REVIEW ARTICLE

Phytomedicine and Prostate Cancer: A Review on Risk Factors, Progression, and Therapeutic Potential of Plant-Derived Bioactive Compounds

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Abstract

Prostate cancer (PC) is the most predominant malignant disease among men, with the highest incidence and fatality rates. Anatomically, the human prostate gland is distinguished into different zones, including the peripheral, central, and transition zones. The genesis of PC usually occurs in the central zone. A multitude of factors, notably aging, elicit an asymmetrical enlargement and inflammation of the prostate. This condition fuels benign infections leading to benign prostatic hyperplasia in the prostate gland and is a pre-cursor to PC. Generally, not all men succumb to this condition; however, the dissemination of the tumor to secondary sites escalates mortality rates. In this context, comprehension of the vulnerability factors and risk stratification can aid in the prognostication of the disease. So far, chemotherapy, radiation, and surgery are integral parts of the exhaustive treatment scheme for PC. Nonetheless, studies reveal that a larger proportion of patients choose phytomedicine as an adjunct to mainstream therapy due to its broad applicability and accessibility. Precisely, numerous plant-derived bioactive compounds provide rationales for the pathobiology of cancer progression. Although traditional phytotherapy has been acknowledged for managing cancer, there is a paucity of literature that incorporates traditional wisdom with modern herbal medicine. In light of this, the objective of this review is to provide a comprehensive insight into the biology, vulnerable factors, grading, and current therapies of PC. In addition, it also highlights a detailed analysis and description of the most recent research on phytomedicine and its multifunctional roles in PC therapy.

Key words: Bioactive compounds, gleason grading, phytomedicine, prostate cancer

INTRODUCTION

Prostate cancer (PC) is a globally prevalent urogenital malignancy. Males typically over the age of 50 are frequently diagnosed with PC. With over 1.4 million incidences and approximately 375,000 mortalities/year, it ranks as the second predominant reason for cancer-associated deaths in males, following lung cancer.[1] Reports claim that almost 70% of the mortality is attributed to metastatic PC and by 2040, these mortality rates are predicted to increase twofold. However, early diagnosis and advances in therapeutic interventions are decisive factors in declining mortality rates. Indeed, age, racial or ethnic background, genetic lineage, and dietary routines are all vulnerable factors for prospective prognosis.

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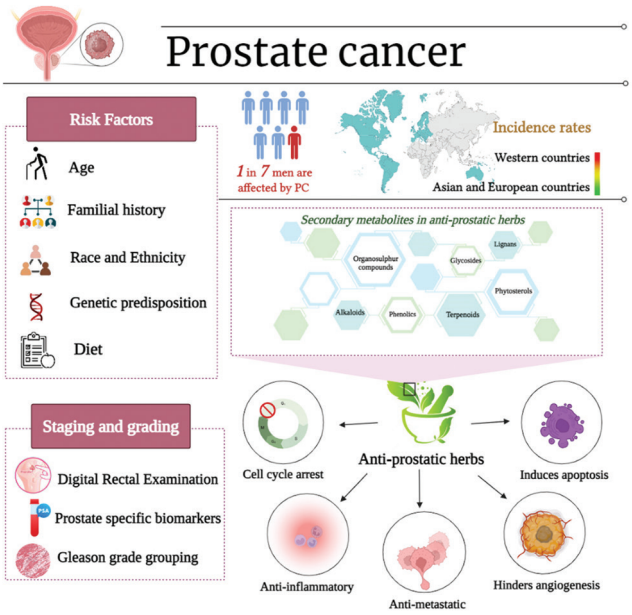
GRAPHICAL ABSTRACT



HIGHLIGHTS

- Prostate cancer remains the most common malignancy in men, with high incidence and mortality worldwide
- Both modifiable (lifestyle) and non-modifiable (genetic/age) risk factors significantly influence prostate cancer development
- Current treatment strategies include surgery, chemotherapy, radiation, and hormone therapy, often complemented by phytomedicine
- Plant-derived bioactive compounds show promising potential in modulating cancer pathways, supporting their role in prostate cancer therapy.

