

Review

Insights on the anticancer potential of plant-food bioactives: A key focus to prostate cancer

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Abstract: Prostate cancer is an international health problem and represents one of the most encountered malignancies among men. In this complex and heterogeneous disease, androgens and their receptors play a crucial role in both progression and development. Although the search for its effective treatment is still ongoing, among other priorities it requires developing better anticancer agents with greater efficacy and fewer side effects. In this regard, herbal medicines, which have been used in cancer treatment, represent a large source of new and bioactive chemical entities for the development of chemotherapeutic agents, many of them exhibiting favorable side effect and toxicity profiles compared to conventional chemotherapeutic agents. In fact, more than 50% of the current anticancer drugs originate from natural sources. Thus, the present review aims to provide an overview of the past and recent trends in the research, the role of secondary metabolites in urogenital disorders, and phytochemical assays in prostate cancer management.

Key words: Prostate cancer; Medicinal plant; Phytotherapy; Secondary metabolites; Plant extract.

Introduction

Prostate cancer is the second most deadly malignancy in men after skin cancer (1) and it is the most commonly diagnosed cancer among men. Its mortality rate is high, so that about 1.6 million new cases of prostate cancer were diagnosed in 2015 and 366,000 deaths were reported (2). In comparison to 2012, those numbers were 1.1 million and 307,000 for incidence and mortality, respectively, revealing an increase of about 45% in incidence and 19% in mortality rate (3, 4). Although it has been difficult to establish the definitive aetiological

clues linking development of prostate cancer to frequency, several studies have consistently linked the disease with common risk factors, namely age, race, dietary and physical activity (5-7). Thus, prostate cancer incidence is, in essence, influenced by age since the risks of being diagnosed with it increases with age (8, 9).

On the other hand, prostate cancer, like other types of cancer, is an expensive disease and imposes a lot of burden on both the health system and patients, and these expenditures are increasing year by year that it may be due to over treatment, over work-up or over diagnosis and increased survival (10). For instance, in

2010, the budget that expended for prostate cancer care in United States was 11.8 billion dollars and in 2013 and 2017 this budget was \$13.0 and \$14.8 billion, respectively (11). In Iran, direct medical costs for prostate cancer was estimated about 12.5 million USD in 2016 for about 500 patients (12) and these costs for metastatic castration-resistant prostate cancer in Italy in 2016 range from €196.5-228.0 million (13). These cost variations may be due to differences in incidence and management protocols between countries (10) and most of these monies were expended for treatment (13). Nowadays, the current treatment for prostate cancer is a combination of surgery, HT, radiation and chemotherapy, including steroidal and non-steroidal anti-androgens, such as cyproterone acetate, bicalutamide and enzalutamide (14). However, these few agents have multiple adverse effects and are not 100% effective (14). Despite the current advances research in the field of anticancer agents, rapidly developing resistance against different chemotherapeutic drugs and significantly higher off-target effects still cause millions of deaths every year (15).

Naturally-occurring agents from dietary vegetables and fruits have received considerable attention for the treatment and prevention of different types of cancer. These natural agents are believed to be safe and cost-effective compare to expensive chemotherapeutic agents, which usually associate significant side effects (16). Several medicinal plant-derived compounds and mixtures, including lycopene and tomato preparations, grape seed polyphenol extracts, soy isoflavones, and green tea extracts, have been shown to prevent prostate cancer cell growth(17). *In vivo* anti-prostate cancer activity of some isolated compounds like curcumin and capsaicin have been documented in murine models (14), as well as the clinical efficacy in human being. So, having preventive strategies and using natural products for managing prostate cancer patients may play an important role in decreasing the economic burden of disease and even in improving the patients' quality of life and health expectancy. Prevention strategies should reduce the detection of insignificant prostate cancer, that it caused decreasing radical treatment of patients, so reducing complications, costs and psychological and economic impacts on patients (18).

The role of secondary metabolites in urogenital disorders

Traditional plants have been used to treat and cure various diseases (19-22), and this has led to an increased use of medicinal plants in search for new drugs from nature (23). The discovery of new drugs was established from the knowledge that plant extracts are used to treat diseases in humans (24). The plants are potential sources of natural bioactive compounds that are, but not limited to secondary metabolites (25). Cragg and Newman (26) have pronounced that any part of plant such as leaves, bark, flowers and seeds may contain these secondary metabolites. Although little is known of the primary processes of the secondary metabolites in plants, Bodeker (27) reported that secondary metabolites are essential and important in plant use by people. The secondary metabolites are divided into three families based on their biosynthetic pathways, and these

large families are alkaloids, phenolic compounds, and terpenes and steroids (28).

In recent years, the importance of antioxidant activities of phenolic compounds and their potential usage in processed foods as natural antioxidant compounds has reached a new level (29, 30). Previous studies have shown that phenolic compounds are widely dispersed throughout plants (31, 32). These compounds form a diverse group that includes the widely distributed hydroxybenzoic and hydroxycinnamic acids. Hydroxycinnamic acid compounds are produced as simple esters with glucose or hydroxy carboxylic acids rather than as free compounds. Plant phenolic compounds are diverse in molecular structure, and are characterized by hydroxylated aromatic rings. There are various groups of molecules within the phenolic compounds; however, there are some that researchers have shown interest based on their beneficial properties against prostate cancer activities (32) as summarized in Table 1. In fact, increasing evidence have shown that inflammatory mediators act as triggers of prostate cancer. As observed, the different anticancer drugs exhibit action directly on pro-inflammatory cytokines, such as interleukin (IL)-6 or tumor necrosis factor (TNF)- α . In addition, reactive oxygen species (ROS) and reactive nitrogen species lead to carcinogenesis by causing a cellular redox imbalance in different cancer cells (33). Thus, among the different classes of secondary metabolites, phenolic compounds are those which have received a higher attention, given its prominent antioxidant effects, therefore contributing in prostate cancer cells inhibition (34).

From a historical perspective to health attributes

Natural bioactive components from plants include phytochemicals that have been used for the treatment of numerous diseases including prostate cancer (Figure 1).

