Phytochemicals in Prostate Cancer

Prostate cancer is a heterogeneous disease, the second deadliest malignancy in men and the most commonly diagnosed cancer among men. Traditional plants have been applied to handle various diseases and to develop new drugs. Medicinal plants are potential sources of natural bioactive compounds that include alkaloids, phenolic compounds, terpenes, and steroids.

Keywords: prostate cancer ; medicinal plants ; phytotherapy ; secondary metabolites ; plant formulas

1. Introduction

1.1. A Brief Overview on Prostate Cancer

The rapid growth of chronic diseases over the past century, including cancers, has emerged as among the most difficult situations for public health systems in underdeveloped and developing countries [1]. Cancer is one of the most prominent health issues in all countries due to its growing prevalence, mortality rate and high treatment cost in both genders and in all ages. In general, cancer remains not only a cause of tremendous damage to health but also the second leading cause of morbidity worldwide [2][3].

Cancer is caused by uncontrolled cell proliferation that can take place in different tissues and spread into surrounding and distant tissues [4]. Despite the main progress made in cancer biology, cancer remains one of the principal causes of mortality, and those who survive can experience permanent complications (e.g., physical, cognitive, psychosocial struggles, and treatment side effects) [5][6]. It is of great concern to note that cancer is a widespread disease and diagnoses are sharply increasing globally. Many risk factors are mentioned for this rise and lifestyle changing play the most important role [7].

Oncology studies have shown several types of cancer that are commonly diagnosed, including prostate, lung/bronchus, colorectal, breast, stomach, and liver cancer [8]. Although there is some variation in cancer prevalence, prostate cancer was the most commonly diagnosed cancer in the United States of America (USA), Europe and Oceania in 2012 [9]. In the past decade, much attention has been focused on prostate cancer [10] due to the alarming number of patients and the high mortality rate [11][12]. In fact, prostate cancer is the second most deadly malignancy in men after skin cancer [13]. Also, it is the most frequently diagnosed cancer among men, with a high mortality rate. About 1.6 million new cases of prostate cancer were diagnosed in 2015, and 366,000 deaths were reported [14]. In comparison to 2012, there was an increase of about 45% in incidence and 19% in mortality rate [15][16][17][18]. According to the American Cancer Society, the risk of cancer diagnosis in men in their lifetime is 1 in 9, and about 1 man in 41 will die due to prostate cancer [19].

The prostate is a glandular organ found under the bladder composed of epithelial cells arranged in a fibromuscular stromal network [20]. Although it has been difficult to establish the definitive etiological clues linking prostate cancer development to incidence, several studies have consistently linked the disease with common risk factors, namely age, race, dietary and physical activity [8][21]. Prostate cancer incidence is, in essence, influenced by age since the risks of being diagnosed with it increases with age [22]. Apart from age and race, Attard et al. [10] have reported that family history, for example a first-degree relative (e.g., father, son, or brother) with prostate cancer has surfaced as the greatest risk factor. According to Pandey, et al. [23], either genetic or somatic mutations contribute 10% or less to the causes of prostate cancer, whilst the remaining 90% has been attributed to epigenetic changes such as lifestyle. However, it is evident that a process that associates risk factors with cancer is inflammation [24]. In order to understand the significant role of inflammation in cancer, it is important to unpack the physiological and pathological processes attributed to inflammation.

Early detection of prostate cancer, like other malignancies, is important for better management and to prevent mortality and reduce morbidity rates, so many studies have been conducted to evaluate the risk of prostate cancer based on signs and symptoms [25]. Some of them have concentrated on lower urinary tract symptoms (LUTS) like hesitancy, nycturia,

urinary retention and frequency, but almost all of them concluded that there are no signs and symptoms that are highly predictive of prostate cancer [26] and because it is vital for primary care providers and family physicians to suspect prostate cancer in patients who developed LUTS, it recommended that prostate-specific antigen (PSA) screening, but also digital rectal examination (DRE) should be performed for all of these patients and if any abnormalities detected, patients should be referred to urologists for complementary work-up and distinguishing between prostate cancer and benign prostatic hyperplasia [27][28].

