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Prostate cancer: Therapeutic prospect with herbal medicine

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ABSTRACT

Prostate cancer (PCa) is a major cause of morbidity and mortality in men worldwide. A geographic variation on the burden of the disease suggested that the environment, genetic makeup, lifestyle, and food habits modulate one's susceptibility to the disease. Although it has been generally thought to be an older age disease, and awareness and timely execution of screening programs have managed to contain the disease in the older population over the last decades, the incidence is still increasing in the population younger than 50. Existing treatment is efficient for PCa that is localized and responsive to androgen. However, the androgen resistant and metastatic PCa are challenging to treat. Conventional radiation and chemotherapies are associated with severe side effects in addition to being exorbitantly expensive. Many isolated phytochemicals and extracts of plants used in traditional medicine are known for their safety and diverse healing properties, including many with varying levels of anti-PCa activities. Many of the phytochemicals discussed here, as shown by many laboratories, inhibit tumor cell growth and proliferation by interfering with the components in the pathways responsible for the enhanced proliferation, metabolism, angiogenesis, invasion, and metastasis in the prostate cells while upregulating the mechanisms of cell death and cell cycle arrest. Notably, many of these agents simultaneously target multiple cellular pathways. We analyzed the available literature and provided an update on this issue in this review article.

1. Introduction

Prostate cancer (PCa) is the second most common type of non-skin solid cancer next to lung cancer and the fifth leading cause of cancer related death in men. PCa mostly affects the population above 55 years. Men over 65 years are predisposed by 65% to the disease, which is 25% in men older than 75 (Fitzpatrick, 2008). Individuals with a family history are at a higher risk of the disease. Lifestyle and westernized diet rich in red or processed meat, sugar, fatty dairy products, refined grains, and fewer fruits and vegetables correlate well with their increased susceptibility to the disease (Torricelli et al., 2011; Attard et al., 2016). It is thought that the western diet does not itself cause the disease rather somewhat lacks the protective property of its counterpart of Southeast and East Asian countries where the PCa incidence is the least in the world (Torricelli et al., 2011; Adlercreutz, 2002; Chan et al., 1998a).

Current treatment strategies for PCa include active surveillance at the initial stages, followed by surgery and androgen deprivation therapy (ADT). Androgen that plays a vital role in the development and normal

functioning of the prostate, has also been implicated in the initiation and growth of PCa about eight decades ago (Huggins and Hodges, 1941). PCa, although responds to ADT in the beginning, acquires androgen independence or castration resistance in subsequent 2 years, indicating a poor prognosis which is then treated with chemotherapy and other adjuvant therapies (Nurgali et al., 2018; de Gonzalez et al., 2013; Pearce, 2017). Despite significant progress with the existing PCa therapy, toxicity towards healthy normal cells, or non-specificity of these treatments remained a crucial constraint for treating PCa patients. Therefore, formulating an alternative therapy regimen to kill the PCa cells in a targeted manner requires an urgent attention. Herbal medicines have gained very high popularity since the early civilization because of their effectiveness against various ailments, including cancer. Research by various independent groups suggests the enormous potential of various plant extracts used in traditional and folk medicine and phytochemicals thereof with a novel mode of action as a potential remedy for deadly diseases like PCa (Cragg and Newman, 2013; Seca and Pinto, 2018).

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Abbreviations

17/3βHSD	17/3β-hydroxysteroid dehydrogenase	MLH1	MutL homolog 1
AP1	Activator protein 1	MMP2/9	Matrix metalloproteinase 2/9
ATM	ATM serine/threonine kinase	MSH2/6	Mut S homolog 2/6
ATP	Adenosine tri phosphate	PALB2	Partner and localizer of BRCA2
CCND1	Cyclin D1	PDCD4	Programmed cell death protein 4
CD147	Cluster of differentiation 147	PMS2	PMS1 homolog2, mismatch repair system component
CHEK2	Check point kinase 2	R1881	Metribolone
ELAC2	Zinc phosphodiesterase ELAC protein 2	RAD51D	Rad51 paralog D
ER-α	Estrogen receptor alpha	RNASEL	Ribonuclease 1
ETV3	ETS variant transcription factor 3	S1P	Sphingosine -1-phosphatate
GSH	Reduced glutathione	SCID	Severe combined immune deficient mice
HMGCoA	3 hydroxy-3-methyl-glutaryl-coenzyme A reductase	SMAD-3	Mothers against decapentaplegic homolog 3
HOXB13	Homeobox B13	SPHK1	Sphingosine kinase 1
IL1/6/8	Interleukine 1/6/8	StAR	Steroidogenic acute regulatory protein
KMT2D	Histone-lysine N-methyl transferase 2D	TGFβ-R1	Transforming growth factor β receptor type 1
MAO-A	Monoamine oxidase-A	TIMP2/3	Tissue inhibitor of metalloproteinases 2
		TP53	Tumor protein 53
		ZFHX3	Zinc finger Homeobox 3

1.1. Epidemiology

Globally, PCa is the second most common in incidence and the fifth-most leading cause of cancer-associated deaths in men. There were 1.276 million cases with 0.359 million deaths in 2018. It is the fourth most commonly diagnosed cancer after lung, breast, and colon in incidence, and the eight most trending causes of death in men and women combined (Bray et al., 2018). If the current trend continues, global PCa cases will rise to 2.2938 million in 2040. Although PCa is the most frequently diagnosed cancer in more than 50% (105 of 185) countries in the world, death due to PCa is the highest in Southern Africa (26.4%), followed by the Caribbean (25.4%) and middle Africa (22.4%). In both the UK and the USA, PCa is the most frequently occurring cancer in men (Bray et al., 2018; Ferlay et al., 2019).

1.2. Etiology

Men beyond the age of 50 are at a higher risk; six out of ten men older than 65 are affected by PCa. Race, ethnicity, and geographic variation can influence one's predisposition to PCa. African-American, African-Caribbean are more prone to develop PCa than Asian-American or Hispanic/Latino men. Developed countries like North America, North-Western Europe, Australia, and New Zealand carry a higher PCa burden. Autopsy results of PCa patients had revealed the highest incidence of PCa in African people (Gleason score 8+) with the lowest incidence encountered in the Asian people (Jalloh et al., 2013; Rebbeck and Haas, 2014; Rebbeck, 2017). Prostate-specific antigen levels (PSA) are significantly higher in African black men than white men (Vijayakumar et al., 1998). Genome-wide association study (GWAS), family-based study, and candidate gene association studies have identified multiple susceptibility markers with PCa. Chromosomes 8q24, 12q24, and 1q24-25 were shown to carry higher risk PCa loci (Cheng et al., 2008; Kote-Jarai et al., 2011; Gudmundsson et al., 2007; Yeager et al., 2007; Benafif and Eeles, 2016). Mutation in *ZFHX3*, *TP53*, and focal deletion in *ETV3*, and *MYC* amplification were associated with higher PCa death in African-American men. Truncation in *KMT2D* and amplification in *CCND1* associate with primary and localized PCa in African-American men (Koga et al., 2020). Stress and consumption of an imbalanced diet act as critical risk factors for PCa (Chan and Giovannucci, 2001; Chan et al., 1998b; Giovannucci et al., 1998; Kolonel, 2001; Wolk, 2005).

Mounting evidence suggests a positive association between obesity and PCa (Calle et al., 2003; Allott et al., 2013). Altered levels of several hormones linked with obesity, such as higher estradiol levels, insulin,

free insulin-like growth factor-1 (IGF-1), leptin, and a lower level of free testosterone and adiponectin add to an aggressive form of PCa (Chan et al., 1998b; Bosland, 2000; Price et al., 2012; Roberts et al., 2010; Buschemeyer and Freedland, 2007; Schnoeller et al., 2013). The meta-analysis revealed that 5–10% of the PCa had inherited genetic background (Watkins Bruner et al., 2003; Gallagher and Fleshner, 1998; Madersbacher et al., 2011). A person is at a higher risk of getting PCa if his father or brother has PCa. PCa is one of the several cancers having a high hereditary link (Lichtenstein et al., 2000). Mutations in breast cancer susceptibility gene 1 (*BRCA1*) and breast cancer susceptibility gene 2 (*BRCA2*) predispose one to a higher risk of developing PCa (Castro and Eeles, 2012; Nombela et al., 2019). DNA damage repair genes such as *CHEK2*, *ATM*, *PALB2*, and *RAD51D* can account for some of the hereditary PCa (Pritchard et al., 2016). Abnormality in DNA mismatch repair genes such as *MSH2*, *MSH6*, *MLH1*, and *PMS2* (Albero-González et al., 2019; Nghiem et al., 2016) and tumor suppressor gene *RNASEL* (Xiang et al., 2003) are associated with heritable PCa (Malathi et al., 2007; Zhou et al., 1997; Rawla, 2019). Mutations in *ELAC2* that support proliferation through the TGF-β signaling pathway, and *HOXB13* an essential gene in prostate gland development, were implicated in hereditary PCa (Meyer et al., 2010; Noda et al., 2006). A small deletion mutation in the Xq26.3-q27.3 of the X chromosome carrying the androgen receptor (AR) gene has been linked with inherited PCa (Xu et al., 1998; Bergthorsson et al., 2000).

Alteration of AR gene expression due to amplification of AR gene, over production of androgen, and AR splice variants, and or its coregulator associate with AR therapy resistance/castration resistance prostate cancer (CRPC). Apart from AR, other cellular pathways such as the WNT signaling pathway play a critical role particularly in the late or advanced stage of PCa such as CRPC (Murillo-Garzón and Kypta, 2017). WNT pathway is deregulated in about a third of PCa (Chesire et al., 2000). Deregulation of both canonical and noncanonical WNT signaling pathways has been shown to be involved in PCa pathogenesis. Canonical WNT pathway (β-catenin dependent) functions through stabilization of β-catenin and subsequent activation of target genes involving β-catenin-TCF/LEF1 transcription complexes (Komiya and Habas, 2008). The noncanonical WNT pathway (β-catenin-independent) which is of two subtypes, the planar cell polarity and WNT/Ca²⁺ pathway were associated with the advanced stage of CRPC regulating genes involved in cell adhesion and migration, cell survival, and angiogenesis (Van Amerongen, 2012). In the canonical pathway, stabilization of β-catenin in the cytoplasm and nuclear translocation is controlled by tight regulation of function of the components of destruction complex composed of adenomatous polyposis coli (APC), glycogen synthase kinase 3 (GSK-3), casein

kinase 1 (CK1), and Axin. Activating mutation of the β -catenin encoding gene CTNNB1 and inactivating mutation in APC and Axin gene associate with many CRPC (Beltran et al., 2013; Grasso et al., 2012). Upregulation of LEF1 gene, a target of β -catenin-TCF-LEF1 transcription complex associates with CRPC. LEF1 correlated with malignant transformation and metastasis of PCa is also a target of ETS-regulated gene (ERG) which is upregulated in about half of PCa (Wu et al., 2013; Bauman et al., 2016). AR overexpression potentiated the expression of WNT- β -catenin target genes involved in PCa metastasis due to its ability to function as a partner of β -catenin-TCF-LEF1 transcription complex driving expression of genes involved in metastasis, although cooperation with β -catenin depends on the activation status of AR (Lee et al., 2015, 2016). Usually, WNT deregulated PCa cells become invasive when they acquire additional genomic changes (Francis, 2013). Evidence demonstrated WNT signaling pathway in immune evasion of PCa cells as well (Wu et al., 2013; Francis, 2013; Linch et al., 2017; Wang et al., 2018). Depending on the context, AR can also repress the expression of LEF1 and Axin2 genes (Lee et al., 2016).

