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Review article

Revolutionizing of bioactive natural products in prostate cancer research and care: Promising discoveries and future directions

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ABSTRACT

Globally, prostate cancer (PCa) is one of the most common cancers to strike men. Diet and lifestyle appear to have a significant impact on PCa biology and carcinogenesis. PCa is the major reason of death by cancer in men. Anti-PCa qualities like growth of tumor inhibition, induction of cell death, and angiogenesis and metastasis inhibition have all been studied in depth. Phytochemicals have been demonstrated to target androgen receptor (AR) signaling as well as PCa stem cells in a selection of investigations. Marine compounds have shown potential in the treatment of PCa. It is discussed in this article, some of the most promising bioactive natural and marine compounds for PCa prevention and treatment, as well as their specific methods of action. An emphasis on specific medicine is one of the future directions in the revolutionization of bioactive natural ingredients for PCa research and therapy. Advances in nanotechnology can enhance the bioavailability and specificity of bioactive substances for cancer cells, maximizing their therapeutic potential and enhancing patient treatment. Bioactive natural compounds represent an innovative field in the study and treatment of PCa. Promising results point to their potential to block cancer pathways and improve on already effective therapeutic approaches. As we advance, modified medicine, nanotechnology, and genomics methods will be fundamental in maximizing the efficacy of these natural substances and ultimately changing the treatment of PCa. But in order to close the gap between exciting findings and therapeutic application, more study, clinical trials, and effective activities are essential.

1. Introduction

Prostate cancer (PCa) is the most frequent cancer among males worldwide, with a high prevalence in Western nations.[1] In nearly ninety percent of patients, PCa is still only locally progressed or organ-confined when they are diagnosed, making prostatectomy or local radiation treatment options.,[2] and androgen-deprivation therapy, which tries to reduce hormone output and/or activity, is the most effective treatment at

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this point, when tumor growth is dependent on androgens. This treatment is pharmacological castration based, which is accomplished by using GnRH agonists in conjunction with antiandrogens or alone[3,4]; recent times, 2 large clinical trials, STAMPEDE and CHAARTED, have proven the advantages of combining hormonal therapy with chemotherapy.[5,6] Even after a positive first reaction, the vast proportion of patients relapse two to three years later, with the tumor expanding to the point that castration is no longer effective.[7] Better treatment options are necessary because chemotherapy and immunotherapy, & novel drugs like abiraterone and enzalutamide, only provide a few months of progress. Patients who are castration resistant have a better probability of survival if they are not castrated.[4,8] Bone metastases, which account for Eighty percent of developed PCa and are commonly dealt with chemotherapy and radiation, are linked to a high rate of morbidity, a poor quality of life, and a variety of skeletal complications.[6,9] Natural chemicals have attracted a lot of attention in recent years as a result of their unique anti-cancer potential. Nutraceuticals have an anti-metastatic, anti-angiogenic, pro-death, and growth-suppressing effect in cell lines of PCa that xenograft, but normal prostate epithelial cells are spared.[10] These medications' anti-PCa effects are attributable to a variety of mechanisms, including androgen receptor (AR) axis suppression as well as cancer stemness targeting.[11–13] As a source of natural medicine ingredients, marine sources have played an important part in humanity's history. The ocean is home to a varied range of habitats and occupies over 70 % of the planet's surface. Biological activity has discovered half of the previously recognized impacts of unique marine natural compounds.[14] The phenomenon of marine ecology is unique. As a result, in order to survive, marine animals must adapt to these harsh conditions. While developing new anticancer treatments, researchers are becoming increasingly interested in marine sources.[15] Prostate cancer is one of the most common cancers affecting men, making its study crucial for early detection and effective treatment. Understanding the disease's progression and risk factors can lead to better screening methods, potentially reducing mortality rates. Research can also contribute to the development of more targeted therapies, improving patient outcomes. Moreover, studying prostate cancer can uncover genetic and environmental influences, aiding in prevention strategies.

2. Etiology and risk factors

2.1. Diet and obesity

Men in Western nations have a greater incidence of PCa than men in developing/non-Western countries, according to ecological research,[16] showing that nutrition and lifestyle may play a role in PCa epidemiological data. Non-Western males who relocated to Western nations implemented identical lifestyles and PCa risks as those in Western nations, validating this putative link.[17–19] Despite this, no prospective studies linking self-reported dietary patterns of healthful foods and the occurrence of PCa have been published since these ecological descriptions.[20,21] Statins have been shown to reduce the risk of advanced PCa, implying that cholesterol may contribute to the establishment of PCa.[22] Regardless, understanding how diet impacts PCa risk is restricted due to the Western diet's complexity and its interaction/association with good behaviors. Obesity has become a national pandemic in the United States (US), with studies showing that obese persons are more prone to get PCa.[23,24] Obesity and PCa are hypothesized to be linked to greater amounts of free IGF-1, insulin, and estradiol, as well as decreased concentrations of adiponectin and free testosterone.[25] Obesity has been linked to lower blood PSA levels and larger prostates, resulting in fewer prostate biopsies, while there is no clear pathophysiological link between obesity as well PCas.[26]

2.2. Inflammation

Chronic inflammation has been linked to the emergence of a lot of cancers, including PCa, and it might similarly be linked to PCa. Viruses, dietary poisons, hormone imbalances, and physical and chronic stress have all been suggested as possible causes.[25] Intra-prostatic inflammation can produce angiogenesis, cellular turnover, epithelial proliferation, and DNA damage.[27] Those who had at least one inflammation biopsy core had an odds ratio (OR) of 1.78 (95 percent CI 1.04–3.06) for PCa in the PCa Prevention Trial (PCPT) compared to men who had no cores of inflammation in the placebo arm.[28] The association was significantly stronger when considering a diagnosis of high-grade PCa (OR 2.24, 95 percent CI 1.06–4.71).[29]

2.3. Medications

As previously stated, HMG-CoA reductase inhibitors have been linked to a lower risk of PCa death after diagnosis.[30] Despite this, the role of statins in prostate carcinogenesis and prevention continues to be a contentious issue. Metformin use has been linked to the same level of optimism as statin use when it comes to PCa outcomes. Metformin has been associated to lower PCa-specific (HR 0.76, 95 percent CI 0.64–0.89 for each extra 6 months of metformin treatment in diabetics) and overall morbidity.[31] According to a meta-analysis and systematic review of observational research evaluating patient clinical outcomes with metformin and PCa, Metformin usage was related with a slightly decreased incidence of biochemical recurrence (HR 0.82, 95 percent CI 0.67–1.01), but not with all-cause death, PCa death, or metastasis.[32]

2.4. Genetics

With chromosomal number changes, structural rearrangements, point mutations, and somatic copy number variations, the genetic makeup of PCa is known to be exceedingly complex.[33] PCa is estimated to be caused by mostly inherited genetic factors in 5–10 % of cases.[13] Only a few examples include HPC1, HPC2, HPC20, HPCX, PCAP, and CAPB.[34] Epigenetic markers for PCa, such as miRNA, have been investigated in recent studies. Since the initial study of miRNA and PCa in 2007, more than 30 different miRNAs have been linked to the disease.[35]

3. PCa development and hyperplasia

The stroma covers the basal and luminal epithelial cell layers of the growing prostate gland. Basal cells are long, elongated cells that function as a wall among the stroma and the lumen. Luminal epithelial cells are polarized, columnar cells that border the prostate lumen. Different biological markers can be used to identify these cells in terms of disease. Luminal epithelia, for example, exhibits high AR levels and is favorable to cytokeratins eight & Eighteen, as well as NKX3.1 and CD57. AR is expressed in basal epithelial cells at modest levels, along with p63, CD44, cytokeratin 5 and 14, and GSTP1. Neuroendocrine cells produce growth factors, post-mitotic, AR-negative, and neuropeptides for luminal cell development.[36] Eventually, although not the focus of this work, stroma may have a significance in PCa progression and epithelial cell homeostasis,[37,38] multiple critical differentiation regulators, as an instance AR, Forkhead box A1 (FOXA1), and NKX3.1, are required for prostate embryonic and postnatal development. The NKX3.1 transcription factor belongs to the NK homeobox gene family, which controls animal organ development. The earliest prostate-specific gene, NKX3.1, can be found in the prostate as early as embryonic day 15.5.[39] The presence of NKX3.1 in luminal epithelial nuclei corresponds to active morphogenesis at the tip of prostate buds in newborn mice, whereas ductal branching and secretory protein synthesis are reduced when nkx3.1 is genetically deleted.[40] Despite the fact that androgens regulate gene nkx3.1 and that adult mouse castration reduces protein expression, NKX3.1 appears to occur before androgen production, indicating that distinct pathways for expression initiation exist during development.[41] After androgen deprivation early in the development of a mouse embryo, ADT causes lumen involution and luminal epithelial cell death in adult prostate glands,

something that could perhaps be reversed by testosterone replenishment.[42] AR signaling promotes pro-development genes and prostate terminal end buds differentiation, but androgens are not linked to PCa risk, and testosterone use does not increase the risk.[43,44] The variations in androgen function between developing and normal prostates, as well as androgens' role in PCa progression and growth (Fig. 1) are highlighted by these findings. FOXA1 transcription factor influences AR target gene expression throughout the prostate's lifecycle. Deletion of FOXA1 in mice leads to immature epithelial cells and stroma in pubertal ducts. Developmental gene dysregulation promotes abnormal growth and proliferation. PCa should be detected and treated promptly. Identifying PCa origin cell susceptible of tumor induction is one aspect of PCa biology that could provide insight into tumor prognosis and therapy possibilities.[45]