The first compendium of natural herbs for medicinal purposes was assembled by the ancient Chinese emperor inside a literature, *Pentsao* in 2,800 BC. Apart from their nutritional benefits and healing attributes for centuries, they have been recognized as a natural pool of bioresources containing many bioactive components containing phytochemicals employed for various therapeutic properties. During the paleolithic age, the archaeological evidence obtained from the first docu-

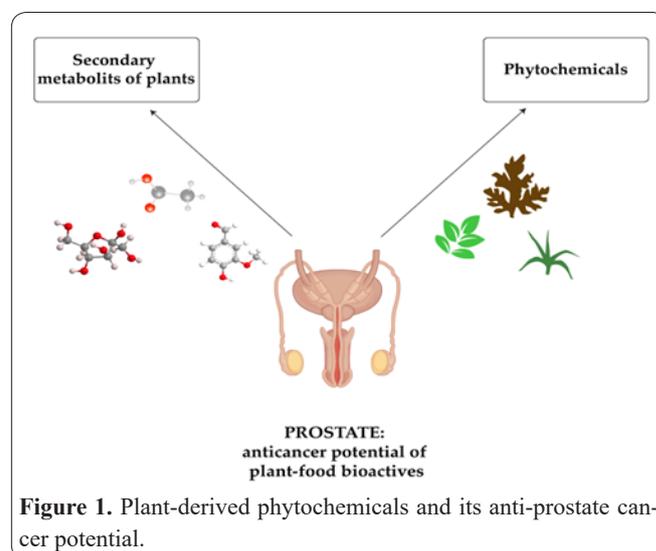


Figure 1. Plant-derived phytochemicals and its anti-prostate cancer potential.

Table 1. Summary of the classification of phenolic compounds with anti-prostate cancer activities.

Compounds	Type of assay	Results
Hydroxybenzoic acids and related compounds		
Cuphiin D1 (tannin)	<i>In vitro</i> human cell lines <i>In vitro</i> murine cell lines	Apoptotic properties Tumor inhibition
Oenothein B (tannin)	<i>In vivo</i> murine models <i>In vitro</i> human cell lines <i>In vitro</i> murine cell lines	Macrophages activation Tumor inhibition
Cuphiin D2	<i>In vivo</i> murine models <i>In vitro</i> human cell lines <i>In vitro</i> murine cell lines	Macrophages activation Tumor inhibition
Woodfordin C	<i>In vivo</i> murine models <i>In vitro</i> human cell lines <i>In vitro</i> murine cell lines	Macrophages activation Tumor inhibition
Coumarins and related compounds		
Dicoumarol	<i>In vitro</i> human cell lines	Enhancement of anticancer drugs
Chalcones		
Chalcone 2',6'-dihydroxy-4'-methoxychalcone 2',6'-dihydroxy-4',4-dimethoxydihydrochalcone 2',6'-dihydroxy-4'-methoxydihydrochalcone Phloretin	<i>In vitro</i> human cell lines	TRAIL mediated apoptosis
Stilbenes		
3,5-dihydroxy-4'-acetoxy <i>trans</i> -stilbene	<i>In vitro</i> human cell lines	Limited potential <i>in vivo</i>
Resveratrol	<i>In vitro</i> human cell lines	Sensitizer of anticancer drugs
Lignins and lignans		
7-Hydroxymatairesinol	<i>In vivo</i> murine models	Cell proliferation reduction Tumor reduction
Flavonols		
Kaempferol Catechin	<i>In vitro</i> human cell lines	Apoptotic properties
Isoflavones		
Genistein	<i>In vitro</i> human cell lines	Proliferation inhibition Downregulation of apoptosis inhibitor
Anthocyanidins		
Delphinidin	<i>In vitro</i> human cell lines <i>In vivo</i> murine models	Cell growth inhibition Caspase mediated apoptosis Tumor size reduction

mented facts by the Sumerians affirmed the application of various parts of the plant for numerous medicinal purposes including the management of prostate cancer (35).

The antineoplastic properties from some of these bioactive components from plants that could serve as functional and nutraceutical foods have been documented. Some of these bioactive components include tea polyphenols from green tea, sulforaphane from broccoli, isothiocyanates from cruciferous vegetables, resveratrol from grapes, curcumin from turmeric, lycopene from tomato, and so on. In view of the aforementioned, this review intends to present an overview of the past and recent trends in the research, assays, and limitations in the application of phytochemicals for the management of prostate cancer.

Drifting from natural to synthetic attributes

During the 20th century, most of the plant extracts were screened for natural bioactive phytochemical and consumed directly without any purification and recommended dosage. Moreover, during the 21st century, the pharmaceutical industry has shifted attention towards

the use of bioactive components for chemical synthesis of drugs (including anticancer drugs) from plants that could serve as a permanent replacement for both treatment and prevention of prostate cancer (36, 37). The introduction of anti-prostate cancer drugs through the form of pills has helped in overcoming many obstacles that have been highlighted with the crude phytochemicals present in raw plant extracts. The separation of this bioactive components depends on the purity, amount of available bioactive component, quality, quantity and polarity of the solvent. The aspects related with the over dosage, solubility, purification, efficacy, bioavailability and other crucial issues relating to contamination are also of utmost importance (38).

In view of the aforementioned, there is a need to develop the most significant bioactive components from the arrays of phytochemicals present in the crude extract of various plant extract, which has been reported for the controlling of prostate cancer. There are a lot of techniques involves in the isolation, purification, characterization and structural elucidation of the active components. Some of the analytical techniques used for the separation of the most active components

Table 2. Phytochemicals and prostate cancer.