Deregulation of upstream regulators i.e., the WNT ligands was also linked with PCa pathogenesis; WNT-1 is upregulated in primary and advanced PCa (Chen et al., 2004). Several WNT ligands associated with noncanonical WNT signaling pathways such as WNT-5A and WNT11 have been implicated in PCa invasiveness and resistance to ADT (Zhang et al., 2013; Volante et al., 2016; Rajan et al., 2014). Deregulation of secretory factors that normally antagonize functions of WNT ligands or WNT signaling components on cell membrane such as frizzled (FZD) have also been demonstrated to influence PCa with some linked with drug resistance (Murillo-Garzón and Kypta, 2017; Pashirzad et al., 2017). It is to be noted however that usually, WNT deregulation requires in combination with another genomic defect progression Downregulation of secreted frizzled-related proteins (sFRPs), Dickkopf-related proteins (DKKs), and WNT1 or increased expression of these inhibitors appeared to play a complex and context-dependent role, for example, a high level of Dickkopf-related proteins 1 (DKK1) was linked with poor treatment outcome (Rachner et al., 2014). Several studies demonstrated the critical roles of the tumor microenvironment (which secrete WNT ligands) in the growth of PCa including many other types of cancer (Hanahan and Weinberg, 2011). A few of the WNT family members secreted by the stromal cells were shown to be involved in tumor initiation, progression, and drug resistance of PCa (Murillo-Garzón and Kypta, 2017).

Like many other cancers and diseases, chronic inflammation is a driver of PCa (Stallone et al., 2014). In general, chronic inflammation is the underlying cause of more than 20% of cancers (De Marzo et al., 2007; Sfanos and De Marzo, 2012; Gurel et al., 2014; Mani et al., 2016; Kwon et al., 2014; Pal et al., 2014; Calcinotto et al., 2018), and close to 80% of prostate biopsy samples indicated the signatures of inflammation (Sfanos and De Marzo, 2012; Andriole et al., 2010; Banerjee et al., 2019). For example, imbalance in gut microbiome structure was linked with PCa (Liss et al., 2018; Sfanos et al., 2018; Golombos et al., 2018; Poutahidis, 2013). Chronic bacterial infection in the prostate results in the inactivation of the tumor suppressor, a homeobox protein NKX3.1 that plays an important regulatory role in DNA repair (Khalili et al., 2010; Bowen and Gelmann, 2010). Inflammatory cells secrete ROS with simultaneous incapacitation of DNA damage repair enzymes. For example, under chronic inflammation, AR signaling induces DNA damage through the recruitment of DNA topoisomerase 2 β with simultaneous inactivation of DNA damage repair genes (de Bono et al., 2020).

2. Current treatment available for prostate cancer

General awareness and timely screening have significantly added to the survival of PCa. Localized PCa (Gleason score <6) in general has a good prognosis. PCa that has attained metastatic state, however, carries a poor prognosis with significantly reduced survival. In this condition, resection surgery, ADT, and radiation alone or in combination are standard treatment options; castration resistance, a more aggressive form of

PCa (Gleason score >7), invariably develops resistance to these treatments within 2 years (Giacinti et al., 2014; Rice et al., 2019). These advanced treatments increase the median failure-free survival (FFS) to 11 months with 29% 2 years FFS, and median overall survival (OS) to 42 months with 2 years OS of 72% (James et al., 2015).

Several androgen inhibitors, such as enzalutamide, apalutamide, abiraterone, or orteronel, along with radiation or chemotherapy, are in use in the treatment regimens (Teply and Antonarakis, 2016). Radiotherapies such as intensity-modulated radiation therapy (IMRT), conformal radiation therapy (CRT), and proton beam radiation therapy help to treat PCa with high efficacy (Yu, 2016; Fischer-Valuck et al., 2017). Docetaxel and cabazitaxel administration improved survival (Oudard et al., 2017). Besides these, immunotherapy with cytotoxic T-cell activators sipuleucel-T, pembrolizumab, nivolumab, and atezolizumab lead to improved overall patients survival (De Velasco et al., 2017). PARP inhibitors such as olaparib, rucaparib, and niraparib are now being studied in detail for developing more efficient PCa drugs (Mateo et al., 2015; Abida et al., 2018; Subudhi, 2019). Despite notable advancements in therapeutic strategies, and recurrences of the disease are often observed (Nurgali et al., 2018; de Gonzalez et al., 2013; Carelle et al., 2002; Chow and Gandhi, 2017). Nevertheless, current treatments associate with toxic side effects on the healthy normal tissues underscoring an immediate need to find an alternate and more targeted therapy. In fact, many independent laboratories from different parts of the world have highlighted anticancer activities with unique mechanisms of action in phytochemicals isolated from different plants used in traditional and folk medicines.

3. Importance of natural products in prostate cancer therapy

PCa epidemiology indicated the geographical variation of the disease incidence and the critical role of diet and nutrients besides the role of genetic factors; there is a relatively lower incidence of the disease in Asia than in the western population. Asians adopting western lifestyles are at a higher risk of getting PCa suggesting the protective role of diets/nutrients of Asian countries on the disease (Torricelli et al., 2011). Notably, many phytochemicals and solvent extracts of plants used in the traditional medicine in India and China showed selective toxicity towards PCa tested in cell and animal-based experiments with minimal toxicity to normal cells, suggesting promising therapeutic potential against the disease (Harvey and Cree, 2010). We reviewed here briefly the activities of phytochemicals which are relatively well studied by listing their clinical trials in a table (Table 1, Fig. 1). Studies on the phytochemicals that were relatively less studied were summarized in tabular form (Table 2). There are solvent extracts prepared off various plants with noticeable anti-PCa cancer activities in the preclinical experimental models are also described here briefly (Table 3). Fig. 1 and Fig. 2 summarised the discussed activities and structures of the phytochemicals respectively. Only phytochemicals tested in both cell and preclinical animal models are considered in this review.

3.1. Apigenin

Apigenin is a dietary flavonoid present in *Anthemis* sp. (Asteraceae) and many other plants with various medicinal properties such as antioxidant, anti-inflammatory, antiviral, neuroprotective, anticancer, and anti-metastatic properties with negligible toxicity to normal cells. It showed anticancer activity against different cancers, including PCa. It inhibited SPOCK1 (SPARC (Osteonectin), Cwcv And Kazal Like Domains Proteoglycan 1) expression and thus SPOCK1-induced expression of mesenchymal markers in different PCa cells, and there by PC3 induced xenograft tumor growth, proliferation, invasion, and metastasis (Chien et al., 2019). It inhibited p-Akt (S473), p-GSK3 β , and p-BAD activities, expression, and autophosphorylation of IGFR and induced apoptotic cell death in vitro and in vivo (Kaur et al., 2008). Apigenin reduced PCa tumor growth and metastasis via targeting PI3K/Akt/FOXO signaling

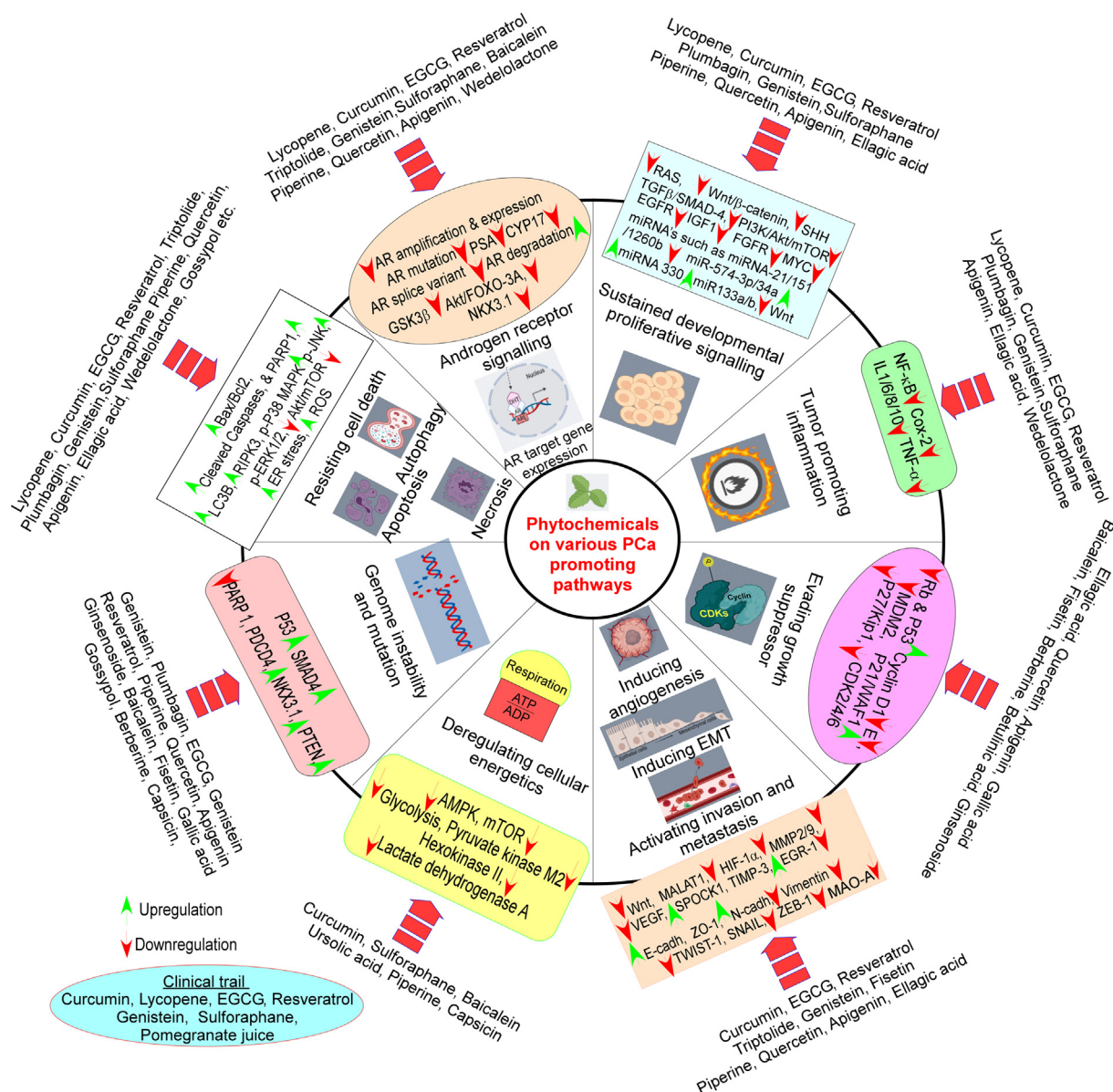


Fig. 1. Mechanism of action of indicated phytochemicals on different cancer-promoting pathways. Abbreviations: AR, androgen receptor; PSA, prostate specific antigen; CYP17, cytochrome P450 17 α -hydroxylase/17,20-lyase; GSK3 β , glycogen synthase kinase 3 beta; Akt, protein kinase B; FOXO-3A, forkhead box O-3A; NKX3.1, NK3 homeobox 1; EGCG, epigallocatechin gallate; Wnt, wingless-related integration site; SHH, sonic hedgehog; TGF β , transforming growth factor beta; SMAD-4, mothers against decapentaplegic homolog-4; PI3K, Phosphoinositide-3-kinase; mTOR, mammalian target of rapamycin; EGFR, epidermal growth factor receptor; IGF-1, insulin like growth factor-1; FGFR, fibroblast growth factor receptor; MYC, myelogenous cyto; miRNA, micro ribonucleic acid; NF- κ B, nuclear factor kappa light chain enhancer of activated B cells; COX-2, cyclooxygenase-2; IL1/6/8/10, interleukin 1/6/8/10; TNF- α , tumor necrosis factor- α ; Rb, retinoblastoma protein; MDM2, mouse double minute 2 homolog; CDK2/4/6, cyclin dependent kinase 2/4/6; MALAT1, metastasis associated lung adenocarcinoma transcript 1; HIF-1 α , hypoxia-inducible factor 1-alpha; MMP2/9, matrix metalloproteinase-2/9; VEGF, vascular endothelial growth factor; SPOCK1, (SPARC (Osteonectin), Cwcv And Kazal Like Domains Proteoglycan 1); TIMP-3, tissue inhibitor of metalloproteinases-3; EGR-1, early growth response protein-1; E-cadherin, E-cadherin, N-cadherin, N-cadherin; ZO-1, zonula occludens protein 1; TWIST-1, TWIST related protein-1; ZEB-1, zinc finger E-box binding homeobox 1; MAO-A, monoamine oxidase-A; AMPK, AMP-activated protein kinase; PARP 1, Poly [ADP-ribose] polymerase 1; PDCD4, programmed cell death protein 4; PTEN, phosphatase and tensin homolog; Bcl2, B cell lymphoma-2; Bax, Bcl-2 associated X-protein; LC3B, microtubule-associated protein 1A/1B-light chain 3; RIPK3, Receptor-interacting serine/threonine-protein kinase 3; MAPK, mitogen-activated protein kinases; p-JNK, phospho-c-Jun N-terminal kinase; p-ERK1/2, extracellular signal-regulated kinase 1/2; ER stress, endoplasmic reticulum stress; ROS, reactive oxygen species.

pathway. It was shown to induce cell cycle arrest at G0/G1 phase, to upregulate BIM and p27/Kip1 levels along with inhibition of cMyc expression and β -catenin signaling (Shukla et al., 2014; Shukla and Gupta, 2008). Apigenin inhibited PCa cell growth through modulating the cell cycle via increased expression of Waf1/p21, Kip1/p27, INK4a/p16, and INK4c/p18, and downregulation of cyclins D1, D2, E and Cdk2, Cdk4, and Cdk6, and Retinoblastoma protein phosphorylation (S780). It enhanced the binding of cyclin D1 to Waf1/p21 and Kip1/p27

by reducing the binding of cyclin E with Cdk2 in both 22Rv1, PC3 cell-induced xenograft tumor. Apigenin helped stabilize p53 activity by phosphorylation at serine 15 in 22Rv1 cell induced tumors (Shukla and Gupta, 2006), and ROS generation and p53-dependent apoptosis in vitro and in vivo, and potentiated p14^{ARF}-mediated downregulation of MDM2 protein accompanied by inhibition of NF- κ B/p65 function (Shukla and Gupta, 2008).