4. Modern treatments for PCa

Most patients can benefit from surgery or radiotherapy when PCa is limited to the adjacent tissues and prostate.[46] For metastatic/advanced disease, androgen restriction therapy is the standard treatment. This approach, however, has become less common in recent years due to the significant risk of resistance.[13] Bilateral orchiectomy is a frequent androgen suppression procedure, but it carries a number of dangers and side effects, including the chance of castration-resistant PCa (CRPC).[47] In affluent countries, this strategy is rarely utilized. Chemical treatments that target gonadotropin-releasing hormone can be used instead of surgical castration. They decrease downstream testosterone synthesis by reducing the production of follicle-stimulating hormone and luteinizing hormone.[48,49] Since 2010, five innovative medications have been approved in the US, with a median life extension of only 3–5 months.[50] Sipuleucel-T, an autologous cellular immunotherapy, is used for less symptomatic disease. Pre- and postdocetaxel therapies include abiraterone acetate (CYP17/androgen biosynthesis inhibitor), enzalutamide (androgen receptor AR inhibitor), and cabazitaxel (microtubule inhibitor). When other therapies are inadequate, radium-223, a radiopharmaceutical, is used to treat post-docetaxel and docetaxel-ineligible symptomatic bone metastases.[51,52] PSA testing and other technologies for early detection of PCa patients may have resulted in a lower mortality rate. However, people with CRPC still have a high mortality rate.[44] Despite the introduction of novel therapeutic techniques, existing drugs seldom cure this cancer, and survival is usually limited to 4–6 months. Because existing approaches to curative and palliative PCa treatments are linked with high costs and melancholy,[45] PCa chemoprevention ought to be the primary plan for decreasing PCa fatality.[51,53]

5. Chemo-dietary prevention of PCa

One of the first chemoprevention treatments was the long-term use of 5α -reductase inhibitors like finasteride, a medication approved by the US Food and Drug Administration (FDA). Finasteride inhibits type II and type III 5α-reductases while having no effect on type I enzymes.[45,46] 5α-reductase is an enzyme that transforms testosterone to DHT, which stimulates cell development, in individuals with untreated PCa. The PCa Prevention Trial, additionally recognized as the Finasteride Clinical Trial, was a seven-year study that enrolled 18,882 men between the ages of 55 and 65.[49] According to an 18-year follow-up of this study, In the finasteride-treated group, high-grade PCa (Gleason 8–10) was somewhat more prevalent than in the placebo group. Additionally, there was no substantial distinction in as a whole survival or survival following PCa diagnosis between the control and treatment groups.[54] Chau et al[55] published a research recently looking at serum finasteride concentrations reported in the PCPT trial. Researchers found no link between finasteride levels and PCa risk, but found two single nucleotide polymorphisms in the CYP3A4 enzyme linked to lower plasma levels, while higher levels were associated with other SNPs.[56] In contrast to the PCPT study, the SELECT experiment, which used oral L-selenomethionine (0.2 mg/day) and Vitamin E (-tocopherol, 400 IU/day)in identical demographic

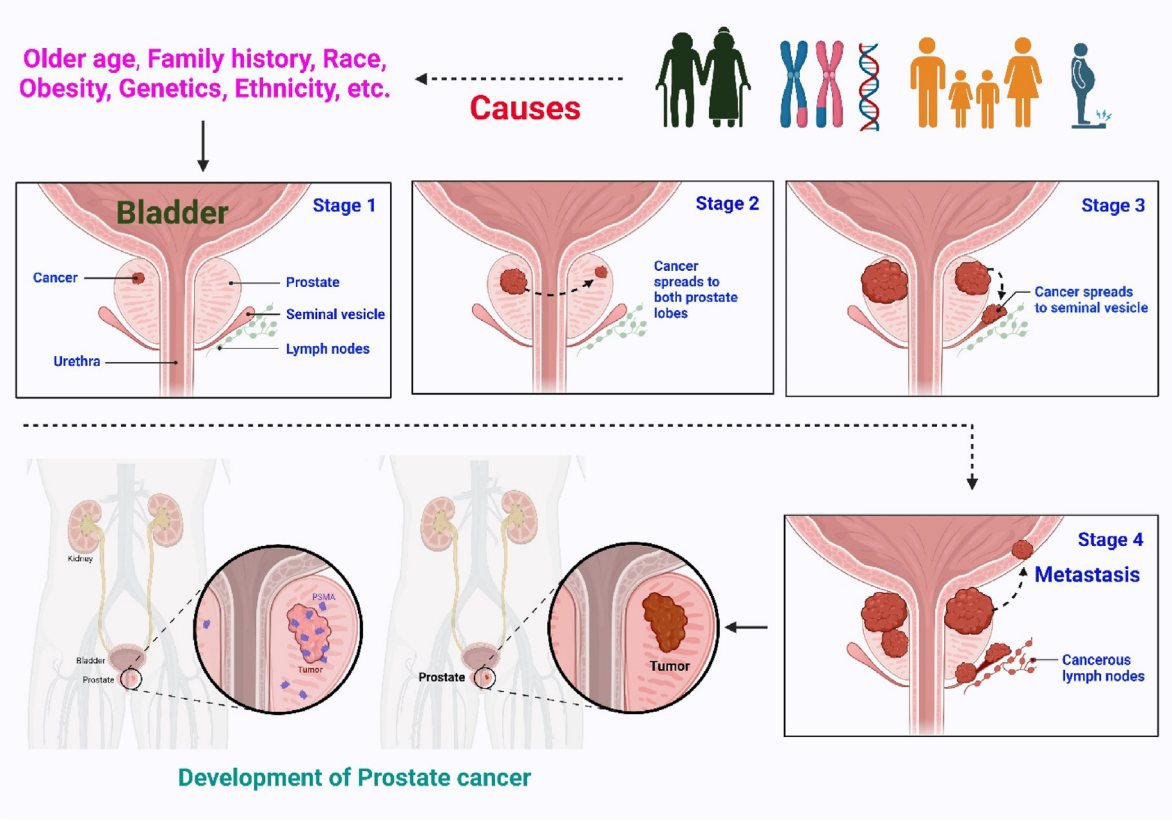

Fig. 1. Causes, stages and progression of PCa.

groups, had a negative outcome.[57] In the SELECT study, selenium supplementation had no effect on PCa risk, whereas vitamin E supplementation had a statistically insignificant effect on PCa risk.[58] The discovery that an exponential growth in 25-hydroxy vitamin D in the blood of the participants reduced PCa incidence was a silver lining in this trial.[59] A new proposal from the PCa treatment and prevention committee suggests that few medicines have been tested in the high-risk or general population groups,[60] patients with PSA4 ng/ml should be given the choice of actively monitoring instead of therapy, emphasizing the relevance of PCa progression prevention techniques. Research on natural-derived substances is needed for chemopreventative therapy for PCa, as 20–30 % of active monitoring patients progress to more aggressive forms.[61]

6. Bioactive natural products against PCa

The most promising bioactive natural compounds for the therapy of PCa, as well as their different modes of action, are discussed, as they affect metastasis, invasion, tumor angiogenesis, autophagy, apoptosis, cell cycle control, and cell proliferation (Table 1) (Fig. 2).