PSA measurement was introduced in 1987 to verify the response to prostate cancer treatment, but was soon adopted for prostate cancer screening too [29][30] and after widespread use of PSA as a screening test, a dramatic rise in incidence was reported from 1989 to 1992 and from 1995 this rise continued with a slight slope until 2001 and after that has fluctuated year to year revealing changes in screening practices [31]. After prostate cancer screening with PSA started in 1991 mortalities have declined and this may be due to early detection and proper management of patients [32]. The cut-off point of 4.0 ng/mL was considered for PSA screening and studies have shown that with this threshold the negative predictive value of PSA for detecting prostate cancer is 89% in men with a median age of 69 years [33], so patients with PSA levels >4 ng/mL in two tests should undergo other work-up like prostate biopsy, multiparametric MRI [34] and whole body bone scans [35]. On the other hand, PSA is not entirely specific for prostate cancer, and other conditions, such as prostatitis, urinary tract infection (UTI), older age, benign prostate hyperplasia (BPH) and bicycle riding can cause elevations in PSA levels, and some medications, like 5α-reductase inhibitors, aspirin, thiazide and statins cause decreases in PSA levels [13][36]. Furthermore, most prostate cancers are not harmful if not diagnosed and treated, and using PSA for diagnosis for prostate cancer results in over-diagnosis and over- treatment, so nowadays there is a vigorous debate about the usefulness of PSA screening for early detection of prostate cancer [37][38]. As a result, researchers have introduced other biomarkers for prostate cancer, such as free PSA, human kallikerin 2, prostate cancer antigen 3, prostate-specific membrane antigen, etc. [39] to better diagnose prostate cancer and avoid over-diagnosis and over- treatment, but there is a public consensus that with evaluation of patient risk factors, physicians can separate high-risk patients and focus on them to not miss any significant cancer, in addition, to decline over-treatment and diagnosis [14][40].

Prostate cancer is a heterogeneous disease, so to anticipate the behavior of cancer, evaluating risk factors is very important [41]. Epidemiological studies have consistently emphasized the notion that naturally-occurring dietary agents possess chemopreventive properties and could easily suppress several malignancies, including that of the prostate [15]. However, there has been an inconsistency regarding a recommended plant-based diet, related nutrients, phytochemicals and prostate health [42].

1.2. Prostate Cancer: Main Risk Factors

The main risk factors can be stratified into two groups: non-modified and modified factors. Non-modified factors are age, family history, ethnicity, and genetic factors [40].

1.2.1. Non-Modified Risk Factors

Age: Before 40 years of age, mens' risk of developing prostate cancer is low. On the other hand, men older than 55 years of age have 17 times more risk of developing prostate cancer than men <55 years old [43]. The mean age when prostate cancer is detected in the United States is 66 years old [44].

Ethnicity: Incidence (60%) and mortality rate (2.4 times) of prostate cancer in African-American men is higher than for other races, and Hispanic men, Asian/Pacific Islanders, American Indian/Alaskan Natives are in lower risk of developing prostate cancer [44] and it has been shown that prostate cancer incidence in men who immigrate to regions with higher prevalence rate, is higher than men in their country of origin and this increase depends on the length of stay in that area [45][46].

Family and genetic factors: Patients with a positive prostate cancer family history have a higher risk of having this disorder than others, especially a positive history among first degree relatives and in multiple relatives and under 65 years old [47]. Until now more than 105 loci show that increased risk of prostate cancer have been identified, suggesting about 30% of heritability [48][49]. **Table 1** showed the relative risk of a family history of prostate cancer [47][50].

Table 1. Relative risk of prostate cancer in patients with a positive family history.

Risk Group	Relative Risk of Prostate Cancer
Father and brother had prostate cancer	9
≥2 first degree relatives having prostate cancer	4.39
Brothers having prostate cancer	3.14
First degree relative with prostate cancer at the age of<65	2.87
Second degree relative with prostate cancer	2.52
One first degree relative with prostate cancer	2.48
Father having prostate cancer	2.35
First degree relative with prostate cancer at the age of ≥65	1.92

Height: Another factor that increases prostate cancer risk is height. Taller men are in greater risk of progressive prostate cancer, not total prostate cancer [51] and an overall relative risk of 1.19 has been estimated for prostate cancer per 10 cm increase in height [52].