Apigenin blocked cell proliferation in vitro and in vivo, modulated

Table 1
List of phytochemicals undergone clinical trials for PCa therapy.

Kind of supplement/ Compound	Type of study	No. of patients and time period	Outcome	Reference
CURCUMIN				
Curcumin	A randomized, double-blind, placebo-controlled trial in patients who received intermittent androgen deprivation (IAD).	n = 97, oral Curcumin (1440 mg/day) or placebo for six months	Curcumin intake did not significantly change the overall off-treatment duration of IAD but PSA enhancement was suppressed. Curcumin was safe and well tolerated by patients.	Choi et al. (2019)
Curcumin	A double-blinded, randomized, placebo-controlled study in patients during radiotherapy	n = 40, Curcumin (total 3 g/day) or placebo during external-beam radiation therapy of up to 74 Gy for 3 months	Curcumin intake significantly increased total antioxidant capacity, with a reduction in SOD activity. PSA level was lowered in both the groups but nonsignificant differences in treatment outcomes between the groups.	Hejazi et al. (2016)
Curcumin	A pilot clinical trial in patients during radiotherapy	n = 40, 3 g/d Curcumin (6 × 500 mg capsules, n = 20), or placebo group (n = 20) during external-beam radiation therapy for 20 weeks	Curcumin intake provided radioprotection by reducing the severity of radiotherapy-related urinary symptoms. But did not reduce the intensity of bowel and other treatment related symptoms.	Hejazi et al. (2013)
LYCOPENE				
Fruit juice containing lycopene	In vivo double-blind placebo-controlled matched study	n = 60, a daily supplement for 28 days	Serum antioxidant, folate and, lycopene level were increased while oxidative stress markers and homocysteine levels were decreased	Kawashima et al. (2007)
Lycopene tablet	A phase II randomized clinical trial before radical prostatectomy	n = 26, 15 mg Lycopene tablet twice a day for 3 weeks	Decreased PSA, IGF-1, and connexin-43 level with a reduction in chance and growth of PCa	Kucuk et al. (2001)
Lycopene with green tea catechins	A phase II randomized placebo-controlled trial	n = 133, daily green tea drink (3 cups, unblinded) or capsules [blinded, 600 mg flavan-3-ol (-)-Epigallocatechin-3-gallate (EGCG) or placebo] and Lycopene-rich foods (unblinded) or capsules (blinded, 15 mg Lycopene or placebo) for 6 months	Reduced PCa risk. Lycopene and EGCG concentration was increased in men having an increased risk of PCa.	Lane et al. (2018)
Lycopene	A human intervention trial	n = 23, 40 mg Lycopene for 2 weeks	Showed cancer-preventive potential through the reduction in oxidative and other DNA damages.	Pool-Zobel et al. (1997)
Lycopene	An unblinded, randomized, Phase I clinical trial	n = 61, 30 mg Lycopene with a multivitamin	Increased serum level of Lycopene with reduced PSA level.	Bunker et al. (2007)
Lycopene	A phase II randomized trial among men with high-grade prostatic intraepithelial neoplasia (HGPIN)	n = 58, 30 mg Lycopene for 6 months	No significant change in serum PSA, IGF-1/3, MCM-2, and p27 levels. People in the Lycopene group had more extensive atrophy and less extensive HGPIN.	Gann et al. (2015)
Lycopene and green tea	The Pro-diet randomized controlled trial	n = 133, daily Lycopene (n = 44 assigned 15 mg capsules/day; 44 assigned a Lycopene-rich diet; 45 assigned placebo) and green tea (n = 45 assigned 600 mg/day epigallocatechin gallate; 45 assigned green tea drink; 43 assigned placebo) for 6 months	Serum Lycopene and EGCG level increased with a little reduction in serum IGF-1/2, IGFBP-2/3 level.	Biernacka et al. (2019)
Lycopene with tomato sauce	A randomized placebo-controlled study with a nonrandomized 5th arm study	n = 32, daily 30 mg Lycopene containing tomato sauce for 3 weeks before radical prostatectomy.	Serum and prostate Lycopene levels were increased with a concomitant decrease in PSA and Leukocyte DNA S-OH deoxyguanosine/deoxyguanosine (SOHdG) level. Reduced DNA damage with high apoptotic index in hyperplastic and neoplastic cells.	Bowen et al. (2002)
Lycopene and soy isoflavone	A phase II clinical trial	n = 71, 15 mg capsule of Lycopene alone or a capsule of Lycopene in combination with 40 mg of soy isoflavone twice daily for 6 months	Lycopene and combinatorial treatment with soy isoflavone did not reduce PSA level instead stabilized its level in the patient's serum. Both can delay the progression of hormone-refractory and hormone-sensitive PCa but did not have an additive effect.	Vaishampayan et al. (2007)
Lycopene	Phase I-II trial relapsed PCa patients	n = 36, Lycopene 15, 30, 45, 60, 90, and 120 mg/day for 1 year	Decreased serum PSA level with an increase in serum Lycopene level	Clark et al. (2006)
POLYPHENOLS FROM TEA				
Green tea, black tea	Randomized Phase II clinical trial	n = 113, 6 cups/day for 3–8 weeks before radical prostatectomy	Modulation of NF-κB in radical prostatectomy tissue, urinary 8-OHdG, and serum PSA levels were significantly decreased mainly in green tea, but not in the black tea group.	Henning et al. (2015)
Green tea	In men with clinically localized PCa	n = 17, 6 cups/day for 3–8 weeks	(-)-Epigallocatechin and (-)-Epicatechin were present in methylated form within prostatectomy tissue and this methylated	Wang et al. (2010)

(continued on next page)

Table 1 (continued)

Kind of supplement/Compound	Type of study	No. of patients and time period	Outcome	Reference
Polyphenon E (PolyE)	A placebo-controlled, randomized clinical trial in men with high-grade prostatic intraepithelial neoplasia (HGPIN) and/or atypical small acinar proliferation (ASAP)	n = 97, 400 mg EGCG for 1 year	EGCG may efficiently modulate its preventive effect on PCa. Serum PSA level was decreased followed by accumulation of EGCG in plasma and was well tolerated in patients	Kumar et al. (2015)
Tea polyphenols polyphenon E (PolyE)	Short term supplementation study in PCa patients	n = 26, 800 mg EGCG, and lesser amounts of (-)-Epicatechin, (-)-Epigallocatechin, and (-)-Epicatechin-3-gallate (a total of 1.3 g of tea polyphenols) daily until radical prostatectomy	Decrease in serum PSA level, hepatocyte growth factor, and VEGF in PCa patients was observed with no increase in liver enzymes.	McLarty et al. (2009)
Polyphenon E	A randomized, double-blind, placebo-controlled trial in patients scheduled for radical prostatectomy.	n = 50, 800 mg EGCG or placebo daily for 3–6 weeks	Low accumulation of EGCG in the prostate tissue, favorable though insignificant changes in PSA, IGF, and oxidative DNA damage in blood leukocytes.	Nguyen et al. (2012)
POMEGRANATE JUICE				
Pomegranate juice	A phase II, Simon two-stage clinical trial for men with rising PSA after surgery or radiotherapy	n = 46, daily 8 ounces of pomegranate 570 mg total polyphenol gallic acid equivalents for	Elongation of PSA doubling time was observed in patients without any adversity along with a reduction in cell proliferation, increase in apoptosis, serum nitric oxide and reductions in oxidative state and sensitivity to oxidation of serum lipids in vitro LNCaP cells	Pantuck et al. (2006)
Pomegranate juice (POMx)	A randomized, multi-center, double-blind phase II study	n = 104, daily 1 or 3 g of POMx for 18 months	Prolongation of PSA doubling time (>6) months without adverse side effects.	Paller et al. (2013)
RESVERATROL AND GRAPES				
Resveratrol	A randomized placebo-controlled clinical study	n = 66, two doses of Resveratrol 150 mg or 1000 mg Resveratrol daily for 4 months.	Decreased (at higher dose) serum levels of the androgen precursors like androstenedione, DHEA, and DHEAS, while prostate volume and circulating levels of PSA, testosterone, free testosterone, and dihydrotestosterone were unchanged.	Kjær et al. (2015)
(MPX) Muscadine grape skin extract (<i>Vitis rotundifolia</i>)	A phase I/II Study in patients with recurrent PCa	n = 14, 500–4000 mg for 6.2–29.7 months	A higher dose of MPX is safe but serum PSA level were not reduced from baseline.	Paller et al. (2015)
MuscadinePlus (MPX), a commercial preparation of pulverized muscadine grape skin	A multicenter, placebo-controlled, two-dose, double-blinded trial in men with biochemically recurrent PCa	n = 125, 500 mg MPX (low), or 4000 mg MPX (high) daily or placebo for 12 months	No significant change in the PSA doubling time in the treated (two concentrations) versus the control group. MPX intake did not cause any adverse toxicity to the patients	Paller et al. (2018)
SOY ISOFLAVONES				
Genistein	A phase II placebo-controlled, randomized, double-blind clinical trial with patients before prostatectomy	n = 47, 30 mg Genistein or placebo capsules daily for 3–6 weeks.	A notable reduction in the mRNA level of androgen-related biomarker KLK4, but non-significant reduction in other PCa attributes like androgen and cell cycle. It changed the expression of several biomarkers related to PCa prediction and progression.	Lazarevic et al. (2012)
Soy isoflavone	A double-blinded, randomized, placebo-controlled trial	n = 86, soy isoflavone capsules (80 mg/d of total isoflavones, 51 mg/d aglucon units) for up to six weeks before scheduled prostatectomy	A short-term intervention did not change serum hormone levels, total cholesterol, or PSA but some genes related to cell cycle control and apoptosis were downregulated in the treated tumor tissue.	Hamilton-Reeves et al. (2013)
Isoflavone	A phase II, randomized, double-blind, placebo-controlled trial in men with rising PSA	n = 158, oral isoflavone (60 mg/day) for 12 months	PSA levels did not change significantly but among all 53 patients aged ≥65 years, showed significantly less PCa incidence in the isoflavone group.	Miyayama et al. (2012)
SULFORAPHANE & BROCCOLI				
Sulforaphane	A double-blinded, randomized, placebo-controlled multicenter trial in patients with increasing PSA after radical prostatectomy.	n = 78, daily oral administration of 60 mg of a stabilized free Sulforaphane for 6 months followed by 2 months without treatment (M6–M8).	Caused a significant reduction in log PSA slope and also prolonged the PSA doubling time by 86% compared to the placebo group. Sulforaphane was well-tolerated among patients.	Cipolla et al. (2015)
Sulforaphane-rich broccoli sprout extracts	A phase II study in patients with recurrent PCa	n = 20, 200 μmoles/day of Sulforaphane-rich extracts for a maximum period of 20 weeks	Appeared safe in the patient, prolonged on-treatment PSA doubling time but did not lead to ≥50% PSA declines in the majority of patients.	Alumkal et al. (2015)
Sulforaphane	A phase II single-arm study in patients with recurrent PCa	n = 20, 200 μmol of Sulforaphane extracts for up to 20 weeks per day	Lowered PSA level altogether, with an increase in PSA doubling time (6 months pre-study vs. 9.4 months on-study) and	Alumkal et al. (2013)