6.1. Apigenin

Apigenin is a Asteraceae family flavone of plants, including *Anthemis* sp., as well as fruits and vegetables.[153] Apigenin has been shown to inhibit cancer cell growth in a variety of cancer cell lines (lung, liver, colon, and breast).[154] Apigenin (5–40 M) inhibits cell growth and indices death in PC-3 cells, according to another study.[155] Apigenin inhibits cell motility and invasion in PC-3M cells (25 for 16 h) through changing the actin cytoskeleton and decreasing FAK/scr signaling.[156] When given at similar concentrations (20–40 M), apigenin suppresses HDACs class I in both 22Rv1 and PC-3 cells, making it an epigenetic modulator.[157] The generation of ROS causes apoptosis in 22Rv1 cells, which then activates both p53-dependent and p53-independent transcriptional pathways.[158] Apigenin's antiangiogenic properties were as evidenced by C4–2B, LNCaP, and PC-3 cells, with lower VEGF production leading to cancer progression and metastasis reduction.[159] Lastly, Apigenin has been proven in vivo to reduce the development of PC-3and 22Rv1 tumor xenografts in athymic nude mice.,[160] as well as inhibiting cancer progression in TRAMP animals.[161]

6.2. Berberine

Isoquinoline alkaloid berberine,[162] found in Berberis plants, is an isoquinoline alkaloid. Berberine reduces DU145, PC-3, and LNCaP cell proliferation and G1 cell cycle arrest in a dosage and time (24–72 h) dependent manner, but has no effect on normal human prostate epithelial cells. Biochemical mechanisms include increased synthesis of Cdk inhibitory proteins (Kip1/p27 and Cip1/p21), increased binding of Cdk inhibitors to Cdks, and inhibition of cyclin-dependent kinase Cdk6, Cdk4, and (Cdk) 2 proteins, as well as cyclins E, D2, and D1. Berberine kills cancer cells by altering the membrane potential of mitochondria, activating poly (ADP-ribose) polymerase, and inducing caspase activation.[163] Ultimately, berberine (at doses of 30 and 50 mg/mL) increases radio sensitivity in human PCa cells via blocking the ROS and MAPK/caspase-3 pathways, as well as reducing the production of HIF-1alpha and VEGF.[36]

6.3. Capsaicin

Capsaicin is a Capsicum plants derivative vanilloid. Capsaicin inhibits PC-3 cell growth in xenograft models (5 mg/kg) and in vitro (IC50 of 20 M) by producing ROS, dissipating the inner transmembrane potential of mitochondria, and activating caspase 3.[164] Ceramide buildup, as well as JNK and ERK activation, has been demonstrated cause PC-3 cells apoptosis.[165] At various dosages (100–500), capsaicin increases apoptosis in both androgen-dependent (LNCaP) and resistant (DU-145) PCa cell lines, and is linked to an boost in Bax, p21, p53 and down-regulation of PSA and AR and decreased proteasome activity.[166]

6.4. Curcumin

Curcumin 210, a diphenylheptanoid derived from *Curcuma longa*, was the first diphenylheptanoid by Inhibiting the EGF-R signaling pathway induces apoptosis in both androgen-resistant and androgen-dependent prostate cancers at dosages ranging from 5 to 50 M.[167] Curcumin promotes apoptosis by interfering with Bcl proteins, producing ROS, and activating mitochondrial stimulation-related pathways. Apoptosis is induced in PC-3 cells by caspase-independent and AIF mechanisms.[168] Curcumin suppresses PCa cell proliferation by downregulating the androgen receptor while activating caspase-dependent apoptosis by upregulating AP-1, NF-κB, CREB, PSA, and cyclin D.[169] Furthermore, PCa cells accumulate in the G1 phase due to proteasome-mediated down-regulation of cyclin E and overexpression of CDKs. Curcumin acts as a chemoprotective medication in early-stage PCa, triggering autophagy and changing Wnt/-catenin pathways.[170] Curcumin likewise suppresses glyoxalases and inhibits histone acetyltransferase, regulating metabolic cellular processes and serving as a histone acetyltransferase blocker.[171] By interfering with cell cytoskeleton architecture and VEGF production, curcumin suppresses PC angiogenesis and metastasis. When given at doses of 5 mg/kg three times a week for four weeks, curcumin decreases invasion and metastasis in DU145 xenografts.[172] In the first in vivo model studied, LNCaP xenograft in nude mice, curcumin inhibited PCa development and reduced metastasis.[173] Liposomal administration, coloaded lipid-based carriers, cellulose nanoparticles, and curcumin-loaded nanospheres have all been shown to improve curcumin transport to cancer cells.[174]

6.5. Fisetin

Fisetin is a flavonol with cytotoxic and cytostatic properties in a range of cancer cell lines (pancreatic, ovarian, melanoma, lung, liver, blood, and breast).[175] *Acacia greggii* is one of the plants that contain it. Fisetin promotes G1 cycle arrest in prostate LNCaP cells by downregulating cyclin-dependent kinases and cyclins and initiating both apoptotic pathways caspase-independent and - dependent when administered at 10–60 M for 24 and 48 h.[176] Fisetin inhibits AR production by competing with the AR ligand.[177] Fisetin is an inhibitor of metastasis, migration, and adhesion in highly metastatic PC-3 cells via interfering with the NF-κB pathway and decreasing MMP-9 and MMP-2 expression.[178] In PC-3, DU145, and LNCaP cells, downregulation of NF–B is associated to an increase in TRAIL-induced apoptosis.[179] Fisetin inhibits the mTOR and PI3K/Akt signaling pathways, causing autophagic cell death.[180] A fisetin treatment (1 mg/animal) twice weekly in the CWR22 Rupsilon1 human xenograft model on Tuesdays reduced tumor progression and PSA levels.[181]

6.6. Genistein

Glycine max contains the flavanone genistein 182. By acting as a inhibitor of tyrosine protein kinase and reducing protein phosphorylation, genistein reduces the proliferation of LNCaP, PC-3, and DU145 PCa cell lines in a dose-dependent manner.[182] Downregulation of mitogen-activated protein kinase 6, cell division cycle 6 (CDC6), DNA topoisomerase II, and survivin, as well as increased regulation of glutathione peroxidase, are all involved in genistein-mediated growth inhibition. In PC-3 cells, IGF-1/IGF-1R signaling pathway suppression has been linked to cell growth suppression.[28,183] As according new research, microRNA regulation is likely to be involved in genistein's apoptotic and antiproliferative activities. As a result, by inhibiting miR-1260b and its targets, sRRP1 and Smad4, genistein promotes apoptosis.[184] Via regulating the expression of miR-34a and HOTAIR, genistein inhibits proliferation of cell in DU145 and PC-3 cells.[185] Apoptosis has also been

Table 1
Anti-PCa bioactive natural compounds.

Sl.No	Compound	Plant	Mechanism of Action	Molecular Pathway	*In vitro*	*In vivo*	References
1.	Apigenin	*Anthemis* sp. (*Asteraceae*)	Apigenin induces G1 cell cycle arrest and apoptosis in androgen-dependent and androgen-independent PC cell lines, while inhibiting class I HDACs in PCa-3 and 22Rv1 cells, acting as a modulator of epigenetic events.	Cyclin D1, D2, E, Bax/ Bcl-2 ratio, NF-κB,ROS, IGF-IGF-IR, PI3k/Akt HDACs Actin, FAK/scr TIGF-I/IGFBP-3, PI3K/ Akt/FoxOGF-β, ↓VEGF	DU145, LNCaP, PC-3, 22Rv LNCaP, PC-3, C4–2B IGF-I/IGFBP-3, PI3K/Akt/FoxO	22Rv1, PC3 xenografts, TRAMP mice	62,63
2.	Berberine	*Berberis* sp. (*Berberidaceae*)	G1 cycle arrest, Apoptosis. Berberine, given at a dose of 5 mg/kg/day, inhibits tumor growth in LNCaP xenografts in nude mice via lowering AR expression.	Cyclins, CDKs, CDKs inhibitors Bax/Bcl2 ratio, caspases, cytochrome c ↓AR expression	DU145, PC-3, LNCaP	LNCaP xenografts	64–67
3.	Capsaicin	*Capsicum* sp. (*Solanaceae*)	Ceramide accumulation and JNK and ERK activation also trigger apoptosis in PC-3 cells.	ROS, JNK, ERK, ↑p53, p21, Bax, ↓PSA, AR	PC-3, DU145, LNCaP	PC-3 xenografts	68–71
4.	Curcumin	*Curcuma longa* (*Zingiberaceae*)	Curcumin inhibits PCa metastasis and angiogenesis by affecting VEGF synthesis and cell cytoskeleton architecture, thereby promoting cycle arrest and preventing apoptosis in PCa-3 cells.	PC-3, LNCaP	LNCaP xenografts Curcumin-loaded PLGA nanospheres, Cellulose, Nanoparticles, Lipid-based carriers	Cyclins, Cdks, Akt. EGF-R, Bcl, ROS, apoptosis-inducing factor (AIF) ↓AR, NF-κB, AP-1, cAMP Response Element-Binding Protein (CREB), PSA.	72–80
5.	Fisetin	*Acacia greggii* (*Fabaceae*)	Cell cycle arrest. Fisetin inhibits the signaling pathways mTOR and PI3K/Akt, resulting in autophagic cell death. In a CWR22 Rupsilon1 human xenograft model, a fisetin injection (1 mg/animal) given 2 times weekly reduced tumor progression and PSA levels.	PC-3, LNCaP	CWR22 Rupsilon1 human xenograft	Cyclins, Cdks, ↓AR NF-κB, MMP2, MMP9, mTOR, PI3K/Akt ↓PSA	81–85
6.	Genistein	*Glycine max* (*Fabaceae*)	Cycle arrest, growth inhibition. Apoptosis is also linked to a number of pathways, including suppression of proteasomal chymotrypsin-like activity, inactivation of NF–B, and inhibition of Akt. Decrease Angiogenesis. No metastasis.	DU145, PC-3, ND1, LNCaP, ALVA31, JCA1	PC-3, DU145 xenografts. Lobund-Wistar rats, TRAMP mice Cabazitaxel + genistein Genistein-loaded liposomes	↑p21WAF1, ↓Cdks, cyclins, survivin, DNA topoisomerase II, ↓IGF-1/ IGF-1R NF-κB, Akt, caspases IL-10 MMP-9.	86–95
7.	Ginsenoside Rh2	*Panax* sp. (*Araliaceae*)	↓Cell proliferation, detachment. In a PC-3 human xenograft model in nude mice, oral Rh2 therapy at a dose of 120 mg/kg suppressed cancer cell proliferation, significantly delayed cancer growth, and ultimately increased the rate of apoptosis.	PC-3, LNCaP	PC-3 xenograft	MAP kinases	96–98
8.	Gossypol	*Gossypium hirsutum* (*Malvaceae*)	Due to variations in TGF-beta 1 expression levels, gossypol has been shown to produce G0/G1 cell cycle arrest in PC-3 cells and prostatic cells from people with benign prostatic hyperplasia.	PC-3, BPH DU145 Docetaxel + gossypol	PC-3 xenograft	TGF-1 Bcl-X/Bcl-2, NF-κB, AP1 P53, Bcl-2, Bcl-xL, caspases Beclin1.	28,99–105
9.	Lycopene	*Solanum lycopersicum* (*Solanaceae*)	Cell cycle arrest. ↓Cholesterol synthesis. Apoptosis ↓Invasion. Apoptosis. Chemoprevention.	LNCaP, PC-3 LNCaP, DU145 LNCaP, PC-3	PC-3 DU145 Xenografts TRAMP mice Clinical trials	Cdk4, cyclins D1, E and Rb PPARγ-LXRα-ABCA1 p21, p27, p53, Bax/Bcl-2, IGF Integrins ↓ROS.	106–115
10.	Quercetin	*Vitis* sp. (*Vitaceae*)	Cell cycle arrest. Apoptosis. ↓Adhesion, metastasis, ↓Angiogenesis, ↓Tumor growth	LNCaP, DU145 PC-3	LAPC-4 xenografts	Cyclins, Cdks, Rb, ErbB Bax, Bcl, caspases, IGF, ↓fatty acid synthase, ↓HS90, ↓AR MMPs.	116–121
11.	Silibinin	*Silybum marianum* (*Asteraceae*)	G1 cycle arrest. G1, G2/M cycle arrest. No invasion, metastasis. ↓Tumor growth, apoptosis, angiogenesis. ↓Angiogenesis.	LNCaP DU145, 22Rv1 PC-3 PC-3MM2, C4–2B	PC3 xenografts TRAMP	Rb, Cdks, PDEF, ↓PSA P21, p27, Wnt/LRp6 HIF1, Wnt/LRp6, cyclins, Cdks NF-κB, vimentin,	122–134
12.	Sulforaphane	*Brassica oleracea* (*Brassicaceae*)	In both androgen-dependent and androgen-independent cells, SFN has been demonstrated to trigger cell cycle arrest and apoptosis	LNCaP, PC-3 DU145	PC3 xenografts, TRAMP	Methyltransferase, cyclins ROS, caspases, HDAC6, ↓AR HIF-1.	135–142