Compounds	Type of assay	References
Isobavachin, glabranin, anthocyanin, eriosemination	bioinformatics	(40)
3,3'-diindolylmethane and indole-3-carbinol	<i>in vitro</i> (LNCaP)	(45)
	<i>in vitro</i> (PC3)	(47)
	<i>in vitro</i> (DU145)	(50)
3,3'-diindolylmethane	<i>in vitro</i> (LNCaP, DU145)	(49)
	<i>in vitro</i> (LNCaP-FGC, PC3)	(52)
	<i>in vitro</i> (PC3)	(53)
	<i>in vitro</i> (PC3)	(54)
	<i>in vitro</i> (C4-2B) and <i>in vivo</i> (CB-17 SCID mice)	(51)
Indole-3-carbinol	<i>in vitro</i> (PC3)	(43)
	<i>in vitro</i> (PC3)	(44)
	<i>in vitro</i> (TRAMP) and <i>in vivo</i> (C57BL/6 mice)	(48)
	<i>in vitro</i> (LNCaP, PC3) and <i>in vivo</i> (nude mice)	(42)
Sulforaphane	<i>in vitro</i> (DU145)	(59)
	<i>in vitro</i> (DU145)	(60)
	<i>in vitro</i> (PC3)	(62)
	<i>in vitro</i> (PC3)	(63)
	<i>in vitro</i> (TRAMP)	(64)
	<i>in vitro</i> (LNCaP, VCaP)	(65)
	<i>in vitro</i> (LNCaP, PC3)	(67)
	<i>in vitro</i> (LNCaP, PC3)	(68)
	<i>in vitro</i> (LNCaP, PC3)	(69)
	<i>in vitro</i> (PC3, SKBR-3)	(70)
	<i>in vitro</i> (PrEC, LNCaP, PC3)	(66)
	<i>in vitro</i> (BPH-1, LNCaP, PC3)	(74)
	<i>in vitro</i> (PC3) and <i>in vivo</i> (nude mice)	(57)
	<i>in vitro</i> (TRAMP, C57BL/6)	(71)
<i>in vitro</i> (BPH-1, PC3, LNCaP)	(58)	
Ampelopsin	<i>in vitro</i> (LNCaP, PC3) and <i>in vivo</i> (immunodeficient mice)	(75)
Cabazitaxel	phase III clinical trial	(81)
Curcumin	<i>in vitro</i> (PC3)	(91)
	<i>in vitro</i> (LNCaP)	(86)
	<i>in vitro</i> (DU145)	(84)
	<i>in vitro</i> (PC3, LNCaP)	(90)
	<i>in vitro</i> (PC3, DU145)	(92)
	<i>in vitro</i> (DU145, LNCaP)	(89)
	<i>in vitro</i> (PC3, DU145)	(94)
	<i>in vitro</i> (LNCaP, PcBra1)	(85)
	<i>in vitro</i> (LNCaP, C4-2B)	(87)
	<i>in vitro</i> (PC3) and <i>in vivo</i> (nude mice)	(93)
Resveratrol	<i>in vitro</i> (TRAMP)	(99)
	<i>in vitro</i> (AsPC-1, MIA PaCa-2, Panc-1) and <i>in vivo</i> (nude mice)	(98)
	randomized placebo controlled clinical study	(97)
Lycopene	<i>in vitro</i> (TRAMP)	(103)
	<i>in vivo</i> (Wistar rats)	(104)
	clinical trial	(102)
	clinical trial	(105)
	phase I-II clinical trial	(106)
Genistein	<i>in vitro</i> (PC3)	(113)
	<i>in vitro</i> (LNCaP, DU-145)	(117)
	<i>in vitro</i> (PC3, CRL-2221)	(111)
	<i>in vitro</i> (PC3) and <i>in vivo</i> (CB-17 mice)	(115)
	pilot trial	(114)
Capsaicin	<i>in vitro</i> (PC3)	(118)
	<i>in vitro</i> (PC3)	(120)
	<i>in vitro</i> (LNCaP, PC3, DU145) and <i>in vivo</i> (nude mice)	(121)

from these phytochemicals includes nuclear magnetic resonance, thin layer chromatography, fourier transformed spectrometry, mass spectroscopy, and high-performance liquid chromatography (39). Moreover, there is a need to determine the anticancer activity of the bioactive phytochemicals during all these processes in a bio-guided assay, *viz in vivo* and *in vitro* anticancer experiments. Some other factors, such as pharmacodynamics, time and concentration dependent, pharmacokinetics, fate of metabolic process, immunogenicity, non-target effect, side effects and drug interaction need to actively be taken into consideration before the anticancer drug would be manufactured (38). Many authors' have reported anticancer potential of various natural plant extracts and its corresponding isolated compounds for the management of prostate cancer (Table 2).

The role of phytochemicals in prostate cancer: an up-to-date vision

Isobavachin, Glabranin, Anthocyanin, Eriosemation

Singh *et al.* (40) used a bioinformatics technique to establish the anti-prostate ability of some selected phytochemicals, that could be used as chemotherapeutic agents against prostate cancer. A total of 803 phytochemicals were screened for its binding affinity against androgen receptor (AR) using molecular docking, based on the following selecting criteria: do not exhibit any inhibitory and cytotoxicity effect and have significant AR inhibition activity. Among those selected phytochemicals, those exhibiting the best binding characteristics were (in the increasing order): isobavachin > glabranin > anthocyanin > eriosemation. Thus, the authors stated these phytochemicals feasible for designing appropriate and effective drugs for both prevention and management of prostate cancer and related diseases.

3,3'-Diindolylmethane and Indole-3-carbinol

Indole-3-carbinol (I3C) and its metabolite 3,3'-diindolylmethane (DDM) have been increasingly assessed for its ability to inhibit prostate cancer cell cultures. It was shown a marked ability to prevent both androgen and estrogen-mediated pathways, at same time that stimulated the xenobiotic metabolism pathway, when applied at concentrations of 1-5 mM. At higher doses (25 mM), these phytochemicals were able to stimulate cyclin inhibitors and prevent the insulin-like growth factor-1 receptor expression. Moreover, and curiously, only little variations were stated between these phytochemicals, namely when looking at: 1) their binding ability to AR; 2) the concentration required to reach inhibitory effects; 3) variation in the level of metabolic pathway, which might be aryl hydrocarbon receptor-dependent and -independent mechanism. To highlight that both phytochemicals revealed no adverse effects on significant cellular pathways. Some years early, Weng *et al.* (41) also proposed that I3C and DDM target multiple aspects of cancer cell-cycle regulation and survival including Akt-NF- κ B signaling survival, caspase initiation, metabolism, estrogen receptors signaling initiation, BRCA gene expression, induction of stress in the endoplasmic reticulum, and activation of cyclin-dependent kinase activities. Also, Weng *et al.* (42) reported that I3C exert anticancer effects through inducing apoptosis, reducing

intracellular levels of phosphorylated Akt, Bcl-xL, and ReIA, and increasing phosphorylated p38 levels.