1.2.2. Modified Risk Factors

Obesity: There is no clear relationship between obesity (body mass index (BMI) >25 kg/m^2 [53]) and increased risk of prostate cancer, but it is proven that obese men are at higher risk of advanced prostate cancer and biochemical recurrence [54][55], and also recent studies showed that risk of recurrence in patients who have weight gain after radical prostatectomy (RP) is higher [56]. Risk of advanced prostate cancer is six times higher than for non-obese men [43] and the risk of mortality increases by 20% for every 5 kg/m^2 increase in BMI [54]. The importance of this issue is highlighted by the fact that we know that the world's obese population has at least doubled since 1980 [57] and this can be due to lifestyle changes of patients that have resulted in lower physical activity and higher fat and red meat intake. Physical activity, especially vigorous activity, decreases prostate cancer risk, advance prostate cancer, mortality and recurrence of prostate cancer, and increases survival and it has been shown that physical activity for at least 3 h/week, even jugging and brisk walking, decreases cancer-specific mortality rate [58][59][60]. On the other hand, an inactive lifestyle has been related to higher PSA [60]. Many studies have revealed that higher intakes of fat, red meat, and dairy foods increase the risk of prostate cancer, but it is not proven yet. Dairy products contain a lot of fat and calcium, and high consumption of calcium increases the risk of prostate cancer, and this is probably due to disturbance of the metabolism of vitamin D [61], but non-dairy calcium intake does not change prostate cancer risk [62]. A 2012 study showed that high amounts of red meat and dairy foods elevate the prostate cancer risk 12-fold [63], and there is no specific amount for daily calcium intake, but some studies revealed that consumption of calcium >2000 mg/day raises the risk of prostate cancer [64].

Infectious disease: Infections and chronic inflammation leading to cellular damage and hyperproliferation cause 16% of worldwide malignancies [65] and some studies have revealed that UTI, sexually transmitted diseases and prostatitis could cause the development of prostate cancer via this mechanism, but it is uncertain [40][66]. At present, no specific infectious agent has been proven to cause prostate cancer. However, some evidence for the role of *Trichomonas vaginalis* in prostate cancer has been shown [67].

Occupational and external exposure: some jobs have a higher risk of prostate cancer due to exposure to specific materials, for example farmers who are exposed to pesticides and other chemical materials have a two times higher risk of prostate cancer [18][68] and also higher exposure to sunlight due to UV and ionizing radiation is related to an increased risk of prostate cancer [69][70].

Smoking: Cigarette smokers have a higher probability of developing prostate cancer, including advanced and hormone resistant forms, spreading metastasis and higher mortality rates and it depends on the amount (pack/year) and duration of smoking and it showed that the risk of mortality and recurrence of prostate cancer in former smoker patients, who quit

smoking 10 years before diagnosing prostate cancer is similar to that of non-smoking patients [58]. Some researchers are interested in the association among prostate cancer and alcohol intake, and many studies on this topic have been done, but mixed results were obtained, although one case-control study revealed that heavy drinkers have lower PSA levels and are in higher risk of advanced disease at detection [71][72].

Endogenous hormones: Androgens cause the proliferation and differentiation of the luminal epithelium of the prostate and play a key role in prostate carcinogenesis and establishing cancer, and because of these facts many patients respond to androgen deprivation treatment. For a long time, researchers believed that high serum androgen level was a risk factor of prostate cancer, but the last pooled analysis could not find any link between prostate cancer and serum androgen levels, but it found a connection among sex-hormone-binding globulin serum concentration and cancer risk [73]. Previously estrogens were a choice of treatment in castration-resistant prostate cancer and have been considered as a protective agent for cancer, but recently more studies have presented evidence for a pro-carcinogenic effect of estrogen on prostate cancer and shown that early exposure to estrogens increases the risk of later prostate cancer [74][75]. A pooled analysis in 2008 showed a strong connection between insulin-like growth factor-I and the risk of prostate cancer [76], but epidemiologic studies reviewed in 2011 revealed mixed findings, although they suggested that the insulin-like growth factor axis affects cancer progression rather than initiation [77]. The core genetic changes that cause activation of oncogenes and inactivation of tumor suppressors are responsible for the start and progression of prostate cancer, and epigenetic and structural genomic changes like deletion, chromosomal rearrangement, and amplification that result in gene fusion with new biologic functions are responsible for these changes. Chromatin remodeling, hypomethylation and promotor methylation that cause epigenetic regulation of gene expression play a significant part in the development and evolution of prostate cancer. Androgen receptors (AR) play a key role in prostate cancer, and changes in ARs like amplification, mutations, and ligand promiscuity are determining factors in progressive castrate-resistant prostate malignancies because these changes sensitize the ARs to low levels of intra-tumoral androgen [78]. The basic drivers for the initiation of prostate cancer are based on gene fusions of TMPRSS2 and the ETS family oncogenic transcription factors [79].

2. Therapeutic Strategies: A Brief Summary

To properly treat prostate cancer, patients should undergo full evaluation, including DRE, checking PSA and LFT, life expectancy and comorbidity evaluation, abdominal-pelvic CT, MRI and radionuclide bone scans if needed, and based on these data and characterizations of tumor (**Table 2**), including clinical stage, Gleason score, tumor volume, invasion and metastasis, patients are stratified into low, intermediate, high and very high risk groups and the cancer divided to localized, locally advance and metastatic prostate cancer [80][81][82].