(*continued on next page*)

Table 1 (*continued*)

Sl.No	Compound	Plant	Mechanism of Action	Molecular Pathway	*In vitro*	*In vivo*	References
			and androgen-refractory PC cell lines. SFN (IC50 of 10 M) causes G2/M phase arrest in DU145 cells. ↓Angiogenesis.				
13.	Resveratrol	Vitis vinifera	Resveratrol is a polyphenol found in grapes that has a number of health benefits, including anti-cancer effects.	PCa models	Target the AR axis	factor 1-α (HIF-1α) decreasing β-catenin-mediated AR signaling	143–149
14.	Luteolin	López-Lázaro	Luteolin is an anti-inflammatory, anti-cancer, and neuroprotective flavone found in celery, broccoli, parsley, thyme, and rosemary.	Secreted PSA levels	In PCa cells	AR-Hsp90 complex to dissociate the proteasome-ubiquitin	150–152

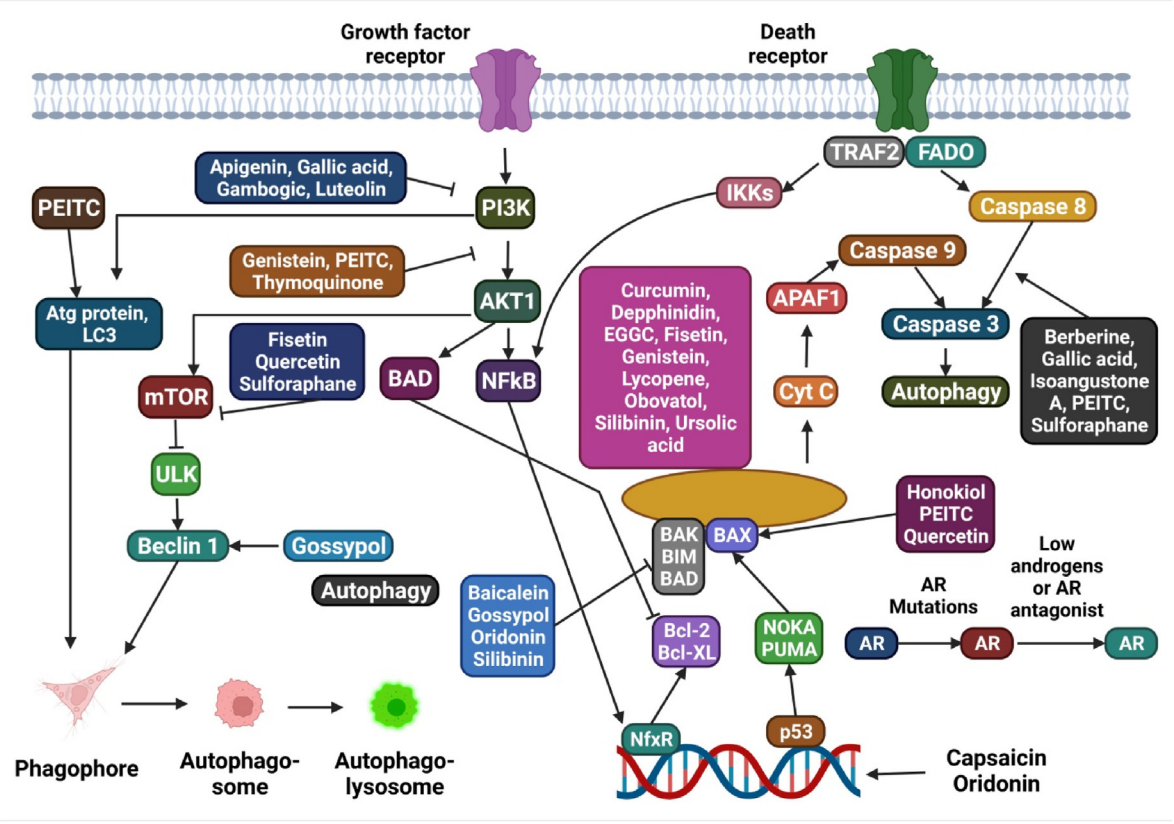

Fig. 2. The mechanism by which bioactive natural compounds interact with PCa cells. Natural substances cause PCa cells to die by activating caspases and mitochondrial-dependent cascades (honokiol), blocking oncogenes (baicalein), and reducing the NF-κB signaling pathway (curcumin).

connected to a number of pathways, including proteasomal chymotrypsin-like activity suppression, NF-κB inactivation, and Akt inhibition.[186] High doses of genistein inhibit growth through regulating the expression of the AR function, which is independent of PSA expression.[39] Genistein, on the other hand, activates mutant forms of AR seen in advanced PC at physiological levels (0.5–5 M).[187] Furthermore, after genistein administration, Many cell migration and adhesion genes (VEGF, uPAR, protease M, MMP-9) are downregulated in PC-3 cells.[30] Cancer stem cells (CSC) are also targeted by genistein and may have an anti-CSC effect, which is significant for reducing metastasis and PC relapse.[188] In DU-145 and PC-3 cells, the epigenetic effects of genistein at 40 M have been shown, where It overturns tumor suppressor gene DNA hypermethylation, resulting in their cancer progression activation and inhibition.[6] Genistein has chemopreventive properties, according to an in vivo investigation. Genistein feeding reduced the incidence of induced prostate-related cancer in L–W rats with spontaneous and generated metastasizing adenocarcinomas in the prostate-seminal vesicle complex.[50] TRAMP mice were less likely to develop cancer when fed a phytoestrogen-rich diet high in genistein (100, 250, or 500 mg per kilogram).[189] Though oral genistein does not reduce PSA levels in PCa patients, a research shows that 30 mg of synthetic genistein administered every day for 3–6 months reduces PSA levels in the blood.[190] Furthermore, it was observed that combining Cabazitaxel with genistein in the treatment of metastatic-castration-resistant PCa boosted the apoptotic impact.[191] Genistein's clinical efficacy against cancer is limited due to low solubility, poor absorption, and pharmacokinetics. Liposomal vehicle compositions enhance cellular dispersion and proapoptotic efficacy.[192] Finally, researchers did a meta-analysis of the evidence relating soy product consumption to the risk of PCa. According to the findings of this meta-analysis, consumption a lot of non-fermented soy foods can help you from getting PCa.[193,194]