Besides, the patient's vigor and the tumor's morphological, histological grade, and molecular characteristics are certain cues in tracking the disease itinerary of an individual.[2,3] The management of PC entails adhering to personalized therapeutic schemes for indolent tumors. Nevertheless, disease relapse often ensues the curative strategy with hostile, or, in rare instances, refractory traits. Hence, a tangible approach to distinguish aggressive from indolent tumors is indispensable.

For decades, groundbreaking advances to understand the biochemistry and genomic architecture governing both local and metastatic PC have evolved. Specifically, the outlook of the hormone-sensitive reflex of PC, treatments geared to several androgen pathways, and novel inhibitors with tremendous therapeutic efficacy are explored.[4] Research intended to discern the molecular profile of primary, recurrent, and invasive diseases would certainly leverage the clinical management of PC. This review aims to discuss the epidemiology, risk factors, staging, and current phytomedicine and bioactive compounds for PC treatment.

EPIDEMIOLOGY

PC ranks among the top five solid tumors in terms of incidence and mortality, imposing a formidable global concern. According to the GLOBOCAN 2020 estimates, globally, 1.41 million new PC cases were reported, constituting nearly 7.3% of all cancer instances and 375,304 recorded deaths, accounting for 3.8% of cancer-related deaths. Further, it is projected that by 2040, such trends could result in 2.43 million additional instances and 740,000 fatalities.[5] The United Nations population division developed a metric, the human development index (HDI) for a more precise analysis of cancer burden. Usually, the global PC incidence is parallel to the HDI and gross domestic product, implying that developed nations typically have greater incidences than developing ones.[6] The highest incidence rates are witnessed in North America, New Zealand, Australia, The Caribbean, and Northern and Western Europe. In contrast, Northern and sub-Saharan Africa, Central, and South Asia possess the lowest prevalence of PC. Subsequently, Asian countries with high HDI – such as South Korea and Japan – have a relatively lower incidence than Western countries. However, higher screening frequency prompted by public awareness inevitably culminates in over diagnosis, a key contributor facilitating a surge in incidence rates in the countries above.[7]

Based on reviews from surveillance, epidemiology, and end results (SEER) 22 2013-2019 (SEER Cancer Statistics Review), the 5-year relative percentage of survival of PC patients is almost 97.1%. Although the death patterns do not vary significantly from the incidence rates, around one in 41 males succumb to PC.[8,9] The mortality rates are highest in Sub-Saharan Africa, South America, Polynesia, and the Caribbean (Jamaica, Barbados, and Haiti). On the other hand, Southeast and Central Asia have documented low death rates. Similarly, there has been a plunge in the mortality rates in Westernized nations, including Europe and the US. The total ratio change in occurrence in India was the highest at 61%. Forecasts indicate a continued rise in PC incidence, with South Asia's ASIR expected to reach 9.34/100 000 by 2031.[10,11] Global dissimilarities in PC incidence and death are due to Disparities in diagnosis, healthcare access, and medical infrastructure. Moreover, lifestyle and hereditary traits among communities may also fuel these discrepancies.

FACTORS AUGMENTING THE PC RISK

Unlike other typical malignancies, PC is virtually idiopathic and therefore a challenge in research investigations. Alternatively, for prevention and prognosis, there are decisive risk factors that are responsible for the onset of prostate carcinogenesis, shown in [Figure 1]. In addition, these factors are polarized into modifiable and non-modifiable variables and are discussed below.[12]