Table 2. Classification of the risk groups of prostate cancer [83].

Risk Group	Clinical Stage	PSA (ng/mL)	Gleason Score	Biopsy Criteria
Low	T1a or T1c	<10	2–6	Unilateral or <50% of core involved
Intermediate	T1b, T1c, or T2a	<10	3 + 4 = 7	Bilateral
High	T1b, T1c, T2b, or T3	10–20	4 + 3 = 7	>50% of core involved or perineural invasion or ductal differentiation
Very high	T4	>20	8–10	Lymphovascular invasion or neuroendocrine differentiation

There are some established options for treating prostate cancer, like watchful waiting (WW), active surveillance (AS), radiation therapy (RT), hormone therapy (HT), and radical prostatectomy (RP) [80]. The goal of conservative management (AS, WW) is to reduce over-treatment [81]. In WW, patients are followed until new symptoms appear or get worse [80], so WW is suitable for poor prognosis patients with low life expectancy [81]. AS is suitable for low-risk prostate cancer or patients with <5 years life expectancy and in AS, physicians monitor patients closely and some periodic work-ups like DRE, PSA checking, prostate biopsy, and MRI are done, and every time the evidence is in favor of cancer progression,

patients then become candidates for other definite treatments [80][84]. RP is the first option introduced for treating prostate cancer [85], and it remains a typical form of management because it is the only method that cures the prostate cancer and the goal of RP is to eradicate cancer while conserving urinary continence and if possible potency [81]. Patients with intermediate and high-risk prostate cancer and life expectancy > 5 years are good candidates for RP, and RT is an option for managing almost all prostate cancer groups alone or with another modality, except got low and intermediate risk prostate cancer patients with low life expectancy (<5 years) [84]. RT and RP are the most common methods for managing prostate cancer, and so far, no study has establish the superiority of one of these two methods over the other and complications in both methods are common, and also there are no significant differences between the survival rates of these two methods [80]. There are different approaches for RP, including perineal, retropubic, laparoscopic and robotic, but until now there is no clear evidence that any one of this methods is better than the others in cancer control, cancer-related urinary continence and erectile function conservation, although some poorly designed studies have revealed that robot-assisted RP is better than laparoscopic methods in reducing positive surgical margins [86]. The most popular methods for RT that could be accompanied with HT are external beam radiotherapy and brachytherapy that have side effects like rectal and bladder toxicity and these side effects are more common in external beam radiotherapy. Other treatments like cryoablation and high-intensity focused ultrasound ablation have been introduced, but there is no proof to support their superiority [83][87]. Finally, physicians should choose the proper treatment based on tumor characterization and the patient's condition after the acceptance of the patient [88].

Many prostate cancer patients have more progressive disease, and management of these patients is different. In patients with symptomatic non-metastatic prostate cancer who are not candidates for curative treatment and patients with symptomatic metastatic prostate cancer, androgen deprivation therapy (ADT) is an option for palliative therapy, but we should not use ADT on patients with asymptomatic locally advanced prostate cancer or biochemical recurrence after curative therapy [82][89]. There are several methods for ADT. The gold standard is bilateral orchiectomy that diminishes the testosterone level below 15 ng/dL on average [90] but this has some disadvantages like irreversibility, physical and psychological pressure on the patients, so HT was introduced [91]. Luteinizing hormone-releasing hormone (LH-RH) agonists (leuprolide, goserelin, triptorelin) and antagonists (degarelix, abiraterone), non-steroidal antiandrogens (bicalutamide, flutamide, nilutamide) are three major drug categories used for ADT with LH-RH agonists being more prevalent, but the risk of flare phenomena is lower when using a LH-RH antagonist [91][92]. Intermittent or continuous ADT are two separate methods for managing systemic prostate cancer, but there is no difference between overall survival and cancer-specific survival of these two methods [82].

It is likely that after any curative management patients eventually relapse, that includes rising PSA or nodal involvement. If patients develop rising PSA after RP, the European Association of Urology guidelines advise early salvage radiotherapy (SRT) [82] and some retrospective studies have revealed that adding ADT to early SRT had some benefits in biochemical progression-free survival after 5 years [93]. In patients with PSA relapsing after RT, salvage RP is the first choice for local control of cancer. Salvage RP increases the risk of anastomotic stricture, urinary incontinence, erectile dysfunction, and rectal injury, so other alternative methods are available, like salvage cryoablation, high and low dose rates brachytherapy [82][94]. For management of nodal relapse, surgical and salvage lymph node dissection (LND) is the only choice. There are no specific criteria for candidate patients for salvage LND, but this should be considered and this method should be used for highly selected patients [82][95].