6.7. Ginsenosides

Ginsenosides are a type of chemical that only Panax plants produce. Among the bioactive ingredients discovered in root extract of ginseng is ginsenoside Rg3.[195] By boosting the synthesis of cyclin-kinase inhibitors p21 and p27, Rg3 has been demonstrated in the G1 phase to arrest LNCaP cells and eventually initiate a caspase3-mediated death pathway. Rg3 was also demonstrated to modify MAP kinase expression and enhance cell detachment in LNCaP and PC-3 cells, with an IC50 of 8.4 M.[13] Rg3 inhibits PC-3M cell migration and metastasis by interfering with the p38 MAPK pathway, resulting in a decrease in AQP1 expression (a water channel protein implicated in cell migration).[59] Combining Rg3 with several chemotherapeutics (docetaxel, cisplatin, and doxorubicin) reduces PC cell growth more efficiently in PC-3, DU145, and LNCaP cells via suppressing NF-κB activation.[60] Rh2 ginsenoside (-D-glucopyranoside) is a glycoside isolated from the roots of Panax ginseng,[53] that inhibits cell proliferation and causes cell detachment in LNCaP and PC-3 cells with an IC50 of 5.5 M through modifying MAP kinase expression.[195] paclitaxel and Rh2 (0.5–40 μM) work together to drastically inhibit LNCaP cell proliferation and tumor formation.[196] In a nude mouse PC-3 human xenograft model, oral Rh2 therapy at a dose of 120 mg/kg suppressed tumor cell proliferation, considerably delayed tumor growth, and finally increased the apoptosis rate.[197] 25-hydroxyprotopanaxadiol (25-OH-PPD) and 20(S)-25-methoxyl-dammarane-3β,12 β,20-triol (25-OCH3-PPD) are also found in Panax ginseng.[198] cyclin D1, E2F1, MDM2, and Cdk 4 and Cdk 2 reduced cell growth-related proteins in PC-3 and LNCaP cells, leading to cell cycle arrest and death. 25-OH-PPD reduced tumor development in PC-3 xenograft tumors dose-dependently.[195]

6.8. Gossypol

Gossypol, a polyphenolic aldehyde found in cottonseed,[192] has been demonstrated to have cytotoxic and antiproliferative effects in cell lines of MAT-LyLu and PC cells transplanted in Copenhagen rats. When given at 0.5–4.0 M for 24, 48, or 72 h, gossypol alters TGF1 and Akt signaling in MAT-LyLu cells, changing the regulatory proteins expression like cyclin D1, phospho-Rb, and Cdk4, and eventually inducing G0/G1 cell cycle arrest.[195] Gossypol causes G0/G1 cell cycle arrest in BPH and PC-3 cells, inhibits Bcl-xL/Bcl-2 heterodimerization with proapoptosis molecules, leading to Apoptotic mechanisms that are caspase-dependent and caspase-independent.[199] Gossypol has recently been displayed to induce autophagy in androgen-independent PCa cells with high Bcl-2 levels and resistance to apoptosis, both in vivo and in vitro (PC xenografts), by disrupting the endoplasmic reticulum interaction among Bcl-2/Bcl-xL and Beclin1, releasing the BH3-only pro-autophagic protein Beclin1, which then causes autophag.[196] Gossypol further hinders angiogenesis and metastatic potential (invasion, migration, and adhesion). GP inhibits AP-1 and NF-κB activity in PC-3 cells, resulting in reduced urokinase plasminogen activator and VEGF production as well as chemokine receptor 4 downregulation.[197] Gossypol reduces angiogenesis in human prostate tumor PC-3 xenografts in mice by reducing VEGF receptor 2 kinase activation, which leads to the inhibition of phosphorylation of focal adhesion kinase, AKT kinase, and important intracellular proangiogenic kinases such Src family kinase.[200] In PC-3 cells, a time - and dose -dependent combination of gossypol and docetaxel was revealed to be apoptotic and cytotoxic.[198] Apoptotic and autophagic processes were reported to trigger cell death in DU-145 cells by gossypol (0.5–10 M) and sorafenib (2–20 M), respectively.[201] Finally, it was discovered that giving AT-101 (gossypol) at a dose of 20 mg/day for 21 days to certain men with chemotherapy-naive, castrate-resistant PCa reduced PSA levels.[198]

6.9. Lycopene

Lycopene is a carotenoid produced mostly by the tomato *Solanum lycopersicum*.[202] In both LNCaP and DU145 cells, stimulation of the PPAR-LXR-ABCA1 pathway resulted in a lycopene-mediated reduction in cholesterol synthesis.[194] High dosages of lycopene (16 mg/kg for seven weeks, two times a week) induced apoptosis in PC-3 cells and xenograft models via altering IGF-I, IGF-IR, and IGFBP-3 expression levels.[203] Lycopene inhibits phosphatidylinositol 3-kinase signaling in PC-3 and LNCaP cells, causing cell cycle arrest and apoptosis. It also reduces integrin expression, inhibiting cell motility and invasion.[193,202] Lycopene, on the other hand, is a chemopreventive drug that can help delay or prevent PCa from developing. Lycopene exerts a chemopreventive impact in LNCaP cells by increasing detoxifying proteins, preventing DNA damage, and reducing ROS production and oxidative stress.[189] Lycopene at 4 mg two times daily for one year was demonstrated to reduce or stop the progression of high-grade prostatic intraepithelial neoplasia into PCa, and whole tomato lycopene at 10 mg two times daily for one year lowered PSA velocity in men with PCa.[204,205] Lastly, recent epidemiological studies suggest that lycopene may aid in the prevention of PCa. 5 research investigations indicate a thirty to forty percent risk reduction when eating lots of tomatoes or lycopene, three studies show a 30 % decrease but the findings aren't statically important, and seven research shows no link.[206]

6.10. Quercetin

Quercetin is a flavonol that can be found in grapes.[207] In a number of cell lines (blood, bladder, colon, breast, bone, mouth, lung, liver, and esophagus), quercetin has been demonstrated to decrease cell proliferation and activate apoptosis.[208] By interacting with the levels of expression of multiple tumor suppressor genes and oncogenes, quercetin inhibits the growth of PC-3, LNCaP, and DU145 PC cells in a dose-dependent way. Quercetin enhances G2/M cycle arrest in LNCaP by upregulating p21 and inhibiting cyclin B.[209] Lower phosphorylation of MAPK, Akt-1, MAPK kinase 1/2 (MEK1/2), c-Raf, ErbB-3, and ErbB-2, as well as a lowered metastasis rate and drug resistance, appear to be the mechanism of growth suppression in PC-3 cells. Furthermore, quercetin has been linked to a reduction in AR.[210] Through interactions with c-Jun and SP1 proteins At dosages of 5–100 M, quercetin has been found to promote PCa cell lines apoptosis by downregulating heat shock protein and blocking fatty acid synthase.[211] Quercetin in PC-3 cells promotes arrest and death in G2/M cycle by lowering IGF-I, and IGF-II, phosphorylated pRb, cyclin B1, Cdc2/Cdk-1, and increasing caspase-3, Bax, and p21, as well as changing the Bcl-2/Bax ratio.[212] Quercetin promotes TRAIL-induced cytotoxicity by activating caspases, reducing survival, and phosphorylating Akt.[213] When given at a dose of 20 mg/kg/day, in vivo and in vitro investigations in prostate xenograft mouse models reveal quercetin has antiangiogenic effects through interacting with the VEGF-R2-regulated autophagic (AKT/mTOR/P70S6K) pathway.[214]

6.11. Silibinin

The *flavolignan silibinin*, commonly known as silybin, was discovered from the *Silybum marianum* fruits.[215] In LNCaP cells, silibinin has been shown to cause G1 cell cycle arrest as well as intracellular and secretory PSA levels are reduced in a time (12–48 h) and dose- (50–200 M)-dependent manner., with phosphorylation status and modulations of retinoblastoma (Rb) levels, as well as decreased CDK activity.[216] The decrease in PSA in LNCaP cells was found to be caused by downregulation of the epithelium-derived Ets transcription factor (PDEF) and the androgen receptor coactivator.[217] As a lipophilic molecule, silibinin reduces DNA synthesis and mitogenic signaling in DU145and LNCaP cells, as well as competing in the EGF-erbB1 interaction and lowering DNA synthesis and mitogenic signaling in DU145 and LNCaP cells.[197] In DU145 cells, Silibinin (50–200 M) triggered G1 cell cycle arrest, which was facilitated by a reduction in p27and p21 expression. Silibinin inhibits Wnt/LRp6 signaling as well as causes apoptosis by suppressing active Stat3, while constitutive NF-κB inactivation makes cells more susceptible to TNF-induced apoptosis.[192] Silibinin causes G2/M and