Chinni *et al.* (43) also established the molecular mechanism behind the antineoplastic activity of I3C on prostate cancer cells. It was related to DNA laddering and poly (ADP-ribose) polymerase (PARP) cleavage. Indeed, the authors stated that I3C plays an active role in G1 cell cycle arrest, and this action might be linked to the stimulation of p21^{WAF1} and p27^{Kip1} CDK inhibitors, tailed by their relationship with cyclin D1 and E, as well as down-regulation of CDK6 protein kinase levels and activity. I3C was also able to prevent the retinoblastoma protein hyperphosphorylation, present in treated prostate cancer cells, and to downregulate the NF- κ B and Bcl-2, consequently preventing the process of cell cycle and G1 arrest, leading to cell death and regulation of genes related to prostate cancer cells death. Besides these authors, some others supported the capability of I3C as a chemotherapeutic and preventive drug against prostate cancer. For instance, Li *et al.* (44) reported that I3C possess a great binding potential with aryl hydrocarbon receptor, which modulates the expression of nuclear receptors. Aryl hydrocarbon receptor is able to up-regulate the gene expression of the Phase I enzyme CYP1A1 and Phase II enzymes glutathione-S-transferase available in prostate cancer cells. Jeon *et al.* (45) also demonstrated that I3C and its metabolite DDM possess effective radio and chemopreventive attributes. This was shown in the sensitization of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) initiated apoptosis against prostate cancer cells containing TRAIL-resistant LNCaP. The process was up-regulated with the two different TRAIL death receptors DR4 and DR5, respectively. Sarkar and Li (46) also reported the LNCaP inhibition by prevention of Akt/NF- κ B signaling. Nachshon-Kedmi *et al.* (47) also showed that both I3C and DDM are able to kill prostate cancer cells depending on concentration and time of exposure, revealing that the level of apoptosis does not depend on p53-independent pathway, with no adverse effects on the amount of Bcl-2, bax and fasL.

Souli *et al.* (48) observed that *in vitro* I3C (20 mg/kg b.w.) reduced the proliferation of prostate cancer cells and *in vivo* reduced the both tumor growth and volume up to 78%. Also, a reduction in the process of angiogenesis was observed.

On the other hand, the anticancer potential of DDM was also stated by some other authors. Vivar *et al.* (49) found that DDM has the potential to arrest G1 cell cycle and to prevent the activity of cdk2 and cdk4 proteins and, therefore, to stimulate the process of the cell cycle from the treated prostate cancer cell regardless of the fact that they might be androgen-dependent and their p53 status. Garikapaty *et al.* (50) reported that DDM enhance the cell cycle arrest, mainly at G1, in DU145 cells, and downregulate the transduction signal pathway of Akt, p-Akt, and PI3 kinase, at same time that enhanced the prevention of essential cell cycle components, like cyclin D1, cdk4, and cdk6. In the same line, Chen *et al.* (51) stated that DDM could induce the signaling pathway of AMP-activated protein kinase, responsible for the AR down-regulation, overpowering the mammalian target of rapamycin (mTOR), and induction of apoptosis in androgen-insensitive and androgen-sensitive prostate

cancer cells. Le *et al.* (52) found that in androgen-dependent human prostate cancer cells, DDM treatment led to a marked decrease in the level of prostate-specific antigen transcription, consequently affecting the intracellular and secreted prostate-specific antigen protein levels. Also, a dose-dependent inhibitory effect was found, as was its involvement in down-regulation of the expression of prostate-specific antigen promoter. Also, it was found a high level of inhibition on androgen-induced AR and restricted its movement into the nucleus. Thus, it was stated that DDM possess a strong inhibitory effect on dihydrotestosterone and prevented the multiplication of prostate cancer cells. Moreover, it was discovered that the proper analogue structure and surface charge of DDM may be on the basis of its ability to disrupt AR function. Kong *et al.* (53) showed that DDM is able to deactivate mTOR and to reduce the Akt activity in platelet-derived growth factor-D overexpression in prostate cancer cells. Also, they found a reduction in the level of cell multiplying and spreading of prostate cancer cells. Finally, Nachshon-Kedmi *et al.* (54) discovered that DDM stimulates the inhibition of prostate cancer cell by a mitochondrial pathway, encompassing the relocation of cytochrome c from the mitochondria to the cytosol. Moreover, they observed the initiation of caspase-9, and effector caspase-3 and -6, resulting in PARP cleavage and stimulation of cell death (55). In short, given the latest findings, both I3C and DDM can be considered both promisory therapeutic and preventive agents on prostate cancer, including on prevention for the reoccurrence of micro-metastases, which often persist in patients with major prostatectomy.

Sulforaphane

Several authors have highlighted the anticancer potential of isothiocyanates obtained from cruciferous vegetables. Sulforaphane is a type of isothiocyanate that has been characterized as an anticancer drug. A progressively high number of studies have assessed the use of sulforaphane as a therapeutic drug. Some of the highlighted modes of action of sulforaphane against prostate cancer cells include: prevention of carcinogen-metabolizing enzymes, stoppage of mutagens, initiation of apoptosis, later preventing the spread of neoplastic cells, stimulation of neoangiogenesis, inhibition of prostate tumors initiation and metastasis development, as also the overpowering of Toll-like receptor (TLR)-4-mediated transcription, alteration of the cell signaling involved pathways, blockage of activities that involves histone deacetylase that regulates epigenetically interceded gene development, and steadiness of the AR (56). Some of the highlighted apoptosis biomarkers and mechanisms are illustrated below.