(continued on next page)

Table 1 (continued)

Kind of supplement/Compound	Type of study	No. of patients and time period	Outcome	Reference
Broccoli rich diet	A randomized open-label trial in patients with high-grade prostate intraepithelial neoplasia (HGPIN)	n = 22, 400 gm of broccoli/week and 400 gm peas/week for 1 year	without any adverse side effects. It blocked HDAC function. Interacted with glutathione S-transferase mu 1 (GSTM1) and modulated signaling pathways such as TGF- β , Insulin signaling, EGF receptor associated with inflammation and carcinogenesis in the prostate.	Traka et al. (2008)

Abbreviations: PSA, prostate-specific antigen; IGF1/3, insulin-like growth factor 1/3; EGCG, epi galloyl catechin 3 gallate; SOD, superoxide dismutase; CM-2, mini-chromosome maintenance protein complex; IGFBP-2/3, insulin-like growth factor binding proteins; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone-sulphate; KLK4, kallikrein 4; HDAC, histone deacetylases.

IGF/IGF-IR signaling via upregulating IGFBP-3 and p27/Kip1, and inhibiting p-Akt, p-GSK3 β , cyclin D1 (Shukla and Gupta, 2009). Apigenin blocked tumor growth by inducing cell cycle arrest and apoptosis through inhibiting class I HDACs (HDAC1, and -3) activities. It promoted acetylation of H3 and H4 and hyperacetylation of H3 on p21/Waf1 promoter; modulated Bax/Bcl-2 ratio, and increased p21/Waf1 expression in the tumor tissue (Pandey et al., 2012). Apigenin inhibited angiogenesis in tumor tissues by decreasing HIF1- α and VEGF expression (Fang et al., 2007).

3.2. Curcumin

Curcumin, a polyphenolic compound isolated from *Curcuma longa*, has been shown to exhibit many pharmacological properties such as anticancer, anti-inflammatory, antioxidant, neuroprotective, and radioprotective activities (Amalraj et al., 2017). Curcumin exerts its effect by targeting multiple signaling pathways such as AR signaling, NF- κ B-, AP-1-, PI3k/Akt/mTOR-, and Wnt/ β -catenin/TGF- β /MYC pathways (Abd Wahab et al., 2020; Katta et al., 2019). Because of the modulation of different signaling pathways simultaneously, it is not surprising that Curcumin acts as a potent inhibitor of PCa cells. This curcuminoid promotes apoptosis in LNCaP and PC3 cells by suppressing the epidermal growth factor receptor (EGFR) tyrosine kinase activity (Dorai et al., 2000). In DU145 cells, Curcumin could induce apoptosis by down-regulating Bcl2 and upregulating caspase-3 and 8 via TNF activation and inhibition of NF- κ B, protein kinase D (PKD), and β -catenin (Mukhopadhyay et al., 2001; Sundram, 2012). Curcumin was reported to induce NRF2 expression and the cellular antioxidant mechanism by restoring the hypomethylation status of CpG islands on the NRF2 promoter in TRAMP cell (Khor et al., 2011). It showed anti-PCa activity in an AR-dependent way by preventing the Wnt/ β -catenin pathway along with inducing cell cycle arrest at the G2 phase and autophagy (Teiten et al., 2011). Curcumin kills PCa cells by inhibiting glyoxalases, increasing methylglyoxal levels, and decreasing cellular ATP and Glutathione (GSH) levels (Santel, 2008). Furthermore, in a PC3-xenograft model combination of Curcumin with α -tomatine inhibited tumor growth (Huang, 2015). Curcumin was found to inhibit cancer-associated fibroblast formation (CAFs), which mediates tumorigenesis, invasion, metastasis, and EMT in PCa. It ameliorates CAFs associated with ROS generation, IL-6, CXC chemokine receptor-4 (CXCR-4) receptor expression in PC3 cells through down-regulating MAO-A/mTOR/HIF-1 α signaling (Du et al., 2015). Analogs of Curcumin inhibited testosterone and DHT-induced AR activity (Schmidt and Figg, 2016).

In a recent study, Curcumin-loaded lipid nanoparticles have shown significant cytotoxicity in docetaxel-resistant PC3 and DU145 cells (Tanaudommongkon et al., 2020). Lipid polymer hybrid nanoparticles (aptamer-PLGA-PEG) of Curcumin and cabazitaxel have shown enhanced drug delivery, cytotoxicity towards PCa cells in vitro, and in vivo (Chen et al., 2020). Treatment PCa cells with a combination of Curcumin and

metformin resulted in enhanced cytotoxicity and apoptosis (Eslami et al., 2020).

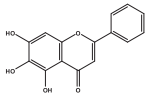
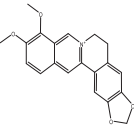
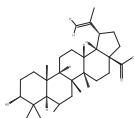
3.3. Epigallocatechin-3-gallate

Epigallocatechin-3-Gallate (EGCG) is a major polyphenolic compound present in green tea *Camellia sinensis*. EGCG carries various pharmacological properties, including anticancer, antioxidant, antidiabetic, cardioprotective, and neuroprotective activities (Chu et al., 2017). EGCG induces apoptosis in PC3 cells when treated alone and in combination with cisplatin, which works through activation of caspase 9 (Hagen et al., 2013). EGCG regresses PCa in TRAMP mice through suppressing AR, IGF-1, and its receptor insulin-like growth factor receptor-1 (IGF-R1) (Harper et al., 2007). From earlier reports, EGCG was shown to induce p53 independent apoptosis in both androgen-dependent (LNCaP) and androgen-independent (DU-145) cells (Gupta et al., 2003). It was reported that EGCG induced cell cycle arrest and apoptosis in LNCaP and DU-145 cells through modulating cyclin kinase inhibitor and cyclin-dependent kinase activities (Gupta et al., 2003). EGCG promoted apoptosis in human PCa cells through activation of p53 and inhibition of NF- κ B by increasing the ratio of Bax/Bcl-2 (Hastak et al., 2003). Besides, EGCG inhibited R1881 induced nuclear localization of AR and its protein expression; it also decreased the androgen-regulated miRNA-21 and elevated the tumor suppressor miRNA-330 in the PCa xenograft model (Siddiqui et al., 2011). EGCG with doxorubicin reduced tumor growth significantly in CB17 SCID mice generated by metastatic PC-3M cells (Stearns et al., 2010). Green tea rich in EGCG combined with quercetin reduced tumor growth induced by androgen-sensitive LAPC-4 cells in the SCID mouse model (Wang et al., 2014a). EGCG reduced testosterone-induced benign prostate hyperplasia and fibrosis in rats through lowering oxidative stress, inflammation, collagen deposition, and angiogenic growth factors. It also blocks the overexpression of HIF-1 α , TGF- β 1, TGF- β RI, AR, ER- α , and p-Smad3 while increasing the levels of ER- β and miR-133a/b (Zhou et al., 2018a). EGCG induced apoptosis in PCa cells and patient tissue samples through activating miR-520a-3p mediated Akt1 downregulation (Zhang et al., 2020a). Vasculogenic mimicry (VM), a process adapted by advanced PCa to forming vessels like networks needed for prostate tumorigenesis and aggressiveness, is restrained by EGCG treatment in PC3 cells through inhibition of vascular endothelial cadherin (VE-cadherin), N-cadherin, twist, vimentin, p-Akt, and Akt (Yeo, 2020). EGCG mediated dysregulation of cellular calcium homeostasis led to apoptotic death in PCa cells (Marchetti et al., 2020).

3.4. Ellagic acid

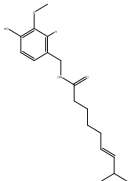
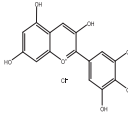
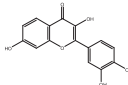
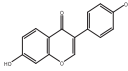
Ellagic acid is a polyphenolic compound found in different fruits and vegetables, like in *Rubus* sp. (Rosaceae), *Vaccinium* sp. (Ericaceae), known for its antioxidant and anticancer properties. It increased

Table 2
List of phytochemicals showing therapeutic promise against PCa in preclinical model.

Compound & chemical nature	Plant name and family	Mechanism of actions	In vitro	In vivo	Combination drug	References
 <p>Baicalein (Flavone)</p>	<i>Scutellariabaicalensis</i> (Lamiaceae)	<p>Inhibited cell cycle regulatory proteins, G0/G1 arrest, CDK6, FOXM1, cyclin B, and Aurora B. Blocked cell proliferation through inducing apoptosis; reduced tumor overload in vivo.</p> <p>Blocked proliferation by inducing cell cycle arrest and apoptosis involving downregulating Ezrin expression. Downregulated cyclin D1, CDK4 while upregulating p53 and p21 levels. Decreased tumor overload in vivo by counteracting Ezrin function.</p> <p>It ameliorated benign prostate hyperplasia (BPH) through androgen-dependent apoptosis. Blocked prostate enlargement, production of DHT, and 5α-reductase activity type II in vivo. Increased Bax/Bcl-2 ratio, caspase-dependent apoptosis (Caspase 3, -8) and p-AMPK level, and reduced AR, PSA, PCNA, and Bcl-2 in vitro</p>	<p>LNCaP, PC3 PC3 NA</p>	<p>LNCaP xenograft PC3 xenograft Chemical (testosterone, DHT) induced BPH</p>	<p>NA NA NA</p>	<p>Yu et al. (2020) (Ma et al., 2020) (Jin and An, 2020)</p>
 <p>Berberine (Isoquinoline alkaloid)</p>	<i>Berberis</i> genus (Berberidaceae)	<p>Inhibits cell growth and induces apoptosis. It decreases transcriptional activity and signaling of AR induces AR protein degradation both in cells and tumor tissue.</p> <p>Metabolomics and network analyses suggested that berberine reversed the abnormality in metabolic biomarker expression by adjusting the perturbed metabolic pathways. Berberine inhibited p38 MAPK signaling to inhibit its downstream pro-oncogenic targets; inhibited tumor burden in vivo through inducing apoptosis.</p> <p>Inhibited benign prostatic hyperplasia induced by testosterone through inhibiting 5 alpha-reductase, AR, steroid coactivator-1 (SRC-1), and ERK signaling.</p> <p>Inhibited proliferation and growth in vitro and in vivo by inducing apoptosis, radio-sensitivity through inhibiting expression of VEGF and HIF1a. Acted in synergy with ionizing radiation.</p> <p>Inhibited tumor growth by facilitating p53 dependent and independent death and growth arrest at G0/G1 phase; enhanced p21 expression while decreasing cyclin D1, E and CDK 4, and -2 expression.</p>	<p>LNCaP, 22Rv1, PC3, LAPC-4 C4-2B 22Rv1 RWPE-1</p> <p>LNCaP, DU145 PC3, LNCaP, PWR1-E</p>	<p>LNCaP grafted tumors 22Rv1 grafted nude mice Male Sprague-Dawley (SD) rats LNCaP grafted Balb/c</p> <p>nude mice PC3, LNCaP grafted Balb/c nude mice</p>	<p>NA NA Ionizing radiation NA</p>	<p>Li et al. (2011) (Li et al., 2017) (Youn et al., 2018) (Zhang et al., 2014) (Choi et al., 2009)</p>
 <p>Betulinic Acid (BA) (Pentacyclic triterpene)</p>	<i>Betula papyrifera</i> (Betulaceae)	<p>Inhibited deubiquitinases to increase the levels of poly-ubiquitinated proteins and apoptosis in ex vivo and in vivo tumor model; lowered the levels of oncoproteins, cyclin D1 and AR protein.</p>	LNCaP, DU145, and PC3	TRAMP mice	NA	Reiner et al. (2013)
	<i>Capsicum</i> genus (Solanaceae)	<p>Oral administration increased the efficacy of radiotherapy and reduced the tumor burden; inhibited colony formation, NF-κB level, and DNA damage.</p> <p>Inhibited cell proliferation synergistically with docetaxel ex</p>	<p>LNCaP, DU145, and PC3 LNCaP, PC3 PC3 PC3, DU145, LNCaP</p>	<p>LNCaP grafted nu/nu athymic nude mice PC3 and LNCaP grafted athymic nude-Foxn1 (nu/nu) mice Transgenic adenocarcinoma of the</p>	<p>Increase radiosensitivity Synergizes docetaxel's activity in vitro and in vivo NA NA</p>	<p>Venier et al. (2015a) (Sánchez et al., 2019) (Venier et al., 2015b)</p>