G1cycle arrest in PC-3 cells by inhibiting the synthesis of CDKs and cyclins as well as the insulin-like growth factor I receptor-mediated signaling pathway in PC-3 cells, causing G2/M and G1cycle arrest[217] at pharmacologically attainable doses (0.02–20 M). PC-3MM2,PC-3, C4–2B LNCaP, as well as DU145 cells have been shown to be resistant to migratory and invasive potential by silibinin 202. In general, silibinin prevents PC cells from transitioning from epithelial to mesenchymal through interfering with the NF-κB pathway, resulting in downregulation of the transcription factors ZEB1 and SLUG, as well as downregulation of vimentin and MMP2.[46] Silibinin also inhibits osteoclastogenesis in PC cells-induced osteoclastogenesis in high-bone metastatic prostate models.[207] Silibinin has antiproliferative, proapoptotic, and anti-angiogenic effects in xenograft models, increasing Kip1/p27, Cip1/p21, IGFBP-3levels, activating ERK1/2, and decreasing VEGF and Bcl-2 levels in PC-3 tumor xenografts.[218] Although only trace amounts of silibinin were found in prostate tissue, considerable blood silibinin concentrations were found in patients who received a silybin-phytosome (13 g/day) for 14–31 days. The paucity of tissue penetration could be described by silibinin's short half-life, the short length of therapy in this study, or an active process of silibinin removal from the prostate.[208]

6.12. Sulforaphane

Sulforaphane (SFN) is an isothiocyanate that occurs naturally in the *Brassica oleracea* plant.[219] In both androgen-refractory and androgen-dependent PC cell lines, SFN has been demonstrated to cause cell cycle apoptosis and arrest. SFN (IC50 of 10 M) causes G2/M phase arrest in DU145 cells,[212] but in LNCaP and PC-3 cells, it causes G1 cell cycle arrest. The antiproliferative effects of SFN are mediated by methyltransferase modulation, which results in a rise in cyclin D2 in LNCaP cells and a decrease in synthesis of protein in PC-3 cells due to reduced phosphorylation of mTOR substrates.[220] Caspases are activated in LNCaP cells, and ROS is produced in PC-3 and DU145 cells, causing intrinsic and extrinsic caspase cascades to be activated.[215] In PC-3, LNCaP, and BPH-1 cells, histone deacetylase 6 is inhibited.[47,221] SFN suppresses prostate cell angiogenesis by inhibiting HIF-1, reducing VEGF production, and inhibiting cell migration in PC-3 and LNCaP cells due to Notch pathway alteration.[214] Oral injection of 7.5 mol per animal per day for twenty-one days reduced tumor volume in PC-3 xenografts in mice that are nude by more than half as a result of a reduction in HDAC activity. Ultimately, broccoli sprouts protected TRAMP rats from PCa.[218]

6.13. Resveratrol

Resveratrol is a polyphenol found in grapes that has a number of health benefits, including anti-cancer effects.[212] It was discovered to target the AR axis in PCa models in vitro and in vivo.[47,210,211,219,220] On the one hand, it blocked β-catenin nuclear translocation in LNCaP cells by downregulating hypoxia-inducible factor 1-α (HIF-1α), thereby decreasing β-catenin-mediated AR signaling[222]; and it also suppressed interleukin-6 (IL-6)-induced AR transcriptional activity.[223] It assisted the proteasomal degradation of the AR splice variant ARV7 in 22RV1 cells by boosting its polyubiquitination. These findings imply that resveratrol could be used to treat castration-resistant tumors that are ARV7-positive as well as androgen-responsive PCa.[224]

6.14. Luteolin

Luteolin is an anti-inflammatory, anti-cancer, and neuroprotective flavone found in broccoli, thyme, parsley, rosemary, and celery.[225,226] It reduced AR mRNA and protein expression in PCa cells, as well as intracellular but also secreted PSA levels, in a dosage and time-dependent manner. It appears to dissociate the AR-Hsp90 complex, allowing the proteasome-ubiquitin route to degrade AR.[227,228]

7. Effects on human PCa cells of extracts from specific plants

Recent research on plant families has identified unique bioactive components that could be used as anti-cancer medicines, highlighting their potential as potential chemotherapeutic drugs (Table 2).

7.1. Juglandaceae

The majority of members of this family lives in temperate climates. Forests consist of trees and vegetation, with walnuts being nut-producing species. Juglone, a phytochemical, reduces EMT, migration, and invasion in LNCap-A1 and LNCaP cells.[259] EMT is especially crucial in the course of malignancies because epithelial cancer cells that change to a mesenchymal phenotype are further invasive and thus extra prone to metastasis. Moreover, because bone metastases diminish patient survival rates dramatically,[260] blocking this route could be a promising therapeutic strategy for preventing prostate and other malignancies from spreading.

7.2. Moraceae

The Moraceae family includes trees and shrubs that are either deciduous or evergreen and are endemic to tropical and subtropical countries. Many genera are known for their edible fruits, while some are famous for their waxy latex. Members of the Moraceae family have yielded a range of phytochemicals, including chlorogenic acid, flavonoids, ascorbic acid, as well as triterpenoids.[52,282] In PC-3 and LNCaP cells, *Ficus deltoidea* extracts from the deltoidea and angustifolia varieties triggered apoptosis and decreased invasion and migration. Furthermore, through altering the production of vascular endothelial growth factor-A in PC-3 cells, these botanical compounds decreased angiogenesis, a process that promotes tumor formation.[224,283] Similarly, preparations containing significant amounts of ascorbic and chlorogenic acids from *Morus nigra* fruit triggered apoptosis in PC-3 cells and exacerbated cell cycle arrest in the Gap 1 phase.[284] Angiogenesis and uncontrolled proliferation are two characteristics of cancer cells. As a result, stopping either pathway has the potential to stop cancer cells from growing and becoming tumors.[285]

7.3. Meliaceae

This family includes shrubs and flowering trees endemic to subtropical and tropical areas. *Azadirachta indica*, also referred as neem, contains nimbolide and terpenoids 28-deoxonimbolide. It inhibits adhesion in LNCaP and PC-3 cells, reduces growth of tumor, and lowers levels of dihydrotestosterone-induced androgen receptors.[286,287] *Trichilia emetic* leaf extracts, on the other hand, have a hormonal effect on PC-3 and LNCaP cells. In PC-3 and LNCaP cells, extracts from the fruit of *Aglaia spectabilis* are cytotoxic.[288] These findings support the idea that Meliaceae plant extracts could be employed in hormone therapy, as well as tumor growth prevention and treatment.[289]

7.4. Rutaceae

This is a genus of woody shrubs, flowering and trees native to subtropical and tropical climates worldwide. The most prevalent phytochemicals found in these plants are berberine alkaloids.[290] The bark of *Phellodendron amurense* has the highest concentration of photoberberine. This phytochemical suppressed C4–2B, DU145, LNCaP, and PC-3 cell invasion by reducing NF-κB activity.[291] Vitamin E micelles of berberine inhibited cell proliferation and induced apoptosis in LNCap and PC-3 cells.[291] Metastasis of PCa has been linked to a poorer survival rate.[287] As a result, it's vital to find compounds that block this pathway.

7.5. Bixaceae

Annatto is a red pigment that is used in colors and artworks, is

Table 2
The effects of extracts from plants on PCa cells are summarized.

Sl.No	Family	Scientific Name	Mechanism of Action	Part	Type of extract	Dominant phytochemicals	Ref.
1.	Juglandaceae	*Juglandaceae*	EMT, migration, and invasion are all inhibited by a GSK-3β/snail-dependent mechanism.	Commercial	97 %	Juglone (5-hydroxy-1,4-naphthoquinone)	229,230
2.	Moraceae	*Ficus deltoidea* L	Stimulation of the intrinsic pathway, modification of the CXCL12-CXCR4 axis to limit both migration and invasion, and manipulation of VEGF-A expression to decrease angiogenesis in PC3 cells	Variety	Crude methanolic extracts: include n-hexane chloroform, and aqueous extracts.	FD1: flavonoid glycosides, furanocoumarin, and chlorophylls FD2: triterpenoids	231–235
3.	Meliaceae	*Azadirachta indica*	LNCaP lowered prostate-specific antigen levels and dihydrotestosterone-induced androgen receptor. In both cell lines, inhibited the activation of focal adhesion kinase, calreticulin, and integrin β1.	Leaves	Supercritical CO_2 dissolved in DMSO and ethanol	Terpenoids: 28-deoxonim-bolide and nimbolide	236
4.	Rutaceae	*Phellodendron amurense*	Invasion inhibition (through reduced NF-κB activation and its downstream target gene FLIP)	Bark	Commercial (methanolic-palmatine chloride hydrate) Dissolved in water	Protoberberine alkaloid (related to berberine)	59,231–242
5.	Bixaceae	*Bixa Orellana*	Growth arrest, G1 arrest, and apoptosis are all caused by inhibiting Src and STAT3.	Commercial	Oil	Tocotrienol	243–258
6	Brassicaceae	*Arabidopsis thaliana*	Cleaved PARP, a biomarker for OS-induced apoptosis; increased mature CD protein synthesis; p53, a CD transcriptional activator; BAX, a CD downstream effector; and p53, a CD transcriptional activator			Phytoalexin: camalexin	259
7.	Geraniaceae	*Biebersteinia multifida*	Apoptosis induction and DNA fragmentation	Roots	From 70 % ethanolic extract dissolved into DMSO	Polysaccharides, peptides, alkaloids such as vasicinone, including flavonoids such as apigenin 7-glucosides, luteolin, and tricetin, along with apigenin 7-rutinosides as well as luteolin	260
8.	Lamiaceae	*Salvia miltiorrhiza* Radix	Apoptosis (increased p21 protein expression and reduced cyclin-dependent kinase 2 (CDK2), CDK4, and cyclin D1 protein levels) as well as cell cycle arrest (increased p21 protein expression and decreased cyclin-dependent kinase 2 (CDK2), CDK4, and cyclin D1 protein levels) were detected.	Commercial	Acetonitrile extract	Lipophilic tanshinones and Hydrophilic phenolic acids, etc.	59,226,241,242,261–271
9.	Apocynaceae	*Thevetia peruviana* L.	The ability to proliferate and move is hampered. Membrane permeability and DNA fragmentation are two characteristics of apoptosis.	Dried roots, leaves, as well as aerial parts	Methanolic extracts dissolved into DMSO	Polyketide *Thevetia* flavone as well as the thevefoline, solanoside, neriifoside cardiac glycosides: peruvosidic acid, peruvoside and neriifolin.	61,225,272–281
10.	Asteraceae	*Achillea wilhelmsii*	Human telomerase reverse transcriptase inhibition induces apoptosis	leaf and Stem	Hydroalcoholic	sesquiterpene lactones and Flavonoids	224