As we said, patients with the progressive disease can be managed with ADT, but some of these patients develop castration resistance, that is, castrated serum testosterone is less than 50 ng/dL, and the patient has biochemical or radiologic progression [96]. First-line treatment for this situation is abiraterone, enzalutamide or docetaxel (DX)-based chemotherapy and second-line treatment options depend on the chosen first-line treatment. If the patient was treated with abiraterone or enzalutamide as first-line treatment, DX-based chemotherapy is the next option and vice versa. If DX-based chemotherapy was used first and the patient responded, we can repeat this chemotherapy regimen again, but there is usually no improvement in the survival of patients [82][97]. Most of these patients developed with painful bone metastasis, but external-beam radiotherapy is very effective in relieving pain [98]. Finally, it is important to say that managing these patients needs teamwork, and the urologist, oncologist, psychologist, nurse, and even social workers should work together to manage patients properly [99].

Prostate cancer, like the other cancers, is an expensive disease and imposes a great burden on both the health system and patients, and these expenditures are increasing year by year which may due to over-treatment, over work-up or over-diagnosis and increased survival [100]. In 2010, the budget expended for prostate cancer care in the United States was 11.8 billion dollars, and in 2013 and 2017 this budget was $13.0 and $14.8 billion, respectively [101]. In Iran, direct medical costs for prostate cancer were estimated at about 12.5 million USD in 2016 for about 500 patients [102] and the cost for metastatic castration-resistant prostate cancer in Italy in 2016 ranged from €196.5–228.0 million [103]. These cost

variations may be due to differences in incidence and management protocols between countries [100], and most of these monies were expended for treatment [103], so having preventive strategies and using natural products for managing prostate cancer patients it is possible to markedly decrease the economic burden of this disease.

3. Plant Extracts and Plant-Derived Bioactives in Prostate Cancer

Traditional plants have been used to treat and cure various diseases [104], and this has led to increased use of medicinal plants in the search for new drugs from nature [105]. The discovery of new drugs is often established based on the knowledge that plant extracts can be used to treat diseases in humans. The plants are potential sources of natural bioactive compounds that are, but not limited to, secondary metabolites [106]. Cragg and Newman [107] have stated that any part of a 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 [108] reported that secondary metabolites are essential and important in plant use by people. In this regard, herbal medicines, which have been increasingly used in cancer treatment, represent a rich pool of new and bioactive chemical entities for the development of chemotherapeutic agents with many exhibiting favorable side effect and toxicity profiles compared to conventional chemotherapeutic agents [6][109]. In this sense, in the following section the plant extracts and corresponding bioactive constituents with anti-prostate cancer potential are carefully described. Lastly, a special emphasis on clinical studies confirming the plant-derived phytochemicals anti-prostate cancer potential is also given.

3.1. Plant Extracts with Anti-Prostate Cancer Potential

Among the plant extracts with anti-prostate cancer potential (**Table 3**), the most remarkable ones belong to the Annonaceae, Apocynaceae, Asteraceae, Combretaceae, Euphorbiaceae, Fabaceae, Lamiaceae, Malvaceae, Phyllantheraceae, Poaceae, Rutaceae, Solanaceae and Zingiberaceae families (**Figure 1**).
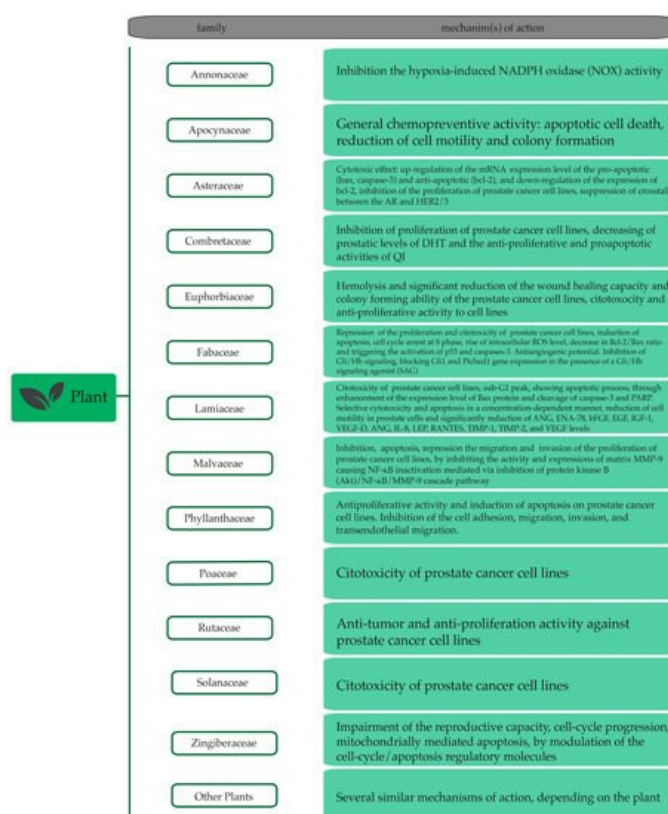
Figure 1. Plant species with anti-prostate cancer potential and its respective modes of action.