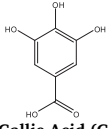
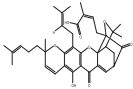
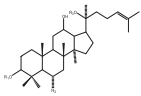
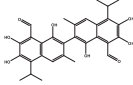
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Table 2 (continued)

Compound & chemical nature	Plant name and family	Mechanism of actions	In vitro	In vivo	Combination drug	References
 <p>Capsaicin (Vanilloid type of compound)</p>		<p>in vivo and in vivo targeting PI3k/Akt/mTOR pathway. Overexpression of PTEN and inhibition of AMPK abrogated the functional synergy with docetaxel.</p> <p>Administration by oral route resulted in reduced metastatic potential, which was correlated with the reduction in p27/Kip1 expression and neuroendocrine differentiation in the tumor tissues; no toxicity to the liver or gastrointestinal tract was observed.</p> <p>Inhibited PC3 cell growth and proliferation both in vitro and in vivo. Antiproliferative effect on PCa cells was associated with increased p53, p21, and Bax level, and NFκB inhibition through suppression of IκBα degradation by blocking proteasome activity</p>		<p>mouse prostate (TRAMP) model. PC3 xenograft</p>		(Mori et al., 2006)
 <p>Delphinidin (Anthocyanin type of compound, specifically Anthocyanidin)</p>	<i>Viola</i> sp. (<i>Violaceae</i>) and <i>Delphinium</i> sp. (<i>Ranunculaceae</i>)	<p>Induced caspase-dependent apoptosis, G2/M arrest with reduction of p-IκB kinase γ; (NEMO), phosphorylation of NF-κB inhibitor protein IκBα and phosphorylation of NF-κB/p65 at Ser536 and NF-κB/p50 at Ser529, and thus NF-κB/p65 nuclear translocation, and NF-κB DNA binding activity. Ameliorated tumor overload in vivo with a decrease in Bcl-2, Ki67, and PCNA levels.</p>	PC3, LNCaP, C4-2, 22Rv1	PC3 grafted nude mice	NA	Hafeez et al. (2008)
 <p>Fisetin (Flavonol)</p>	<i>Acacia greggii</i> (Fabaceae)	<p>Reduced cell viability in vitro. Enhanced the ability of cabazitaxel to block cell proliferation through induction of apoptosis; reduced tumor growth, invasion, metastasis with reduction of PCNA, Ki67 levels while enhancing the level of Bax. Disrupted microtubule dynamics in PCa cells. Blocked PCa progression by inhibiting hyaluronan (HA) synthesis and degradation enzymes; increased the level of antiangiogenic high molecular mass hyaluronan (HMM-HA). Blocked tumor progression in TRAMP mice model and tumor xenograft studies. Blocked the expression and EGF-induced phosphorylation of Y-box binding protein-1 (YB-1) and markers of EMT (Vimentin, slug) while increasing E-cadherin to restrain EMT in vitro and in vivo. Prevented angiogenesis in vitro and in vivo by reducing VEGF endothelial NO synthase expression. Caused cell death by caspase-dependent apoptosis and increased Bax/Bcl-2 ratio and p53 level. Inhibited tube formation in HUVEC cells. Induced cell cycle arrest at G1 (strong) and G2/M (moderate) phases together with reducing cyclin D level.</p>	PrEC, 22Rv1, and C4-2, PC3M-luc-6, NCI/ADR-RES, RWPE, NB11, NB26, RWPE-1, LNCaP, DU145, 22Rv1, PC-3, NB26, DU145, HUVEC	22Rv1 and PC3 M-luc-6 grafted mice, NB11 and NB26 grafted nude mice and TRAMP mice, NB26 grafted nude mice, Matrigel implanted Swiss albino mice	Enhanced the efficacy of cabazitaxel	Mukhtar et al. (2016) (Lall et al., 2016) (Khan et al., 2014) (Bhat et al., 2012)
 <p>Formononetin (Isoflavone derivative (O-methylated isoflavone))</p>	<i>Trifolium pretense</i> (Fabaceae)	Inhibited cell proliferation by facilitating G1 arrest in PCa cells via downregulation of Akt/Cyclin D1/CDK4. Inhibited tumor overload in vivo.	PC3, DU145	PC3 grafted nude mice	NA	Li et al. (2014)
	<i>Vitis vinifera</i> (Vitaceae)	Blocked PCa progression through inhibiting histone deacetylase 1, 2,	LNCaP, PC3, DU145,	PC3 grafted in BALB/c nu/nu male mice	NA NA	Jang et al. (2020)


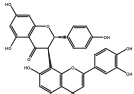

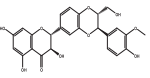
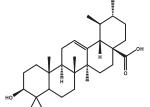
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Table 2 (continued)

Compound & chemical nature	Plant name and family	Mechanism of actions	In vitro	In vivo	Combination drug	References
 Gallic Acid (GA) (Polyphenolic compound)		<p>and PCNA and upregulation of acetyl-p53. Enhanced intrinsic caspase-dependent apoptosis, DNA fragmentation with a decrease in mitochondrial membrane potential, and cyclin D1, -E1, and PCNA levels while upregulating p21/Waf1 level. Induced PCa cell death by apoptosis and reduced microvessel density and tumor overload in vivo. Inhibited tumor growth by apoptosis; reduced PCNA level, cell cycle markers cyclin B1, -E1, CDK2, -4, -6, and Cdc2 level. GA present in pomegranate peel extract reduced tumor burden in vivo accompanied by inhibition of TNF-α and VEGF expression.</p>	22Rv1 NA PC3	DU145, 22Rv1 grafted nude mice TRAMP mice PC3 xenograft	NA NA	(Kaur et al., 2009) (Raina et al., 2008) (Ma et al., 2015)
 Gambogic Acid (Xanthone derivative)	<i>Carciniahanburyi</i> (Clusiaceae).	Inhibited human umbilical vascular endothelial cell (HUVEC) proliferation, migration, invasion, tube formation, and microvessel growth at the nanomolar concentration in vitro. Reduced angiogenesis, VEGF-2, c-Src, focal adhesion kinase, and Akt level in vivo.	PC3, HUVEC	PC3 grafted SCID mice	NA	Yi et al. (2008)
 Ginsenosides (GN) (Triterpene saponin)	<i>Panax ginseng</i> (Araliaceae).	<p>GN Rh2 blocked the growth of tumors developed with three different PCa cells by suppressing angiogenesis by inhibiting the expression of CNNM1, CD31, VEGF, and PDGF genes. GN-Rg3 showed synergistic activity with chemotherapeutics in killing PCa cells. Induced arrest in G0/G1 phase and apoptosis. Inhibited NF-κB, Bcl-2, IAP-1, XIAP, cyclin B, D1, E, and CDK 2, -4. Combination with docetaxel and cisplatin exhibited functional synergy in blocking PCa. GN-Rh2 blocked tumor growth and invasiveness. Activated TGF-β receptor signaling, regulators of cell cycle mediators, and MMPs. Downregulated cyclin D1, B1, MMP2/9 while increasing the level of pSMAD2 and p27.</p>	LNCaP, PC3, DU145 LNCaP, PC3, DU145 PC3	LNCaP, PC3, DU145 grafted nude mice NA PC3-luc xenograft	NA Synergism with docetaxel and cisplatin NA	Huang et al. (2019) (Kim et al., 2010) (Zhang et al., 2015)
 Gossypol (Polyphenolic)	<i>Gossypium hirsutum</i> (Malvaceae)	<p>Blocked in vivo tumor proliferation by inducing DNA damage, p53, and apoptosis. Inhibited the expression of VEGF, Bcl-2, Bcl-xL, and tumor overload in vivo. Suppressed microvessel growth and sprouting in vitro and ex vivo. Inhibited p-Src (Tyr416), p-FAK (Tyr 397), p-Akt (S473), and p-ERK1/2 (Thr 202/Tyr 204) levels. Inhibited cell proliferation in vitro, and induced caspase-dependent apoptosis (Caspase3, -8), and blocks Bcl-2, PCNA, CD31 expression, and microvessel density in tumor tissue. Potentiated cell death in vitro and in vivo by apoptosis in combination with radiation; inhibited tumor angiogenesis. In combination, Sorafenib killed PCa cells more efficiently, involving apoptosis and autophagy in vitro and in vivo with reduced Bcl-2 level, Inhibited growth by apoptosis through mitochondrial pathway in</p>	LAPC4, PC3, DU145 HUVEC, HMEC-1, PC3, DU145 PC3 PC3 PC3, DU145 PC3, DU145, LNCaP, WI38	DU145 xenograft in NOD/SCID mice PC3 xenograft and Sprague Dawley RAT PC3 xenograft PC3 grafted NCr-nu/nu nude mice PC3, DU145 xenograft PC3 grafted NCr-nu/nu nude	NA NA NA Enhances the efficacy of radiotherapy Works synergistically with sorafenib Enhanced docetaxel efficacy in vitro and in vivo	Volate et al. (2010) (Pang et al., 2011) (Zhang et al., 2010) (Xu et al., 2005) (Lian et al., 2012) (Meng et al., 2008)

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Table 2 (continued)

Compound & chemical nature	Plant name and family	Mechanism of actions	In vitro	In vivo	Combination drug	References
 Matrine (Quinolizidine alkaloid)	<i>Sophora flavescens</i> (Leguminosae)	PC3 cells and synergistically increased the anticancer activity of docetaxel both in vitro and in vivo. Blocked the expression of Bcl-xL while increasing the expression of Puma and Noxa.	DU145, PC3 DU145, PC3	DU145 xenograft DU145, PC3 xenografted nude mice	NA NA	Chang et al. (2018) (Huang et al., 2017)
 Morelloflavone (Biflavonoid)	<i>Garcinia dulcis</i> (Clusiaceae)	Blocked invasion through downregulating MMP2/9 and NF-κB signaling in vitro and in vivo. Prevented angiogenesis by reducing VEGF mediated microvessel formation and the RhoA and Rac1 GTPases. Blocked the phosphorylation and activation of Raf/MAPK/ERK pathway. Reduced tumor overload in vivo.	PC3, HUVEC	PC3 xenograft	NA	Pang et al. (2009)
 Noscapine (Benzylisoquinoline alkaloid)	<i>Papaver somniferum</i> (Papaveraceae)	Prophylactic feeding of Noscapine limited tumor growth and lymphatic metastasis. Enhanced the activity of paclitaxel and the Bax/Bcl-2 ratio. Reduced the mRNA levels of AR and PSA.	PC3 LNCaP, PC3	PC3 xenografted athymic, Sim (NCR) nude mice NA	NA Showed synergism with paclitaxel	Barken et al. (2010) (Rabzia et al., 2017)
 Silibinin (Flavolignan (Flavanoid unit linked to Phenyl Propane through an oxeran ring))	<i>Silybum marianum</i> (Asteraceae)	Hampered HIF-1α mediated signaling, angiogenesis, and lipogenesis in PCA cells. Reduced tumor load in vivo through inhibition of tumor vascularity; reduced the levels of HIF-1α, lipid, FASN, ACC, and NOX.	LNCaP, 22Rv1	22Rv1 xenograft	NA	(Deep et al., 2017)
 Ursolic Acid (Pentacyclic triterpenoid)	<i>Cornus officinalis</i> (Cornaceae)	Inhibited PI3K/Akt/mTOR pathway to induce apoptosis in vitro and in vivo	LNCaP, PC3	LNCaP xenograft	NA	Meng et al. (2015)