produced by a large number of members. When PC-3 cells are exposed to a phytochemical tocotrienol, produced from *Bixa orellana* oil, their growth is suppressed. Furthermore, inhibiting Src and STAT3 causes cells to enter in the cell cycle's G1 phase and perish.[283] Deregulation of Src and STAT expression has been associated to a variety of malignancies. Src2 inhibition has also been associated to the suppression of PCa development and metastasis in a mouse model.[292] These findings raise the prospect that these compounds could be employed to treat human cancers.[293]

7.6. Brassicaceae

The family of flowering plants, including broccoli and cabbage, produces isothiocyanate and phytoalexins. Camalexin, found in *Arabidopsis thaliana* extracts, reduces PCa cell viability by increasing oxidative stress and promoting apoptosis proteins.[294] An extract made from the *Brassica juncea* var seed. *Pusa Jaikisan* which includes 3-butenyl isothiocyanate, likewise promotes apoptosis in PC-3 cells. PC-3 cells, revealed a rise in caspase-3 activity in the latter investigation.[295]

7.7. Geraniaceae

These are dicotyledon-flowering shrubs that are indigenous to temperate areastricetin, apigenin 7-rutinoside, and Apigenin 7-glucosides, luteolin, and luteolin are polysaccharides, peptides, alkaloids, and flavonoids discovered in ethanolic extracts of *Biebersteinia multifida* roots. DNA fragmentation and death are enhanced when DU145and PC-3 cells are exposed to this extract.[296] While fragmentation of DNA can

happen by accident, it is a defining feature of apoptosis and thus a prospective chemotherapeutic target.[297]

7.8. Lamiaceae

Flowering aromatics that are endemic to temperate areas all over the world belong to this family of plants. The majority of the plants are herbs, both perennial and annual, with fragrant leaves and blooms. Triterpenoids, lipophilic tanshinones, and Phenolic acids are all members of this family. *Salvia miltiorrhiza*, and *Salvia miltiorrhiza*. All displayed cytotoxic effects on LNCaP, PC-3, or DU145 PCa cells, producing apoptosis and cell cycle arrest through a number of methods.[28,35,297,298] PC-3 cells treated with *Scutellaria altissima* extract, primarily scutellarin, exhibit enhanced GAP2/mitotic phase entry due to increased production of cyclin B1 and Cdc2.[299] *Salvia miltiorrhiza* acetonitrile extract causes cell cycle arrest in PC-3 cells by increasing p21 expression and reducing cyclin-dependent kinases 2 through 4 and cyclin D1.[300] The herb has been found to have hormonal effects on PC-3 and LNCap cancer cells, suggesting potential use in PCa hormone therapy.[301,302]

7.9. Apocynaceae

Thevetia peruviana, a genus of tropical and subtropical plants, contains flavones that inhibit cell proliferation, motility, and DNA fragmentation in HTB-81 PCa adenocarcinoma cells, while increasing membrane permeability.[303] *Biebersteinia multifida* is a Geraniaceae family member, that also includes flavonoids, causes DNA fragmentation.[304] Flavonoids may be the reason for DNA fragmentation and subsequent death in PCa cells.[305]

7.10. Asteraceae

Flowering herbs, shrubs, and trees from all over the world belong to this family. Many of the species have previously been used as decorative or food plants. Phytochemicals derived from this plant family include flavonoids, sesquiterpenes, and phenols. Anti-proliferative and cytotoxic activities of extracts from *Achillea wilhelmsii*, and *Melampodium leucanthum*, *Verbesina virginica*, against PC-3 as well as DU145 PCa cell lines.[306–308] *Melampodium leucanthum*, containing tricyclic sesquiterpenes and germacranolide sesquiterpene lactones, causes PC-3 and DU145 cells to stop dividing during the GAP2/mitotic phase, leading to an abnormal mitotic spindle.[309] This family appears to have a number of possible chemotherapeutic pathways, making it a promising candidate for further study.

8. Marine bioactive products having potential for PCa treatment

8.1. Marine bacteria

Microorganisms that live in the marine have a special source of anticancer medicines. Scientists have recently become interested in marine microorganisms in order to improve the development of these medications. *Scytonemin, manoalide*, topsentins, and scytonemin are anti-inflammatory compounds found in sea microorganisms.[307,308] Certain substances such as Kahalalide F, have been shown to be cytotoxic to cancer cell lines like PCa-3, but have no effect on hormone-sensitive LNCaP cells in vitro.[300,310] KF has anticancer properties in solid PCa, with clinical trials showing partial responses in one patient and good health in five. It can be safely given as a 1-h infusion on five days in a row once every three weeks.[311,312]

8.2. Marine fungi

Marine fungi contain biologically active metabolites, but few researches have explored their effects on androgen-independent cell growth. The South China Sea metabolite 1386A showed inhibitory concentrations of 25.31, 8.62, and 4.79 mol/L.[313] In diseases like PCa, this activity could be used as a medicine or a food supplement.[314] Marine gut fungus known as aspochalasins that is found in Ligia oceanica's gut, have been identified as bioactive compounds with cytotoxic, anti-HIV, anti-TNF-alpha, and melanogenesis inhibitory effects.[315–317] The PCa PC-3 cell line was tested for cytotoxicity using the MTT method. At IC50 values of 30.4 μM, apochalasin V was shown to have just minor activity.[318]

8.3. Marine sponges

In marine sponges, alkaloids can be discovered in large quantities. Rhizochalin is one such bioactive molecule obtained from *Rhizochalina incrustata* that is a marine sponge. Rhizochalin reduced promoted apoptosis and autophagy in human castration-resistant PCa cells.[319] Rhizochalinin, a cytotoxic compound derived from rhizochalin, induces apoptosis and cell cycle arrest in human PCa cell lines at low concentrations, with aglycones being more cytotoxic.[320] Functional investigations revealed Rhiz's anti-migratory effect on PC-3 cells, validated by Western blot analysis, and prosurvival effects in Rhiz-treated PCa cells, suggesting a possible resistance mechanism.[321,322] In addition, heliclonadiamines (HCA), which are made from the marine sponge *Haliclona* spp. ethanol extracts, have a substantial cytotoxic effect on PC-3 cells, at 100 M with 50 % viability.[323] HCA treatment inhibited PRL-3 cell upregulation, enhanced E-cadherin expression, and suppressed N-cadherin expression, while Latrunculin A, a macrolide from *Negombata magnifica*, showed anti-invasive properties against PC-3 cells.[324] Halichondramide is a trisoxazole-containing macrolide that affects the transcriptional and translational levels of PCa indicators such MMP2, E-cadherin, MMP9, and N-cadherin 321. PCa biomarkers that show the epithelial to EMT represent the metastatic potential of the disease.[323] A macrocyclic lactone from *Spongia* sp. has been found to trigger cell death and apoptosis in DU-145 cells without the need for caspases.[325] Spongistatin 1 targets microtubular complex and MCL-1 to upregulate BIM, a pro-apoptotic BCL-2 family member in PCa, regulating Apoptotic signaling pathways.[323] Under hypoxic conditions, furospinosulin-1, a furanosesterterpene derived from marine sponges, inhibits the proliferation of DU-145 cells.[326] By deactivating HIF-1, sodwanone and yardenones generated by *Axinella* sp. inhibited PC-3 cells.[327] Niphatenone B, a natural chemical from *Niphates digitalis*, induces castration-recurrent PCa by promoting LNCaP cell proliferation, preventing AR assistance for specific targets, and binding to AR N-terminus domain activators.[328] Ultimately, Agelasine B was separated using *Agelas clathrodes* is a marine sponge. PC-3 cells have been demonstrated to have a high viability rate. It promotes DNA breakage and significantly reduces the Ca^{2+} concentration in these cells.[326]