Table 3. Medicinal plants with anti-prostate cancer effects.

Plant Species	Family	In Vitro	In Vivo	References
Acacia catechu	Fabaceae	+	-	[110]
Achillea santolinoides	Asteraceae	+	-	[111]

Plant Species	Family	In Vitro	In Vivo	References
Achillea teretifolia	Asteraceae	+	-	[112]
Allium wallichii	Amaryllidaceae	+	-	[113]
Aloe perryi	Xanthorrhoeaceae	+	-	[114]
Anaxagorea brevipes	Annonaceae	+	-	[115]
Angelica gigas	Apiaceae	-	+	[116][117]
Annona muricata	Annonaceae	+	-	[118]
Anogeissus latifolia	Combretaceae	+	-	[110]
Apocynum venetum	Apocynaceae	+	-	[119]
Arachis hypogaea	Fabaceae	+	-	[120]
Baliospermum montanum	Euphorbiaceae	+	+	[121]
Berberis libanotica	Berberidaceae	+	-	[122]
Byrsonima crassifolia	Malpighiaceae	+	-	[123]
Calliandra portoricensis	Fabaceae	+	-	[124]
Capsicum chinense	Solanaceae	+	-	[123]
Carica papaya	Caricaceae	+	-	[125]
Cascabela peruviana	Apocynaceae	+	-	[126]
Chenopodium hybridum	Amaranthaceae	+	-	[127]
Cnidoscolus chayamansa	Euphorbiaceae	+	-	[123]
Cornus mas	Cornaceae	+	-	[128]
Costus pulverulentus	Costaceae	+	-	[129]
Crataegus Pinnatifida	Rosaceae	+	-	[130]
Crocus sativus	Iridaceae	+	+	[131][132][133]
Curcuma longa	Zingiberaceae	+	-	[131][134]

Plant Species	Family	In Vitro	In Vivo	References
Cymbopogon citratus	Poaceae	+	-	[135]
Cymbopogon giganteus	Poaceae	+	-	[135]
Euphorbia microsciadia	Euphorbiaceae	+	-	[111]
Euphorbia szovitsii	Euphorbiaceae	+	-	[111]
Eurycoma longifolia	Simaroubaceae	+	+	[136]
Fagara zanthoxyloides	Rutaceae	+	-	[137]
Fagopyrum esculentum	Polygonaceae	+	-	[138]
Fagopyrum tataricum	Polygonaceae	+	-	[138]
Ficus deltoidea var. *angustifolia*	Moraceae	+	-	[139]
Ficus deltoidea var. *deltoidea*	Moraceae	+	-	[139]
Formosa lambsquarters	Amaranthaceae	+	-	[138]
Glycine max	Fabaceae	+	-	[140]
Glycyrrhiza uralensis	Fabaceae	+	-	[141]
Haplophyllum perforatum	Rutaceae	+	-	[111]
Helicteres hirsuta	Malvaceae	+	-	[142]
Hertia angustifolia	Asteraceae	+	-	[111]
Hibiscus sabdariffa	Malvaceae	+	+	[143]
Leucaena leucocephala	Fabaceae	+	-	[123]
Lysimachia ciliata	Primulaceae	+	-	[144]
Malmea depressa	Annonaceae	+	-	[123]
Maytenus royleana	Celastraceae	+	+	[145]
Medicago sativa	Fabaceae	+	-	[111]
Melissa officinalis	Lamiaceae	+	-	[146][147]