Abbreviations: Bax, Bcl2 associated protein X; Bcl2, B-cell leukemia/lymphoma 2; PI3K/Akt, phosphatidylinositol-3-kinase/protein kinase B; EMT, epithelial to mesenchymal transition; ERK, extracellular signal regulatory protein kinase; NF-κB, nuclear factor kappa-light chain enhancer of activated B cells; CDKs, cyclin dependent kinases; AR, androgen receptor; PSA, prostate specific antigen; HIF-1α, hypoxia inducible factor-1 alpha; VEGF, vascular endothelial growth factor; STAT-3, signal transducer and activator of transcription 3; JNK, c-Jun-N-terminal kinase; PARP, poly (ADP-ribose) polymerase; AMPK, AMP-activated protein kinase; PTEN, phosphatase and tensin homolog; NKX3.1, NK3 Homeobox 1; PUMA, p53 upregulated modulator of apoptosis; NOXA, phorbol-12-myristate-13-acetate-induced protein 1; FOXO3a, forkhead box transcription factors 3a; TNF-α, tumor necrosis factor-α; MAPK, mitogen-activated protein kinase; Gn-Rh2, gonadotropin releasing hormone 2; CDKN1A, cyclin dependent kinase inhibitor 1A; Bak, Bcl-2 homologous antagonist/killer; Bad, Bcl-2 associated cell death; IκBα, I kappaB-alpha; PDK1, PIP3 dependent kinase 1; CRPC, castrate resistant prostate cancer; RhoA, ras homolog family member A; Rac1, ras-related C3 botulinum toxin substrate 1; PDEF, prostate epithelium-derived ETS transcription factor; Ki67, marker of proliferation Ki-67; PCNA, proliferating cell nuclear antigen; FOXM1, forkhead box M1; DHT, dihydrotestosterone; TRAMP, transgenic adenocarcinoma of mouse prostate; c-Src, phospho-proto-oncogene tyrosine-protein kinase c; phospho-focal adhesion kinase; Cdc2, cell division control 2; CD31, cluster of differentiation 31; FASN, fatty acid synthase; acetyl-CoA carboxylase; CNNM1, cyclin and CBS domain divalent metal cation transport mediator 1; IAP-1, inhibitor of apoptosis protein 1; XIAP, X-linked inhibitor of apoptosis protein; p-SMAD-2, phospho-mothers against decapentaplegic homolog 2; Raf, rapidly accelerated fibrosarcoma; VEGF-2, vascular endothelial growth factor-2.

microtubule assembly but reduces tubulin polymerization by cabazitaxel. Ellagic acid inhibited drug efflux in castration-resistant PCa/22Rv1 cells but did not change the efficacy of docetaxel in vivo (Eskra et al., 2019). It blocked tumor progression by activating caspase 3 mediated apoptosis in a TRAM tumor model, modulated Bax/Bcl2 ratio, caspase 3 level. It decreased LNCaP cell growth, increased cell cycle-related proteins, p21Waf, P27Kip, cdk2, and cyclin E accompanied by downregulation of cyclin D1 and Cdk1 expression levels in Sprague-Dawley (SD) rats (Nai-ki-Ito et al., 2015). Combined with luteolin and punicic acid, Ellagic acid

inhibited tumor growth, metastasis, and angiogenesis in PCa cell induced xenograft and allograft tumors. Ellagic acid was shown to reduce CXCR-4, p-Akt/PI3K activities and block tube formation, IL-8, VEGF, and angiogenesis in HMVEC cells (Wang et al., 2014b).

3.5. Genistein

Genistein, an isoflavone, is isolated from leguminous plants (family Leguminosae) such as soybean (*Glycine max*), broad bean (*Vicia faba*),

and chickpea (*Cicer arietinum*). The anti-inflammatory properties of Genistein are well known (Ghosh et al., 2016). Numerous studies revealed the cytotoxic potential of Genistein on multiple cancers, including PCa, which functions through modulating AR, PI3K/Akt, NF- κ B, Hh, and Wnt signaling pathways. Genistein was shown to suppress different oncogenic miRNA expression, bone metastasis, and stemness in PCa (Fontana et al., 2020). It suppressed proliferation and metastasis in PC3 cells by inhibiting the expression of p38MAPK and MMP2 and inducing apoptosis through activating caspase 3 (Shafiee et al., 2020). A nanoliposome formulation of Genistein and anti-inflammatory drug Celecoxib induced ROS mediated apoptotic death in PC3 and LNCaP cells sparing the normal fibroblasts mainly through downregulation of cellular GSH and Prx-6 level along with inhibition of expression of COX-2 synthesis and Glut-1 transporters (Tian et al., 2019). A nanoliposome formulation of Genistein and Plumbagin was shown to induce apoptotic death in PC3 and LNCaP cells and in vivo mouse model through inhibiting PI3K/Akt signaling and Glut-1 transporters (Song et al., 2020).

Genistein combined polysaccharide (GCP) impedes intracrine androgen synthesis by downregulating testosterone levels by 3 fold and reducing the PSA level. It blocked the synthesis of 3 β HSD, 17 β HSD, StAR, SRB1, and CYP17A enzymes involved in the intracrine synthesis of AR while hindering cell growth, proliferation in LNCaP, and PC346C CaP cells through inducing apoptosis (Batra et al., 2020). Genistein elevates the effect of a shallow dose of irradiation (20 mGy/h) in DU145 cells to induce apoptotic cell death more efficiently (Altaf et al., 2019). A recent study with Genistein showed that it hindered the pathways involved in the transformation of a simple form of PCa to a highly lethal motility phenotype and long term use of soy product; Genistein can instigate compensatory changes in the response of biomarkers involved in cell motility (MEK4, MMP2) in human PCa cells (Zhang, 2019). In a clinical trial, Genistein pre-treatment showed differential DNA methylation and gene expression in PCa patients compared to placebo-treated ones. Overall, Genistein treatment resulted in reduced expression of MYC activity with enhanced PTEN function (Bilir et al., 2017).

3.6. Lycopene

Lycopene is a carotenoid pigment available abundantly in many fruits and vegetables such as, in tomato *Lycopersicon esculentum* or *Solanum lycopersicum*. Lycopene, through its antioxidant potentials, lowers the risk of cardiovascular diseases and skin damage (Chapter 11 - Lycopene: A, 2013). Lycopene was reported to carry chemopreventive and induce PCa cell death by the mitochondrial apoptotic pathway (Gioti and Tenta, 2015; Konijeti et al., 2010; Goo et al., 2007). Lycopene was shown to inhibit different cancer cells, including PCa, by inhibiting HMG-CoA reductase and Ras function. The apoptotic cell death was also accompanied by induction of cell cycle arrest and inactivation of NF- κ B and JNK and Akt (Palozza et al., 2010; Ivanov et al., 2007). Lycopene also inhibited the migration and invasion of PCa cells by inhibiting integrins (Gioti and Tenta, 2015). It was reported to induce apoptosis by decreasing Akt expression while increasing miR let-7f1 expression (microRNA Lethal-7) (Mirahmadi et al., 2020). Clinical trials revealed that Lycopene as a chemopreventive agent could reduce PCa malignancy from 24% to 36% by avoiding conversion of high-grade prostate intra-epithelial neoplasia to PCa (Mohanty et al., 2005). Indonesian patient-derived PCa cells (Gleason score 6) were shown to be sensitized by Lycopene through reducing IGF-1 level (Tjahjodjati et al., 2020). Lycopene was reported to show anti-inflammatory activities by inhibiting IL1, -6, -8, and TNF- α in DU145, PC3, and LNCaP cells and tumor burden mice model (Jiang et al., 2019). It was reported to downregulate AR metabolism and signaling in in vitro and animal model of PCa (Applegate et al., 2019).

3.7. Piperine

Piperine is an alkaloid abundantly available in the Piperaceae family, specifically in species *Piper nigrum* commonly known as black pepper, used as a spice. Piperine shows many bioactivities like anxiolytic, anti-aggregant, antioxidant, antispasmodic, antidepressant, antiasthmatic, and anticancer (Shityakov et al., 2019). Piperine induces cell death in a dose-dependent manner in PCa cells, PC-3 and LNCaP, through induction of apoptosis via obstructing voltage-gated K⁺ current (IK) and cell cycle arrest (Ba and Malhotra, 2018; George et al., 2019). It has also been reported that Piperine inhibited the migration and induced apoptotic cell death in DU145 cells through the downregulation of phospho-Akt/phospho-mTOR/MMP-9 (Zeng and Yang, 2018). Reports suggested that Piperine-mediated suppression of CYP3A4 activity helps enhance the docetaxel anticancer potency in the human CRPC xenograft mouse model when co-administered (Makhov et al., 2012). Piperine also induced apoptosis in LNCaP, PC3, and DU145 cells through enhancing the activation of caspase-3, PARP cleavage and inhibiting prostate PSA, STAT-3, and NF- κ B (Samyktuty, 2013). Piperine augmented docetaxel activity against taxane-resistant PCa tumors through the attenuation of cytochrome p450 (CYPs), especially CYP1B1, P-glycoprotein (P-gp) activity. CYPs are mainly involved in docetaxel's hepatic metabolism, and P-gp is a well-known multidrug-resistant protein involved in lowering docetaxel amount and effectivity inside the body (Li et al., 2018a).

3.8. Plumbagin

Plumbagin is a naphthoquinone isolated majorly from the roots of *Plumbago rosea*, an Indian medicinal plant (Anuf et al., 2014). Plumbagin shares many medicinal properties, such as antifertility, anticoagulant, antitumor, antimalarial, antimicrobial, and antidiabetic (Nayana et al. Mamta). Plumbagin was reported to exhibit selective inhibition of growth and invasion by promoting apoptosis via inhibiting Akt and NF- κ B in hormone-refractory PCa DU145 but not in normal epithelial cells RWPE-1. Furthermore, it significantly slowed down DU145 induced xenograft in mice (Aziz et al., 2008). Plumbagin was also found to provoke apoptosis associated with ROS production and ER stress in DU145 and PC3 cells and the xenograft regression with minimal toxicity (Huang et al., 2018). Efficacy of ADT and subsequent survival of a mouse improved by the inclusion of Plumbagin in the treatment regimen (Abedinpour et al., 2017). Nanoemulsion formulation with Plumbagin showed potent antiproliferative activity towards PTEN-P2 PCa cells compared with Plumbagin alone (Chrastina et al., 2018). A recent report indicated that Plumbagin reduced the PTEN-P2 induced tumor growth only in castrated mice but failed in intact mice, and this revealed that dihydrotestosterone (DHT) was synthesized in testes mainly responsible for blocking prostate cell death (Rondeau et al., 2018).

3.9. Quercetin

Quercetin, a penta-hydroxylated flavonoid, is found in various fruits and vegetables, tea, berries, onions, apple, and tomatoes. This compound is endowed with multifarious medicinal properties such as anti-inflammatory, antioxidant, immunomodulatory, and anticancer properties. Quercetin impeded cell proliferation, invasion, migration, EMT, and in vivo tumor growth via downregulating lncRNA MALAT1, and inhibition of PI3K/Akt signaling (Lu et al., 2020a). It reversed docetaxel resistance through modulating AR and PI3K/Akt signaling in vitro and in vivo. Quercetin induced apoptosis and downregulated P-glycoprotein (P-gp), TWIST-1, and PSA level in vivo and enhanced docetaxel efficacy by reversing chemoresistance (Lu et al., 2020b).