8.4. Marine Diatoms

Diatoms have few natural bioactive chemicals, but Fucoxanthin, a marine substance found in Sargassum sp., is used to treat PCa by inhibiting LNCaP cells.[329] Fucoxanthin, a naturally occurring compound, has been shown to be generally safe in treating PCa by inhibiting the growth of GADD45A and G1 cells.[330] White Leghorn fed brown seaweed F. serratus deacetylated fucoxanthin in intestinal lumen, transmitting it via circulation, resulting in fucoxanthinol, a major carotenoids found in egg yolks.[331] In a study on the biotransformation of fucoxanthinol in ICR mice, Asai et al found an unknown metabolite in the marine tunicate Amaroucium pliciferum that had previously been identified as amarouciaxanthin A. Fucoxanthin, fucoxanthinol, and amarouciaxanthin A had 50 % inhibitory doses of 3.0, 2.0, and 4.6 μM,[332] respectively, and Fucoxanthinol with amarouciaxanthin are both antioxidants. PC-3 cell viability was lowered. However, there is a scarcity of research on the subject.

8.5. Holothurians

Holothurians (sea cucumbers) are marine crustaceans that have been utilized for thousands of years in traditional Asian medicine.[333] Frondoside A (FrA) is a triterpene glycoside found in an extract of the edible sea cucumber *Cucumaria frondosa.* In human PCa cells, including cell types resistant to current therapy, the FrA molecule exhibited high efficacy and low toxicity. It has a one-of-a-kind set of features, including apoptosis induction, cell cycle arrest, pro-survival autophagy regulation, and immunological modulatory effects.[334] 12-MTA suppressed PCa cell proliferation and induced apoptosis in PC-3 cells, potentially providing a unique complementary therapy for PCa by preventing 5-HETE synthesis[251]

8.6. Cyanobacteria

Cyanobacterium, a diverse bacterial phylum, was found in the marine cyanobacteria *Nostoc* spp., which produces an anticancer chemical called Cryptophycin 52.[252] A novel cyclic depsipeptide was discovered in *L. majuscula*, a marine cyanobacterium from Singapore's Pulau Hantu Besar. PC3 cells were tested with Lagunamide C, which has an IC50 of 2.6 nM. It has anti-malarial effects as well.[334] *Dolabella auricularia* is a bacterial species that produces cytotoxic peptides, including Dolastatin 10 and its synthetic analogs, which cause cell cycle arrest during the G2/M phase.[335] Marine cyanobacteria compounds, such as C-phycocyanin, have anticancer effects. Combining 10 % of topotecan with C-PC was found to be more effective in killing cancer cells, with enhanced caspase-9 and caspase-3 activity observed.[336] The BCL-2 protein family is a crucial regulator in PCa that can cause apoptosis or cell death. Cryptophycin 52 increases phosphorylation of BCL-2 and BCL-xL in a number of PCa cell lines, including DU-145, PC-3, and LNCaP.[337] Iejimalide B is active in LNCaP and PC-3 cell lines at nanomolar doses, but its effects vary significantly, with less than 30 nM causing cell cycle arrest.[338]

9. Numerous molecules play a role in the beginning or progression of PCa to CRPC

Many molecules have been implicated in the initiation or progression of PCa to CRPC, and many of these can be inhibited in vivo (Fig. 3). Understanding that not all cell-specific Myc targets are created equal could lead to the discovery of sites that effectively limit Myc activity in PCa initiation.[339] Overall, our understanding of PCa progression to CRPC much outnumbers our understanding of disease etiology. It is certain that PCa treatments will gradually transition to ward precision medicine as whole genome sequencing becomes more common. The ability to pinpoint which mutations and genetic abnormalities are present in a patient's tumor could pave the path for more efficient CRPC treatment. Technological advancements require understanding vast data to develop effective treatments for PCa. Whole genome research can widen the molecular spectrum, but complete understanding of biological circumstances and mutational cross-talk is impossible.[340]

10. Conclusion and future perspectives

Using phytochemicals to treat PCa has a number of advantages. Natural products, for starters, are frequently safe, well-liked, and cost-effective. In vivo and in vitro, they have anti-tumor features such as growth anti-invasive, suppression, pro-death, as well as anti-angiogenic effects. However, nutraceutical intake has been linked to chemoprevention and PSA reduction rather than tumor eradication, suggesting that these potential pleiotropic effects in PCa patients have only been partially verified. As a result, more clinical trials targeted at confirming nutraceutical efficacy in humans are directly required.[341] Academics in the US and worldwide have recognized the resistance of marine chemicals

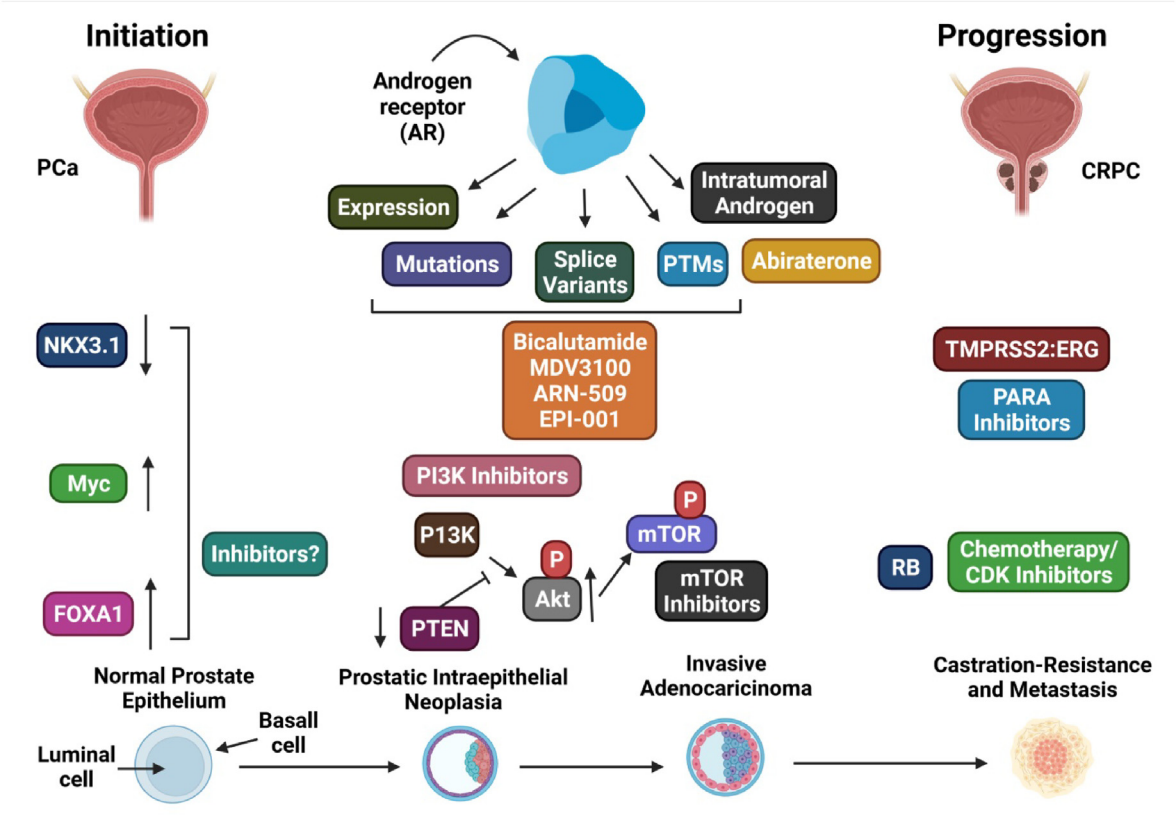

Fig. 3. Molecules linked to the onset and progression of PCa. Several signaling pathways are deregulated with the onset of PCa and progression to castration resistant PCa.

against PCa. The direct effects of marine chemicals on tumor cells through enhancing host immune function are being investigated in the investigation of anti- PCa effects of marine compounds. To summarize, marine chemicals offer a lot of potential as anticancer drugs. PCa has become more prevalent in recent years. Medicinal compounds from land-grown animals and plants face challenges in collection due to duplicates and resource competition, especially for endangered species. Marine sources could help with PCa research. However, very little research has been done on this subject. The species used to assess the anticancer properties of marine compounds are a small part of the ocean's millions of species. There is a lot of maritime flora in nature, and it has been used to extract various anticancer bioactive compounds.[231] This study looked at a number of sea-derived bioactive natural compounds and molecules that have been linked to PCa. Both natural and marine chemicals have the potential to improve PCa patients' quality of life. To develop novel anti-PCa therapies, more study on these substances is required.

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Declaration of competing interest

The authors declare that there are no conflicts of interest.

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