effects against prostate cancer 
carcinoma xenograft growth in nude mice. Pharm Res 2009; 26: 
2133–2140
77 Liesenklas W, Auerthoff H. [The constitution of gambogic acid and its 
isomerization. 4. Chemistry of gum-resin. Arch Pharm Ber Dtsch 
Pharm Ges 1966; 299: 797–798
78 Lu L, Tang D, Wang L, Huang LQ, Jiang GS, Xiao YQ, Zeng FQ. Gambogic acid 
inhibits TNF-α-induced invasion of human prostate cancer 
PC3 cells in vitro through PI3K/Akt and NF-kappaB signaling pathways. 
Acta Pharmacol Sin 2012; 33: 531–541
inhibits angiogenesis and prostate tumor growth by suppressing vas-
cular endothelial growth factor receptor 2 signaling. Cancer Res 2008; 68: 
1843–1850
80 Walter ED. Genistin and its aglucone, genistin, from soybeans. JACS 
1941; 63: 3273–3276
81 Rokhlin OW, Cohen MB. Differential sensitivity of human prostate 
cancer cell lines to the effects of protein kinase and phosphatase 
82 Lee J, Jia LP, Park S, Huang SJ, Yoon S. Inhibition of IGF-1 signaling by genis-
tin: modulation of E-cadherin expression and downregulation of be-
ta-catenin signaling in hormone refractory PC-3 prostate cancer cells. 
Nutr Cancer 2012; 64: 153–162
83 Vink-Baker MK, Nagy TR, Barnes S. Role of phytoestrogens in cancer 
therapy. Planta Med 2010; 76: 1132–1142
84 Hirata H, Hinouda Y, Shahryari V, Deng G, Tanaka Y, Tabatabai ZL, Dahiya 
R. Genistin downregulates once-miR-1260b and upregulates sFRP1 and 
Smad4 via demethylation and histone modification in prostate cancer 

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144 Kim SH, Sehrawat A, Sakao K, Hahn ER, Singh SV. Notch activation by phenylthiocyanate attenuates its inhibitory effect on prostate cancer cell migration. PLoS One 2011; 6: e26615


149 Yuan H, Gong A, Young CY. Involvement of transcription factor Sp1 in quercetin-mediated inhibitory effect on the androgen receptor in human prostate cancer cells. Carcinogenesis 2005; 26: 793–801

150 Huynh H, Nguyen TT, Chan E, Tran E. Inhibition of ErbB-2 and ErbB-3 expression by quercetin prevents transforming growth factor alpha (TGF-alpha)- and epidermal growth factor (EGF)-induced human prostate cancer cell proliferation. Int J Oncol 2003; 23: 821–829


Sarkar SM. Isolation from argemone oil of dihydrodsanguarine and sanguinarine; toxicity of sanguinarine. Nature 1948; 162; 265


Rowe EJ, Orr JE, Uhl AH, Parks LM. Isolation of oleandric acid and ursolic acid from Thymus vulgaris, L. J Am Pharm Assoc Am Pharm Assoc 1949; 38: 122–124