Singh *et al.* (57) described the sulforaphane stimulatory effect on caspase induction, leading to cell death on human prostate cancer cells and their inhibitory effect by preventing the spreading of the cancerous growth from PC-3 xenografts. Sulforaphane inhibits prostate cancer cells through the release of cytochrome c, cleavage of Bid, expression of Bim EL and Bok, and Fas protein level. Also, it has been established that sulforaphane (15 mM) could prevent the histone deacetylase activity in BPH-1, LnCaP, and PC-3 prostate epithelial cells. Also, they revealed that 1.5- to 2-fold rise in p21Cip1/Waf1

and Bax protein expression, as well as down-regulation of the cell cycle, led to variation in the cell cycle kinetics, initiation of multi-caspase activity and cell death (58). Singh and Xiao and Lew and Dhir and Singh (57) also stated that the way by which sulforaphane inhibits prostate cancer cells includes DNA fragmentation, PARP cleavage, bax and Bcl-2 protein expression, stimulation of caspase-3, -8 and -9. Wang *et al.* (59) established the molecular modes of action of sulforaphane for inhibition of androgen-independent DU145 human prostate cancer cells, sulforaphane down-regulated the expression of bcl-2 and activated caspases to execute apoptosis. Also, Cho *et al.* (60) reported the role of c-Jun N-terminal kinase in G2/M inhibition and caspase-stimulated cell death. Singh *et al.* (61) found that sulforaphane has the ability to induce ROS, which culminates in prostate cancer cells apoptosis. The mechanism behind this effect involves the release of cytochrome c, DNA fragmentation and the release of its content, cleavage of pre-caspase-8, and increase of oxidative stress. Moreover, Xu *et al.* (62) validated the inhibitory effect of three different isothiocyanates on human BPH-1 cells, through activation of AP-1, expression of Bcl-2, ERK1/2, JNK1/2, Elk-1, and c-Jun phosphorylation.

Xu *et al.* (63) demonstrated that phenethyl isothiocyanate (5 and 7.5 μ M) and sulforaphane (20 and 30 μ M) expressively repressed gene expression of NF- κ B-regulated vascular endothelial growth factor (VEGF), NF- κ B transcriptional activity, nuclear translocation of p65, cyclin D1 and Bcl-XL in treated prostate cancer cells. Moreover, these molecules prevented the phosphorylation process in IKK β and IKK α , as well as significantly repressed the IKK β phosphorylation *in vitro*, when facilitated by IKK β .

Singh *et al.* (64) using sulforaphane synthesized from a cruciferous vegetable (D, L sulforaphane), administered orally at the rate of 6 μ mol, 3 times/week starting from 6 weeks after the mice growth, stated that sulforaphane-treated mice exhibited a substantial reduction in the rate of cell proliferation and enhanced the NK cell lytic activity. Histology data reaffirmed the inhibitory effect of sulforaphane on prostate carcinogenesis, which showed a well-differentiated carcinoma as well as the proper development of prostatic intraepithelial neoplasia when compared to the control that had a dorsolateral prostate which could be linked to the overpowering of T-antigen expression in the transgenic adenocarcinoma of mouse prostate (TRAMP) mice treated. In the same year, Gibbs *et al.* (65) established that sulforaphane could inhibit prostate cancer cell by prevention the enzymatic activity of histone deacetylase 6, which had an adverse effect on AR, thereby playing an active role in the AR signaling down-regulation. Also, AR was degraded in the proteasome, which later resulted to a decrease in AR target gene expression and AR possession available at its target genes.

Beaver *et al.* (66) revealed the sulphorophane potential as a chemopreventive and hopeful dietary anticancer agent by highlighting its ability to regulate the development and expression of long noncoding RNAs. Moreover, sulforaphane-treated cells enhanced the gene activities that controls the glycolysis activity (GAPDH), autophagy (MAP1LC3B2) and development of chromatin structure (H2AFY). Also, sulforaphane-treated

cells decreased the activity of LINC01116 gene by preventing colony formation up to 4-fold in prostate cancer cells (CRISPR/CAS9). Moreover, sulforaphane (20 and 40 μM) revealed to prompt cell death on prostate cancer cells in a mitochondrial-dependent way. Indeed, it was established that sulforaphane inhibits prostate cancer cells through its ability to trigger changes in the cancer cell mitochondria leading to cell death and protection of non-cancer cell against oxidative problems which avoid cell death. The mechanism of action involves an expression from the family of B cell lymphoma 2 homologs, phase II enzymes, mitochondrial redox balance, initiation and deactivation of caspases, mitochondrial respiratory complex actions, oxygen utilization and bioenergetics, action of kinase pathways and the control of proapoptotic proteins generated from mitochondria. Choi *et al.* (67) reported that some inhibitor protein and Apaf-1 could trigger prostate cancer cells autolysis, when treated with sulforaphane. Shankar *et al.* (68) revealed that sulforaphane was able to enhance the release of ROS, to up-regulate TRAIL-R1/DR4, TRAIL-R2/DR5, to collapse the mitochondrial membrane, to initiate caspase-3 and -9, as also to prevent the restrained expression of Bcl-2, Bcl-XL, and Mcl-1, and to initiate Bax, Bak, Bim, and Noxa, in an orthotopic model in mice. Similarly, Xiao *et al.* (69) observed that sulforaphane prevented the activity of mitochondrial respiratory chain enzymes, raised the cell death, at same time that possessed the ability to generate mitochondrial ROS, which can stimulate various cellular reactions involved in both destruction and complete inhibition of human prostate cancer cells. Wiczek *et al.* (70) discovered that sulforaphane possesses the capability to destroy the protein synthesis, referred to as survivins, which are short-lived proteins. This represents another targeted mode of action of sulforaphane against prostate cancer cells, which single them out as an anticancer drug and chemotherapeutic activity. This shows that sulforaphane could prevent the process of protein translation necessary for cancer cell growth and multiplication and played an active role in down-regulating the necessary signaling pathways. Conversely, a decrease in glycolysis level was detected in mitochondria, while the ATP level remained unaffected in untreated cells. Keum *et al.* (71) found a marked reduction in the level of Keap1 and Bcl-XL proteins by administering 200 mg and 500 mg of sulforaphane, while western blot analysis revealed an enhanced Nrf2, HO-1, cleaved-caspase-3, cleaved-PARP and Bax proteins. Moreover, a reduction in phosphorylation and Akt levels and a downregulation of the activity of kinase and target proteins was also stated. Traka *et al.* (72) discovered that consumption of broccoli for a period of 6 months interrelate with glutathione-S-transferase mu 1 (GSTM1), which induces a drastic change in the signalling pathways related to infection and carcinogenesis in prostate. Also, it was stated that isothiocyanate chemically interrelates with transforming growth factor beta 1 (TGF β 1), epidermal growth factor (EGF) and insulin peptides to form thioureas, and boosts TGF β 1/Smad-mediated transcription. Traka *et al.* (73) also observed that sulforaphane subdues transcriptional alterations prompted by PTEN deletion and prompts further alterations in gene expression related to cell cycle inhibition and cell death in PTEN null tis-

sue, although no influence was found on transcription process in wild-type tissues. Not least interesting was that Hsu *et al.* (74) observed that sulforaphane led to a marked reduction in the level of DNA methyltransferases, particularly DNMT1 and DNMT3B, as well as to a decrease in the methylation of cyclin D2 promoter, which signifies an improvement in the level of cyclin D2 transcript levels necessary for de-repressing methylation-silenced cyclin D2, through influencing epigenetic pathways.