Plant Species	Family	In Vitro	In Vivo	References
Mentha arvensis	Lamiaceae	+	-	[148]
Mentha spicata	Lamiaceae	+	-	[148]
Mentha viridis	Lamiaceae	+	-	[148]
Moringa oleifera	Moringaceae	+	-	[110]
Nepeta cataria	Lamiaceae	+	-	[149]
Nigella sativa	Ranunculaceae	+	-	[131][150]
Oryza sativa	Poaceae	+	-	[151]
Paeonia lactiflora	Paeoniaceae	+	-	[152].
Paramignya trimera	Rutaceae	+	-	[153]
Phyllanthus amarus	Phyllanthaceae	+	-	[154]
Phyllanthus niruri	Phyllanthaceae	+	-	[154]
Phyllanthus urinaria	Phyllanthaceae	+	-	[154]
Phyllanthus watsonii	Phyllanthaceae	+	-	[154]
Plumbago zeylanica	Plumbaginaceae	+	-	[155]
Polygonatum sp	Asparagaceae	+	-	[156]
Pseudocedrela kotchyi	Meliaceae	+	-	[137]
Psidium guajava	Myrtaceae	+	+	[138][157][158]
Punica granatum	Lythraceae	+	+	[5][159][160][161]
Quisqualis indica	Combretaceae	+	+	[162]
Remotiflori radix	Campanulaceae	+	+	[163]
Salvia multicaulis Vahl	Lamiaceae	+	-	[111]
Salvia trilobal	Lamiaceae	+	-	[164]
Sigesbeckia orientalis	Asteraceae	+	-	[165]

Plant Species	Family	In Vitro	In Vivo	References
Sophora alopecuroides	Fabaceae	+	-	[111]
Sutherlandia frutescens	Fabaceae	+	+	[166]
Terminalia bellerica	Combretaceae	+	-	[110]
Terminalia catappa	Combretaceae	+	-	[123]
Urtica dioica	Urticaceae	+	-	[111][167]
Vitis rotundifolia	Vitaceae	+	-	[168]
Wedelia chinensis	Asteraceae	-	+	[169][170]
Withania coagulans	Solanaceae	-	+	[171]
Xylopia aethiopica	Annonaceae	+	-	[172]
Zanthoxyli fructus	Rutaceae	+	+	[173]
Zingiber officinale	Zingiberaceae	+	+	[131][174][175]

+: Showed in vitro or in vivo antiproliferative effect; -: Not found.

3.2. Plant-Derived Bioactives with Anti-Prostate Cancer Potential

Many classes of metabolites isolated from medicinal plants have been reported for their activity against prostate cancer, namely alkaloids, phenolic compounds, and terpenoids (**Table 4**).

Table 4. Plant derived-compounds with anti-prostate cancer effects.

Bioactive Compounds	In Vitro	In Vivo	References
Alkaloids			
(−)-Anonaine	+	-	[176]
(−)-Caaverine	+	-	[176]
(−)-Nuciferine	+	-	[176]
6-Hydroxycrinamine	+	-	[177]
7-Hydroxydehydronuciferine	+	-	[176]
Capsaicin	+	-	[178]
Crinamine	+	-	[177]

Bioactive Compounds	In Vitro	In Vivo	References
Emetine	+	+	[179][180]
Liriodenine	+	-	[176]
Lycorine	+	+	[177][181]
Matrine	+	-	[182]
Oxymatrine	+	-	[182]
Oxysophocarpine	+	-	[182]
Schisanspheninal A	+	-	[183]
Sophocarpine	+	-	[182]
Tetrandrine	+	-	[184]
Carotenoids			
Crocetin	+	-	[133]
Crocin	+	-	[132]
Fatty acid			
(*E*)-ethyl 8-methylnon-6-enoate	+	-	[123]
Phenolic compounds			
α-Mangostin	+	+	[185].
γ-Tocopherol	+	-	[186]
δ-Tocotrienol	+	-	[186]
(-)-5,7-Difluoroepicatechin-3-*O*-gallate	+	-	[187]
(-)-Epicatechin-3-*O*-gallate	+	-	[187]
10-Gingerol	+	-	[175]
6-Gingerol	+	-	[175]
6-Prenylnaringenin	+	-	[188]

Bioactive Compounds	In Vitro	In Vivo	References
6-Shogoal	+	-	[175]
7-*o*-Galloyl catechin	+	-	[189]
8-Gingerol	+	-	[175]
8-Prenylnaringenin	+	-	[188]
Afzelin	+	-	[190]
Altholactone	+	-	[191]
Apigenin		+	[192]
Camptothin B	+	-	[141]
Catechin	+	-	[189]
Catechin-3-*o*-gallate	+	-	[189]
Chlorogenic acid	+	-	[130]
Chrysin	+	-	[193]
Cinnamaldehyde	+	-	[194]
Cornusiin A	+	-	[141]
Cornusiin H	+	-	[141]
Curcumin	+	+	[195][196][197][198]
Decursin	+	-	[117]
Decursinol angelate	+	-	[117]
Dehydrozingerone	+	-	[199]
Delphinidin	+	+	[200][201]
Ellagic acid	+	+	[202][203]
Eugenol	+	-	[194]
Fisetin	+	+	[204]