With Resveratrol, Quercetin modulated promoter methylation, cell cycle, IGF1, Bcl-2, and PTEN signaling, and downregulated levels of EGFR, EGR3, and IL6, and upregulated IGF1BP7 and NKX3.1 levels to reduce tumor overload by apoptosis (Singh et al., 2020a). Quercetin in combinatorial with metformin induced caspase-dependent apoptosis,

Table 3
Extracts of plants with anti-PCa activities.

Plant name and plant part	Extract name	Mechanism of action	In vitro	In vivo	References
Leaves of <i>Polyalthia longifolia</i>	Methanolic extract (1)	Enhanced G1/S phase arrest, intrinsic apoptosis (Caspase3, -9), and ER stress (upregulated GRP78, ATF4, and IRE1 α levels). XBP1, Calnexin, CDK4, -6, Cyclin A2, and Cyclin D1 were downregulated; reduced tumor overload in nude mice.	PC3, DU145, C4-2, PC3M-LUC-C6	PC3M-LUC-C6 cell xenograft	Afolabi et al. (2019)
The root of <i>Taraxacum officinale</i> and <i>Cymbopogon citratus</i>	Aqueous extract of <i>Taraxacum</i> (Dandelion) (DRE) and <i>Cymbopogon</i> (lemongrass) ethanolic extract (LGE) (2)	Induced oxidative stress, and apoptosis via caspase cascade; reduced tumor overload alone and in synergy with taxol and mitoxantrone.	PC3, DU145	DU145, PC3 xenograft	Nguyen (2019)
The seed extract of <i>Litchi chinensis</i>	n-butyl alcohol extract (3)	Induced mitochondrial-dependent apoptosis, G1/S phase arrest by blocking Akt signaling; Inhibited cell migration, invasion, and EMT through downregulation of AKT/GSK-3 β signaling, Vimentin, and Snail while upregulating E-cadherin and β -catenin; ameliorated tumor overload in nude mice without toxicity to normal cells.	PC3, DU145, RM1, and C4-2B	PC3 xenograft	Guo et al. (2017)
Whole plant extract of <i>Wedelia chinensis</i>	Ethanolic extract (rich in flavonoids) (4)	Blocked the AR, HER2/3, and Akt signaling networks and increased the therapeutic efficacy of androgen ablation in PCa as well as in an in vivo adapted castration-resistant PCa (CRPC) model.	PC-3, DU145, 22Rv1, and LNCaP	LNCaP, 22Rv1 xenograft	Tsai et al. (2017b)
Leaves of <i>Maytenus royleanus</i>	Methanolic extract (5)	Potentiated caspase-mediated apoptosis, G2 arrest, and downregulation of cyclin/cdk networks; suppressed AR/PSA signaling ex vivo as well as in vivo; reduced tumor growth.	C4-2 and CWR22Rv1	CWR22Rv1 xenograft	Shabbir et al. (2015)
Vegetative material of <i>Sutherlandia frutescens</i>	Methanolic extract (6)	Inhibited cellular growth via modulating Gli/Hh signaling; blocked the formation of poorly differentiated carcinoma in prostates of TRAMP mice.	PC3, LNCaP, TRAMP-C2	Male B6FVB-F1 TRAMP mice	Lin et al. (2016)
Roots of <i>Kalanchoe gastonis-bonnieri</i> (BIRM)	Liquid extract (7)	Induced caspase 8 mediated apoptosis; degraded AR through the proteasome pathway; inhibited p-Akt and in vivo tumor growth.	DU145, LNCaP, PC-3ML	PC-3ML grafted in FOXN1 inbred athymic mice	Shamaladevi et al. (2016)
<i>Acanthopanax trifoliatum</i>	Extract rich in triterpenoids (8)	Potentiated cell death by apoptosis by suppressing NF- κ B and STAT-3 in vitro and in vivo.	PC3	PC3 xenograft	Li et al. (2015)
Leaves of <i>Hibiscus sabdariffa</i>	Polyphenol rich aqueous extract (9)	Induced cell death; blocked cell invasion via down-regulation of Akt/NF- κ B/MMP-9 pathway in vitro and in vivo.	LNCaP	LNCaP xenograft	Chiu et al. (2015)
Roots of <i>Eurycoma longifolia</i>	Quassinoids rich containing methanolic extract (10)	Induced apoptosis; inhibited cell cycle arrest (G0/G1 and G2/M); modulated cyclin/cdk levels; blocked AR translocation to the nucleus and thereby PSA level; suppressed tumor growth in vivo.	LNCaP, PC-3, RWPE-1, WRL 68	LNCaP xenograft	Tong et al. (2015)
Leaves and roots of <i>Arum Palaestinum</i>	Aqueous extract (11)	Inhibited PCa spheroid formation and tumor overload in vivo.	22Rv1	PC3-MM2 grafted nu/nu mice	Cole et al. (2015)
Knots of <i>Pinus sylvestris</i>	Lignan and stilbenoid rich ethanol-water extract (12)	Induced apoptotic death in vivo via enhancing TRAIL pathway at well-tolerated doses to the normal cells.	PC3M-luc2	PC3M-luc2 grafted Foxn1 ^{nu} nude mice	Yatkin et al. (2014)
Leaves of <i>Azadirachta indica</i>	Supercritical CO2 extract of leaves (13)	Inhibited dihydrotestosterone-induced androgen receptor and PSA levels; blocked Integrin b1, Calreticulin, and Focal adhesion kinase activation; ameliorated tumor growth and enhanced AKR1C2 level in vivo.	LNCaP-luc2, PC3	LNCaP-luc2 xenograft	Wu et al. (2014)
Leaves of <i>Piper betel</i>	Methanolic extract (14)	Induced apoptosis in cells in vitro and in vivo tumor model.	PC3, DU145, 22Rv1, RWPE-1, PC3-luc cells	PC3-luc xenograft	Paranjpe et al. (2013)
Leaves of <i>Ipomoea batatas</i>	Polyphenol (Quinic acid (QA), caffeic acid, its ester clonogenic acid, and isochlorogenic acids, 4, 5-di-CQA, 3,5-di-CQA, and 3,4-di-CQA) rich methanolic extract (15)	Inhibited growth, proliferation of the cell, and progression of tumor xenograft.	PC3, PC3-luc cells	PC3-luc xenograft	Gundala et al. (2013)
Whole <i>Zingiber officinale</i>	Methanolic extract (16)	Induced cell cycle arrest and mitochondria-dependent apoptosis in vitro; reduced tumor burden and induced apoptosis in vivo.	PrEC, LNCaP, C4-2, C4-2B, DU145 and PC3	PC3 xenograft	Karna et al. (2012)
Leaves of <i>Hibiscus sabdariffa</i>	Aqueous extract (17)	Induced apoptosis by intrinsic and extrinsic pathways in androgen-dependent PCa cells; reduced tumor burden in vivo.	Human CaP, LNCaP, PC3 and DU145	LNCaP xenograft	Lin et al. (2012)
Leaves of <i>Ipomoea batatas</i>	Polyphenol rich methanolic extract (18)	Induced cell cycle arrests, and mitochondria-dependent apoptosis in vitro; reduced tumor burden via apoptotic death in tumor cells.	LNCaP, DU145, PC3, C4-2, C4-2B, PC3-luc	PC3-luc xenograft	Karna et al. (2011)

(continued on next page)

Table 3 (continued)

Plant name and plant part	Extract name	Mechanism of action	In vitro	In vivo	References
Leaves of <i>Camellia pitlophylla</i>	Aqueous extract (19)	Induced cell cycle arrest and caspase-mediated apoptosis; inhibited nuclear translocation and phosphorylation of NF- κ B, and activation of IKK α , while inhibition of phosphorylation and degradation of I κ B α and regressed tumor growth in vivo.	PC3	PC3 xenograft	Peng et al. (2010)
Aerial parts of <i>Saussurea involucrata</i>	Different solvent extracts (20)	Ethyl acetate fraction blocked the proliferation of PCA cells, caused G1 arrest, modulated cell cycle markers, and induced mitochondria-dependent apoptosis; lowered the phosphorylation of EGFR, activation of Akt and STAT3 activity in vitro, and tumor growth in vivo.	PC3 and LNCaP	PC3 grafted BALB/c nude mice	Way et al. (2010)
Rhizome of <i>Bergenia ligulata</i>	Polyphenol rich ethyl acetate fraction (21)	Induced death of PC3 cells ex vivo and in vivo by oxidative stress-mediated by overactivation of MAO-A	PC3	PC3 grafted SCID mice	Ghosh (2021)

Abbreviations used in the table: ATF4, activating transcription factor; IRE1 α , serine/threonine-protein kinase/endoribonuclease inositol-requiring enzyme 1 α ; XBP1, X-Box binding protein 1; TRAIL, TNF-related apoptosis-inducing ligand; GRP78, glucose regulated protein 78; ER stress, endoplasmic reticulum stress; p-GSK3 β , phosphoglycogen synthase kinase 3 beta; STAT3, signal transducer and activator of transcription 3; HER2/3, human epidermal growth factor receptor 2/3; AKR1C2, aldo-keto reductase family 1 member C2; IKK α , inhibitory κ B kinase α ; I κ B α , nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha; EGFR, epidermal growth factor receptor.

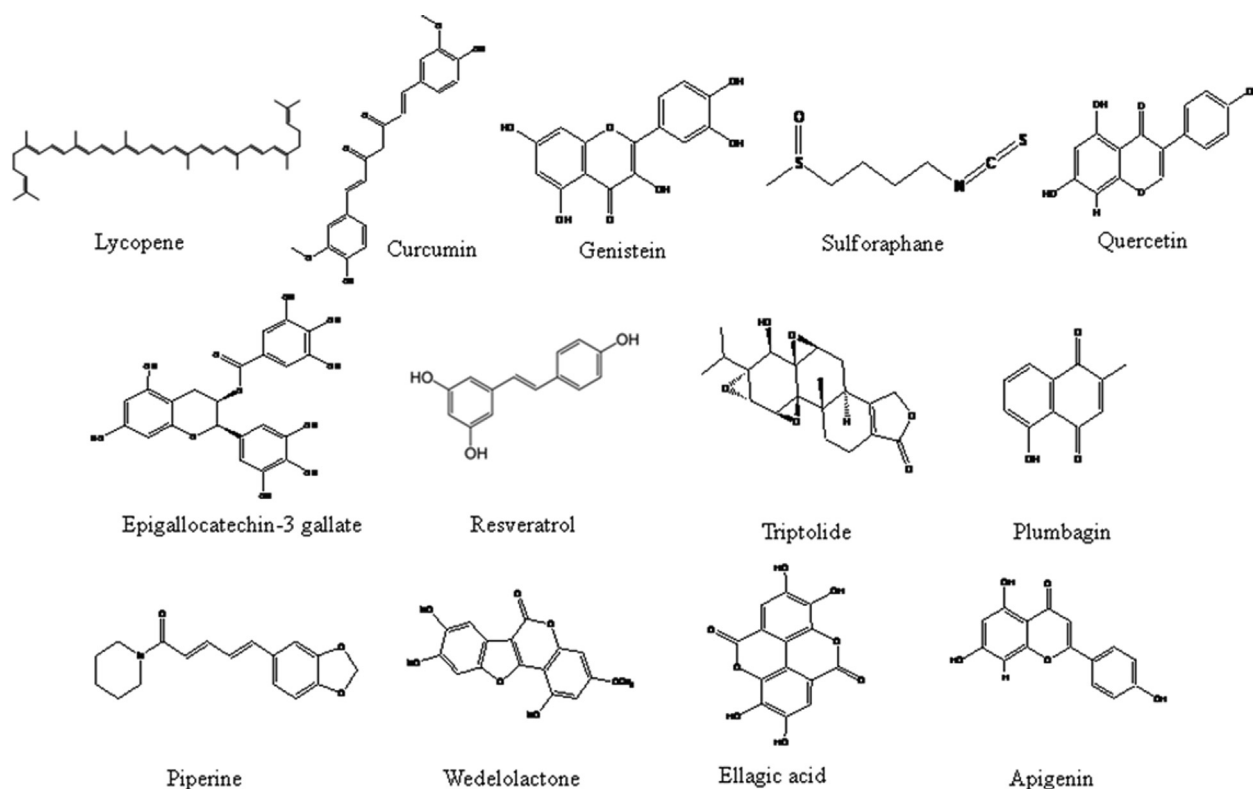


Fig. 2. Chemical structures of indicated phytochemicals with demonstrated therapeutic promise against PCA in preclinical models.

and reduced invasion and Bcl-2, VEGF, and Akt/PI3K activities ex vivo and in vivo tumor model (Sun et al., 2018). It enhanced the therapeutic efficacy of paclitaxel, potentiated G2/M phase arrest, apoptosis, ER stress, produced ROS generation, and inhibited cell proliferation and migration in vitro and in vivo (Zhang et al., 2020b). Quercetin killed cells by inducing apoptosis by mitochondrial/ROS pathway accompanied by a reduction in the tyrosine-protein kinase-met (c-met) and PI3K/Akt pathway activities and could reverse doxorubicin resistance in vitro (Shu et al., 2018). Acted in synergy with next-generation anti-androgen enzalutamide in killing drug-resistant PCA cells by reducing expression of

hnRNPA1, ARV7, AR, and AR-regulated genes PSA, NKX3.1, FKBP5, and UBE2C in vitro and in vivo (Tummala et al., 2017). Quercetin nano-micelles killed PCA cells in vitro and in vivo by apoptosis (Zhao et al., 2016).