In short, with the above referred findings, it is possible to state that a diet containing the nutritional phytochemical sulforaphane may offer additional benefits and exert a huge impact on both prevention and treatment of prostate cancer. Indeed, multiple modes of action have been attributed to this nutritional phytochemical, showing the multiplicity of potentialities arising from this molecule, all of them dose- and target site-dependent. Also, interesting to emphasize is that, given the sulforaphane potentiality to epigenetically regulate the cyclin D2 expression, it may offer innovative understandings on the regulation of gene expression relating to the development of prostate cancer drugs. Moreover, it has been increasingly stated that it may be highly effective as a chemopreventive drug to both prevent androgen-dependent or androgen-independent prostate cancer.

Ampelopsin

To the flavonoid ampelopsin, derived from the *Ampelopsis grossedentata* leaves, remarkable anti-prostate cancer effects have been also stated. Ni *et al.* (75) discovered that ampelopsin had the ability to prevent the spreading and extension of the CXCR4 protein, involved in prostate cancer onset. This involvement of ampelopsin as an antimetastatic agent has been also stated both using cell and animal models, in *in vivo* and *in vitro* experiments (76, 77). Moreover, ampelopsin also downregulated the Bcl-2 activity (78, 79).

Cannabinoids

Appendino *et al.* (80) validated the anticancer influence of cannabinoids present in *Cannabis sativa* leaves against prostate cancer cells, when tested *in vivo* and *in vitro*. de Bono *et al.* (81) reported the presence of cabazitaxel, obtained from *Taxus baccata*, as an active component that suppressed prostate cancer cells in a randomized open-label trial, establishing that the presence of cabazitaxel could serve as an alternative to the DX drug, which has been associated with the development of resistance, especially to metastatic castration-resistant prostate cancer cells.

Curcumin

To turmeric, several anticancer effects at different levels of prostate cancer growth have established (82-87). Dorai *et al.* (88) stated that curcumin possesses the potential to inhibit the action of EGF receptor available on prostate cancer cells. Mukhopadhyay *et al.* (89) found that curcumin work based on the fact that it can downregulate the expression of Bcl-2 and Bcl-xL and activate procaspase-3 and -8. Holy (90) observed that curcumin presented important chemopreventive potential in cell shape in prostate cancer cells. Chendil *et al.* (91) described its ability to downregulate the

action of TNF- α -mediated NF- κ B, which consequently leads to Bcl-2 protein down-regulation. This might be another factor that supported the radiation-inducing cell death by liberating cytochrome c and stimulating caspases. Hour *et al.* (92) discovered that curcumin could influence the level of cytotoxicity induced on prostate cancer cells, when paclitaxel and 5-fluorouracil were tested as chemotherapeutic drugs. This drug works by overwhelming the constitutive initiation of NF- κ B. Li *et al.* (93) demonstrated that curcumin could exhibit a radiosensitizing activity by downregulating MDM2 oncogene via the phosphatidylinositol 3 kinase (PI3K)/mTOR/ETS2 pathway. In 2002, Ohtsu *et al.* (94) found that curcumin has the ability to regulate the AR against the growth of prostate cancer cell.

This is a novel observation that may represent an important mechanism by which curcumin functions as a chemopreventative agent, and as an inhibitor of angiogenesis and metastasis.

Resveratrol

Resveratrol is another phytochemical component that has been highlighted as a chemopreventive and therapeutic drug which might be linked to its antiproliferative effects recorded when tested on animal tumor models and during clinical trials (95, 96). Kjaer *et al.* (97) demonstrated that resveratrol reduces the level of androgen precursors, comprising androstenedione, without any effect on the level of prostate serum antigen and prostate size, when tested *in vivo* over 4 months in middle-aged men. In 2010, Harikumar *et al.* (98) reported the effect of gemcitabine, which has the same anticancer effect like resveratrol, as a chemotherapeutic drug that could be used for prostate cancer cells growth inhibition by preventing markers involved in proliferation, penetration, metastasis, and angiogenesis. Similar findings were stated by Seeni *et al.* (99), who found that resveratrol decreased the development of prostate cancer cells when tested in rat models. Some of the modes of action responsible for their inhibitory activity include preventing expression involving AR and inhibition of prostate cancer cells in transgenic mice having adenocarcinoma prostate cancer.

Lycopene

Lycopene and several tomato-derived products have been highlighted to possess anticancer effect, namely through preventing the spread of cancer cells, control androgen signaling pathways, cell cycle inhibition, and prompt cell death (100). Moreover, tomato has been documented to have a high rate of antioxidant compounds, that consequently lowers the rate of oxidative stress and removes any available free radicals that could destroy DNA whenever ROS is liberated (101). Chen *et al.* (102) reported the effect of incorporating a tomato-based sauce containing 30 mg of lycopene into the diet of patients with localized prostate adenocarcinoma for a period of three weeks. The lycopene present in the tomato sauce caused a reduction in the level of oxidative damage in the prostate tissue, also leading to 21.3% reduction in the level of leukocyte from a patient affected with prostate cancer.

In 2010, Konijeti *et al.* (103) conducted a randomized experiment with tomato paste containing an equal

amount of lycopene on mice affected with transgenic adenoma of mouse prostate for a period of 20 weeks, and found that the lycopene fed mice showed a significant reduction in the level of prostate cancer when compared to mice fed without lycopene. Boileau *et al.* (104) revealed that tomato powder intake could decrease the occurrence of prostate cancer, which might be linked to the availability of lycopene. Also, the presence of lycopene minimized the number of ROS generated and prevented the prostate cancer cells proliferation. Kucuk *et al.* (105) confirmed the apoptosis effect of lycopene supplements in a patient suffering from prostate cancer. Lycopene inhibited the prostate-specific antigen level and decreased the tumor size by downregulating AR nuclear translocation. Gontero *et al.* (106) reported the anticancer effect of a supplement containing lycopene, selenium and green tea catechin administered for 6 months in patients suffering from severe prostatic intraepithelial neoplasia and atypical small acinar proliferation. In short, several authors have increasingly reported that the inclusion of lycopene in the diet tends to decrease the menace of prostate cancer (36, 107, 108).