Bioactive Compounds	In Vitro	In Vivo	References
Flavokawain A	+	+	[205]
Flavopiridol	+	+	[206]
Garcinol	+	+	[207][208]
Ginkgetin	+	+	[209]
Hesperetin	+	-	[210]
Hirsutenone	+	-	[211]
HLBT-100 or HLBT-001 (5,3′-dihydroxy- 6,7,8,4′-tetramethoxyflavanone)	+	-	[212]
Honokiol	+	-	[213]
Icarisid II	+	-	[214]
Isoangustone A	+	-	[215][216]
Isovitexin	+	-	[139]
Juglone	+	-	[217]
Licoricidin	+	-	[215][216]
Magnolol	+	-	[218]
Mangiferin	+	+	[219][220]
Maysin	+	-	[221]
Methyl gallate	+	-	[189]
Osthol	+	-	[4][222]
Oxyfadichalcones A	+	-	[223]
Oxyfadichalcones B	+	-	[223]
Oxyfadichalcones C	+	-	[223]
Oxyfadichalcones D	+	-	[223]
Oxyfadichalcones E	+	-	[223]

Bioactive Compounds	In Vitro	In Vivo	References
Oxyfadichalcones F	+	-	[223]
Oxyfadichalcones G	+	-	[223]
Paeonol	+	+	[224]
Peperotetraphin	+	-	[225]
Physangulatins I	+	-	[226]
Plumbagin	+	+	[155][227]
Punicalagin	+	-	[228]
Quercetin	+	+	[229][230][231]
Resveratrol	+	+	[232][233][234]
Rutin	+	-	[235]
Tannic acid	+	-	[236]
Tricin	+	-	[237]
Xanthohumol	+	-	[182][238]
Protein			
Agglutinin	+	+	[239]
Diffusa cyclotide 1	+	-	[240]
Diffusa cyclotide 2	+	-	[240]
Diffusa cyclotide 3	+	+	[240]
Lectin ConBr	+	-	[241]
Lectin ConM	+	-	[241]
Lectin DLasiL	+	-	[241]
Lectin DSclerL	+	-	[241]
Terpenoids			

Bioactive Compounds	In Vitro	In Vivo	References
α-Santalol	+	+	[242]
4S,5R,9S,10R-Labdatrien-6,19-olide	+	-	[243]
(20R)-Dammarane-3β,12β,20,25-tetrol (25-OH-PPD)	+	+	[244]
Andrographolide	+	+	[245]
Celastrol	+	+	[246]
Citral	+	-	[135]
Diosgenin	+	-	[247].
Euphol	+	-	[248]
Isocuparenal	+	-	[183]
Jungermannenone A	+	-	[249]
Jungermannenone B	+	-	[249]
Muricins M	+	-	[250]
Muricins N	+	-	[250]
Nummularic acid	+	-	[251]
Oenotheralanosterol B	+	-	[252]
Plectranthoic acid	+	-	[253]
Sutherlandioside D	+	-	[166].
Widdaranal A		-	[183]
Widdaranal B	+	-	[183]
Widdarol peroxide	+	-	[183]
Withaferin A	+	-	[254]

-, no effect observed; +, positive effect.

4. Evidence from Clinical Studies

Prostate cancer patients are progressively using complementary and alternative medicines in order to support the immune system in addition to conventional treatments (**Table 5**). This minimizes morbidity related to conventional treatments, enhances the quality of life, eventually, in the hope of finding a cure when conventional treatment fails [255].

Table 5. Clinical trials showing the anti-prostate cancer potential of plant-derived phytochemicals.

Phytochemicals/Formulae	Bioactive Effect	Reference
Danshen (*Salvia miltiorrhiza*)	Protective effects; Improved survival (5–10%)	[256]
TCM formulae (Chai-Hu-Jia-Long-Gu-Mu-Li-Tang)	Improved survival	[257]
Pomegranate juice	Extension of PSA doubling time, with no adverse effects	[258][259][260]
Pomegranate, green tea, broccoli, turmeric	Decreased PSA levels	[261]
Resveratrol	Decreased the circulating levels of androgen precursors	[262]
	Extension of PSA doubling time, with no adverse effects	[263]
PC-SPEC	Decreased PSA levels	[264]

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