Quercetin reduced tumor burden by inhibiting angiogenesis and metastasis through upregulating expression of anti-angiogenesis factor thrombospondin-1 (Yang et al., 2016). It inhibited the EGFR and PI3k/Akt pathway and the expression of PCNA, Vimentin, N-cadherin, cyclin D1, and mRNA level of snail, slug, and twist to ameliorate chemical (MNU + T) induced tumor overload in Sprague-Dawley male rats and

inhibit (Firdous et al., 2014). Quercetin was also reported to block tumor growth by apoptosis through inhibition of proliferative activities of IGF1R, AR, and Akt (Sharmila et al., 2014).

3.10. Resveratrol

Resveratrol (RES) is a polyphenolic compound isolated from the dried stem of *Vitis Vinifera* (Tian and Liu, 2019; Park and Boo, 2013). The *trans* isomer of RES shows various biological activities such as anti-inflammatory, antioxidant, antiaging, anticancer, immunomodulatory, neuroprotective, and cardioprotective activities. RES was shown to induce apoptotic death in LNCaP, DU145, and PC3 cells (Jasiński et al., 2013). RES induced increased apoptotic death in PCa cells in synergy with doxorubicin, taxol, methotrexate, cytarabine, actinomycin D via inhibiting survivin and promoting apoptosis (Gupta et al., 2011). It was shown to sensitize PC-3M-MM2 cells through the downregulation of Akt, ERK-1/2, estrogen, and IGF-1 and its receptor (IGF-1R) activities (Sheth, 2012). Furthermore, studies on Resveratrol reveal that it inhibits cyclooxygenase-2 (COX-2) and NF- κ B in PCa cell lines and enhance apoptosis signals (Athar et al., 2009). Oral administration with Resveratrol reduced highly aggressive and androgen-receptor negative PCa cells PC-3M-MM2 and in SCID mouse through negative regulation of Akt and PCa associated microRNA such as miR21 and up-regulation of tumor suppressor PDCD4 levels (Sheth, 2012). RES inhibited PCa in vitro and in vivo model by inhibiting the antiapoptotic SphK1/S1P and prosurvival pathway, a downstream effector of the ERK1/2 pathway (Brizuela et al., 2010). RES tested clinically on benign prostate hyperplasia patients and found notably decreased androgens levels in serum without prostate tumor growth (Kjaer et al., 2015). RES, combined with Quercetin, reduced tumorigenesis in the TRAMP model by decreased oxidative stress and increasing apoptotic signals (Singh et al., 2020b). RES reduced PCa cell proliferation and apoptosis by inhibiting the expression of AR, AR-V7, and Akt pathway (Ye, 2020). RES blocked tumor invasion and migration through upregulating-eleven translocation-1 (TET1) along with TIMP2/3 levels and downregulating MMP2/9 and TNF-receptor associated factor 6 (TRAF6)/NF- κ B/SLUG axis in PCa cells (Wang et al., 2020; Khusbu et al., 2020). Prostate fibrosis caused by inflammation was reduced by RES (Vicari et al., 2020). RES was shown to block hepatocyte growth factor (HGF) secretion by stromal cells, thus inhibiting invasion and EMT in PCa cells (Hsieh and Wu, 2020).

3.11. Sulforaphane

Sulforaphane, a natural isothiocyanate, is isolated from *Brassica oleracea* (family Brassicaceae). From ancient times numerous studies have revealed the efficacies of cruciferous vegetables in the amelioration of various ailments, including PCa. Sulforaphane (SFN) in these vegetables was shown to be majorly responsible for cytotoxicity towards PCa by inhibiting metastasis, invasion, and stemness via modulating AR, NF- κ B, PI3k/Akt signaling pathway, energy metabolisms such as glycolysis, pentose phosphate pathway, and lipogenesis (Fontana et al., 2020). In a recent study, SFN treatment inhibited energy metabolism, i.e., enhanced glycolysis (Warburg effect) in PCa cells in-vitro and in vivo TRAMP and Hi-Myc mice model. SFN treatment blocked real-time extracellular acidification rate in LNCaP but not in PC3 cells, occluded the expression of hexokinase II (HKII), lactate dehydrogenase A (LDHA), and pyruvate kinase M2 (PKM2) involved in the glycolysis pathway in LNCaP and 22Rv1 cells (Singh et al., 2019). SFN treatment-induced lysosome-associated membrane protein-2 (LAMP-2) expression. RNAi of LAMP2 resulted in death in PC3 and 22Rv1 cells by autophagy (Hahm, 2020). A metabolite of SFN, Sulforaphane-cystein (SFN-Cys), and Sulforaphane-N-acetyl-cysteine (SFN-NAC) treatment caused apoptotic cell death via microtubule disruption and ERK1/2 activation in DU145 and PC3 cells with a longer half-life than SFN (Zhou et al., 2018b). SFN-Cys hindered invasion of DU145 and PC3 cells via downregulation of galectin-1 (helps in the invasion) mediated by ERK1/2

phosphorylation (Tian et al., 2016).

Inhibition of LNCaP and DU145 cells by SFN treatment was mediated through repression of activity of hTERT, the catalytic subunit of telomerase. This was mediated by changes in histone post-translational modifications linked with a higher risk of PCa recurrence, such as acetylation of histone H3 lysine 18 and di-methylation of histone H3 Lysine 4 in the regulatory elements within the hTERT promoter region. Moreover, SFN drives chromatin condensation through altered expression and recruitment of chromatin compactor MeCP2 resulting in hTERT repression (Abbas et al., 2016). SFN repressed the expression of 100 long non-coding RNA, especially LINC0116 in PC3, LNCaP, and normal prostate epithelium (PREC) cells, which are known to mediate, cell cycle, signal transduction metabolism and are involved in PCa tumorigenesis (Beaver et al., 2017). A double-blind, randomized controlled clinical trial was conducted with 98 men scheduled for a biopsy. Patients who were given broccoli sprout extract (BSE, rich in SFN) or placebo showed a marked increase of SFN isothiocyanates and SFN level in plasma and urine along with the differential expression of 40 genes, including downregulation of AMACR and ARLNC1 involved in PCa development (Zhang et al., 2020c).

3.12. Triptolide

Triptolide, a diterpene, was isolated from *Tripterygium wilfordii*. Triptolide exhibits many potent pharmacological properties, such as an inhibitor of autoimmune, inflammatory, neurodegenerative, and cancer (Brinker et al., 2007). Triptolide induced apoptosis in LNCaP and PC-3 cells and inhibited tumor growth in the PC3 induced xenograft model in nude mice (Huang, 2012). It was shown to suppress invasion and migration of PCa cells through down-regulating the expression of caveolin-1, CD147, and MMPs (Yuan et al., 2016). Triptolide increases the sensitivity of metastatic castration-resistant PCa (mCRPC) cells and xenograft model towards the enzalutamide treatment via blocking AR binding and TFIID and RNA polymerase II to its target promoter (Han et al., 2017).

Minnelide, a pro-drug of Triptolide pro-drug, reduced the tumor growth induced by CRPC 22Rv1 subcutaneously; the results revealed that minnelide had shown a significant tumor regression compared to Docetaxel and Enzalutamide via downregulating the expression of androgen receptor (Isharwal et al., 2017). Triptolide was shown to synergize doxorubicin activity in PC3 cells (Xu et al., 2018). Triptolide treatment caused AR protein degradation in LNCaP cells through intracellular Ca²⁺ accumulation and calpain activation (Li et al., 2018b). Benign prostate hyperplasia induced by testosterone propionate (TP) in the rat was regressed by Triptolide treatment (Yu-Rong et al., 2017).

3.13. Wedelolactone

Wedelolactone, a polyphenol, is isolated from *Wedelia chinensis* and *Eclipta alba*. Wedelolactone exhibited various pharmacological activities such as anticancer, antihypertensive, antihepatotoxic, anti-inflammatory, antiphospholipase, and antidote activity for snake poison (Xu et al., 2014). Wedelolactone showed a potent anticancer effect on PCa cells and tumor xenograft by inhibiting c-Myc at the transcription and translation level and promoting apoptosis. Moreover, Wedelolactone also showed functional synergy with enzalutamide in triggering apoptotic death in PCa cells (Sarveswaran et al., 2016). Wedelolactone treatment activated apoptosis in androgen-dependent and androgen-independent PCa cells by activating JNK and caspase 3 and suppressing PKC ϵ but not Akt (Sarveswaran et al., 2012). Oral treatment of standardized herbal extract rich in Wedelolactone and other constituents like luteolin, and Apigenin inhibited tumor growth and metastasis in xenograft model of PC-3 and DU145. Also, it was shown that herbal extract in combination with docetaxel inhibited NF- κ B activation with reduced general toxicity induced by docetaxel alone (Tsai et al., 2017a).

4. Conclusion

This review article with a brief overview of epidemiology and etiology of PCa gives a recent progress on anti-PCa activities of various phytochemicals and plant extracts reported from different laboratories. As it appeared significant insights had been achieved on the mode of actions of many of these agents/phytochemicals making them attractive for consideration for further development. Several of these agents target cancer hallmark pathways such as growth regulatory/metabolic (PI3/Akt/mTOR/cyclin-cdk, AR), angiogenesis (VEGF), pro-inflammatory (NF- κ B), tumor suppressor (p53/Rb), and invasion and metastasis (WNT/ β -catenin) pathways. In addition, some of these agents were shown to act in synergy with FDA-approved therapy regimens. Notably, many of the compounds were reported to simultaneously target multiple cellular pro-proliferative pathways making them, at least in principle, ideal candidates for consideration as alternate anticancer chemotherapeutic agents or for development in that direction given that a cancer cell is thrived by mutations/aberrations in multiple signaling pathways. Testing the immunomodulatory function of these agents is still lacking. Although, several compounds and extracts mentioned in the review were in different forms of human/clinical trials to carry forward the findings a step further for bedside application, progress in this direction is not much visible. Much needed progress will be achieved through active collaboration of basic scientist with practicing/clinical oncologists associated with the hospitals where a large number of eligible patients could be available for consideration for the trial. However, it should be noted that before taking up these steps, the candidate agents should be again undertaken for rigorous testing with healthy animals and PCa cell induced tumor xenograft. Anyway, many of the plant extracts described here are in many cases are promising sources for isolation of active principles to understand their potentials for further development.

CRedit authorship contribution statement

Suvranil Ghosh: Conceptualization, Data curation, Resources, Writing – original draft, Writing - review & editing. **Joyita Hazra:** Data curation, Resources, Writing – original draft. **Koustav Pal:** Data curation, Resources, Writing – original draft. **Vinod K. Nelson:** Data curation, Resources, Writing – original draft. **Mahadeb Pal:** Conceptualization, Project administration, Supervision, Validation, Writing - original draft, Writing - review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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