Genistein

Genistein is a typical example of isoflavones that has been shown to possess an antitumor effect, since this phytochemical has the potential to inhibit prostate cancer growth through NF- κ B/Notch/Akt/Wnt/AR signaling networks control. Sarkar *et al.* (109) reported that genistein could down-regulate the AR expression and minimized the rate of interaction of nuclear binding connecting androgen responsive elements, thereby preventing the prostate-specific antigen activity. Also, it was hypothesized that the retraction of NF- κ B signaling may be the utmost significant mode of action through which isoflavones perform their chemopreventive effects. Indeed, genistein repressed the nuclear relocation of NF- κ B and subsequent transactivation of NF- κ B target genes together with modulation of IKK and I κ B (110, 111). Moreover, isoflavones have been reported to prevent Wnt and Notch signaling and to inhibit the Akt phosphorylation (112).

On the other hand, genistein has been shown to possess the ability to destroy the development of prostate cancer through prevention of the NF- κ B activity, initiation of a regulatory protein that controls cell cycle, and prompting of cell cycle stoppage at G2/M (113). Hussain *et al.* (114) discovered that a soy isoflavone supplement (NovasoyTM) having genistein, diadzein, and glycitin, could exhibit a reduction in the prostate-specific antigen serum level. Also, Li *et al.* (115) reported that genistein demonstrated antitumor effect by decreasing NF- κ B initiation and signaling. Moreover, Nagata (116) reported that this phytochemical (50 μ M) was able to prevent the proliferation and expansion of serum growth factor in some Asian men who consume soy as a great percentage of their diet. Conversely, there was no adverse effects observed on the EGF receptor responsible for autophosphorylation (117).

Capsaicin

To capsaicin, a phytochemical constituent present in red and chili peppers, interesting anticancer effects on prostate cancer cells have been attributed. In fact, it

has been stipulated that capsaicin regulates the transient receptor capability via vanilloid-1 (TRPV-1), which might be both receptor-based or receptor-independent. For instance, Malagarie-Cazenave *et al.* (118) discovered that capsaicin (>10 μM) inhibited the development of prostate cancer cells, mostly through significant apoptosis, triggered by ROS generation, initiation of caspase-3, and disintegrating the innermost mitochondrial transmembrane ability.

In addition, Ziglioli *et al.* (119) stated that capsaicin specifically prevents the enlargement of tumors, a process that requires a large amount of energy. Sanchez *et al.* (120) also found that capsaicin has the capability to initiate stress on the endoplasmic reticulum of prostate cancer cells. This might be linked to the stimulatory and expression of transcription factor 4, phosphorylation of eukaryotic initiation factor 2 α and growth inhibition. Finally, Mori *et al.* (121) reported that capsaicin may interfere with and reduce the process of AR transcription, besides to prevent the prostate-specific antigen supporter stimulation, NF- κB , and nuclear movement.

Other phytochemicals

Several authors have documented the anticancer effect of phytochemicals, and specifically its anti-prostate cancer effects have been assessed both in animal models and humans. Tsai *et al.* (122) isolated silibinin as an active ingredient from *Sylibum marianum*, and reported that the presence of silibinin is responsible for the prostate cancer inhibition when tested in an *in vitro* and *in vivo* trial. Lee and Choi (123) showed that withaferin A, isolated from *Withania somnifera* roots, possess anticancer effects through a pleiotropic mode of action.

Kumari *et al.* (124) established the anticancer potential of *Camelia sinensis* leaves, and linked the observed efficacy to the presence of various phytochemicals, including epigallocatechin, picatechin, epicatechingallate. For instance, Hsieh and Wu (125) reported that different phytochemicals, containing (-)-epigallocatechin gallate, quercetin, and genistein blocked the spreading of prostate cancer cells by reducing the activity of AR, p53, and quinone reductase. Ohigashi and Murakami (126) demonstrated the anticancer effect of tea polyphenols when combined with other phytochemicals could be used as a chemopreventive drug against prostate cancer cells. Moreover, Bettuzzi *et al.* (127) established that green tea catechins could be utilized for prevention of cancer cells when administered orally. On the other hand, Srikanth and Chen (128) also reported the anticancer effect of Bowman-Birk inhibitors, which are plant protease enzymes capable of inhibiting prostate cancer cells in an *in vivo* trial. The active component was obtained from the *Glycine max* seed.

Formulas in the treatment of prostate cancer

Nexrutine (NX), an herbal extract of *Phellodendron amurense* used as nutrient supplement in China and America revealed to suppress c-FLIP protein levels, and expression in androgen-independent prostate cancer cells (PC-3) (129). NX showed ability to potentiate the therapeutic efficacy of DX which resistance mechanism include up regulation of the anti-apoptotic protein c-FLIP. Indeed, NX combination with DX further decreased levels of c-FLIP by suppressing c-FLIP

promoter activity (containing NF- κB binding sites) by preventing p65 binding, resulting in reduced growth of PC-3 cells (130).

Five herbal supplements: FB, FM, PP, HF and FBL101 containing different combinations of various natural herbs such as licorice, black cohosh, Dong Quai, false unicorn and vitex berry root extracts, fennel seed extract, red clover blossoms extract, genistein and gamma oryzanol showed antitumor activity in severely combined immunodeficient mice bearing CWR22R and PC-3 prostate cancer xenografts. FB, FM, PP, HF and FBL101 inhibited PC-3 tumor growth similarly to CWR22R tumors by 53%, 75%, 80%, 81% and 87%, respectively with no alteration in the total plasma testosterone levels and decrease the intratumoral microvessel density in PC-3 tumors treated for all supplements but only in CWR22R tumors treated with HF. Only PP and FBL101 significantly reduced VEGF levels in PC-3 and CWR22R tumors, respectively (131).

"Horchata" is an herbal mixture infusion consisting in 66% anti-inflammatory plants, and 51% analgesics plants. Three out nine varieties of horchata prepared traditionally showed weak cytotoxic effects against PC-3 without any effect on normal cells with percentage inhibition of < 30% (132).

BIRM is an aqueous extract of dried roots of *Kalanchoe gastonis-bonnieri* with known immunomodulatory, antitumor and anti-metastatic activity against prostate cancer models (133). In fact, BIRM inhibited cell proliferation and clonogenic growth of the metastatic hormone-refractory prostate cancer cells with IC50 value of 3 $\mu\text{l/ml}$ (0.3% v/v) for LNCaP, and 8 $\mu\text{l/ml}$ (0.8% v/v) for DU145 and PC-3ML cells by increasing cell accumulation in the G(0)/G(1) phase by 33.8% and decreasing the proportion of cells in S phase by 54.6%. Apoptotic cell death in BIRM-treated cells was associated with activation of cell death-associated caspases by activation of caspase-8 via death receptor and FADD-mediated pathways. BIRM inhibited the activity of hyaluronidase, a hyaluronic acid-degrading enzyme, at 1 $\mu\text{l/ml}$ (134). BIRM showed 2.5-fold cytotoxic in presence of androgen (DHT) compared to cells grown DHT free culture in AR-expressing prostate cancer cells. While in AR-positive cells (LAPC-4 and LNCaP), BIRM showed a dose and time-dependent down-regulation of AR and increased apoptosis. BIRM also decreased levels of p-AKTser 473 in prostate cancer cell lines (PC-3 and DU145) (133). MAT LyLu tumor-bearing rats treated orally with BIRM showed a significant reduction in tumor incidence (50%), tumor growth rate (18.6 \pm 1.3 days for 1 cc tumor growth in control rats and 25.7 \pm 2.6 days in BIRM-treated rats), and only one out of six BIRM-treated rats versus four out of six in the control group developed lung metastasis (134). In addition, mice bearing PC-3ML tumors showed selective efficacy on tumor growth before tumors are established but limited efficacy when treated on existing tumors. Moreover, BIRM inhibited the LNCaP tumor generated by orthotopic implantation into dorsal prostate of nude mice (133). Three proteinase and heat (100°C) resistant active ingredients was identified from BIRM with a relative molecular mass (Mr) of ≥ 3500 by ultracentrifugation and gel filtration chromatography (134) and partial purification of BIRM by liquid-liquid extraction and

further fractionation by HPLC showed 4-fold increased specific activity on Prostate cancer cells supporting the anti-tumor activity of BIRM (133).

Aneustat (OMN54), a multivalent plant-derived therapeutic, showed marked synergistic tumour growth inhibition in combination with DX. A first-line treatment of advanced prostate cancer in the LTL-313H subrenal capsule patient-derived metastatic prostate cancer xenograft model (135). DX+Aneustat inhibited C4-2 cell migration and LTL-313H lung micro-metastasis/kidney invasion, downregulated expression of cancer driver genes such as FOXM1 (and FOXM1-target genes) and improved patient outcome by inhibiting prostate cancer tissue invasion and metastasis (135).

SH003 is an herbal preparation from *Astragalus membranaceus*, *Angelica gigas*, and *Trichosanthes Kirilowii* Maximowicz combined at a 1:1:1 ratio. 30% ethanol extract of SH003 induced apoptosis in dose-dependent manner in prostate cancer cell lines DU145, LNCaP, and PC-3, independently to AR, increased intracellular ROS levels and inhibited Ras/Raf1/MEK/ERK/p90RSK phosphorylation in androgen-independent DU145 cells, but not androgen-dependent LNCaP and PC-3 cells (136).

The immunostimulant Deep Immune (DI) is an extract of eight different medicinal herbs that stimulated phagocytosis and expression of a panel of inflammatory mediators (CXCL3, C4b, lymphotoxin, TLR1, NOS2, TNFSF14, and TNF) in cultured macrophages and increased tumor killing of both macrophages and TRAMP mouse splenocytes. Daily intake of this herbal product significantly suppressed the tumor size in TRAMP mice, by increasing splenocyte cytotoxicity against tumor cells and numbers of CD8 T cells, macrophages, and dendritic cells in the spleens and thereby preventing prostate cancer progression after diagnosis of low-risk prostate cancer (137).

Herbal formula (KMKKT) containing Korean *A. gigas* Nakai (AGN) root and nine other oriental herbs inhibited growth in the androgen-dependent LNCaP human prostate cancer cell model. It suppresses the expression of PSA mRNA and protein (IC₅₀, approximately 7 µg/mL, 48-h exposure) and an inhibition of androgen-induced cell proliferation through G1 arrest and of the ability of androgen to suppress neuroendocrine differentiation at exposure concentrations that did not cause apoptosis (138).

PC-SPES is a Chinese formula consisting in eight medicinal plants, that significantly reduce serum testosterone and prostate-specific antigen in patients with prostate cancer in a time- and dose-dependent manner (139, 140). Alcoholic PC-SPES extract significantly inhibit the growth of prostate cancer cell lines in culture by apoptosis and reduced tumor volume in immunodeficient mice xenografted with the PC-3 cell line (139). In Dunning R3327 rat prostate cancer model, dietary PC-SPES at levels of 0.05% and 0.025% did not exhibit any toxicity and exhibit a dose dependent inhibitory on both tumor incidence and rate of tumor growth when tumors were induced by intradermal injections of MAT-LyLu cells that are known to metastasize in the lung and lymph nodes (141).

Conclusions and future perspectives

Although prostate cancer has alarming incidence rates, where both androgens and their receptors play a crucial role in both progression and development, recent advances point to a more effective intervention with fewer side effects through using plant-food bioactives. In fact, and considering the adverse effects and toxicity associated with the use of antineoplastic agents, the discovery of new matrices containing bioactive molecules with promisor therapeutic potential may not only fill the existing gaps, but also ensure a more effective therapy when combined with conventional drugs. In this regard, it should not be neglected that more than 50% of anti-neoplastic drugs originate from natural sources, thus, besides to the updated data presented here, more in-depth research on this subject should be highly encouraged.

Author contributions

All authors contributed to the manuscript. J.S.-R., B.S., M.M., C.F.R., R. A. and N.M critically reviewed the manuscript. All the authors read and approved the final manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

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