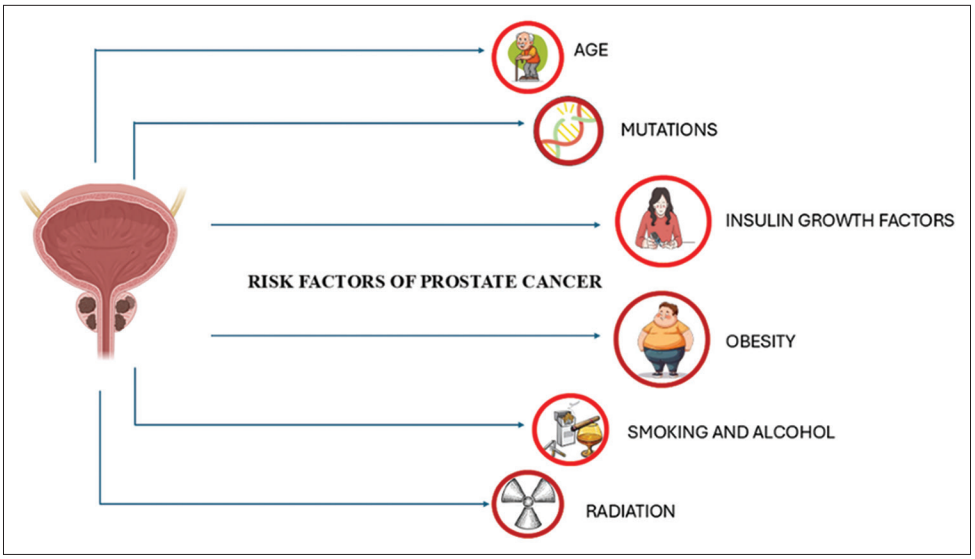


Figure 1: Common factors augmenting the prostate cancer risk

Non-modifiable risk factors

Age

PC cases in men <50 years of age account for merely 0.1%, which contributes relatively to low incidence in the patient population. Conversely, elderly men over 65 years re often afflicted with PC, which constitutes almost 85% of all PC cases. According to recent US cancer data, the risk of PC advances with age, from 1.8% in men aged 60–69 to 9.0% in men aged 70 and above, yielding a global cumulative risk of 12.5%. Surprisingly, histological analysis from autopsy inspections implies that 40% of unscreened males over 60 years possess PC lesions and the figure rises to 60% in males over 80 years of age.[13]

Ethnicity and race

PC incidence greatly varies across different races and ethnic groups. In retrospective studies in the United States, Black or African American males are 1.7 times more prone to PC than White men, and the death rates are 2.1 times higher. Hispanics, on the other hand, are estimated to have a 14% lower incidence and a 17% lower death rate than white men.[14] Despite black men tend to encounter PC more than white men; there is strong evidence that when both groups of men undergo the treatment upon equal access to healthcare and are diagnosed with PC of a similar grade and stage, the outcomes remain identical. Still, a vicious PC is detected in Black men. Although the rationales underpinning this data are uncertain, perhaps genetics correlated with ancestral descent, socio-demographic roots, and environmental health parameters and comorbidities may be reliable factors for these disparities.[15]

Family history

Familial aggregation of PC is a well-recognized risk factor, which maximizes the probability of its incidence as well as the development of lethal variants of tumors. Several cohort studies report that the number of afflicted family members, the degree of familial connection (first vs. second degree), the age of diagnosis, and death due to PC or other related comorbidities all ripple through an individual's likelihood of developing PC.[16]

Genetic predisposition

Gene linkage studies reveal that PC is more genetically transmissible than other malignancies, with an estimated 58% of inheritance. Hereditary PCs are a subclass of familial PCs that feature a disease distribution trend that fits Mendelian inheritance of a susceptibility gene. Environmental and lifestyle facets underlie a few of the disease's genetic characteristics. The whole genome screening of PC patients revealed mutations in the *HPC1* gene encoding an enzyme ribonuclease L. This enzyme is crucial for regulating interferon-mediated signaling pathways involved in innate immune defense mechanisms against retroviruses.[17] Also, indications of retroviral infections in certain PC cases demonstrated the genetic interplay ensuing the chronic retroviral infection and consequent tissue inflammation with the onset of carcinogenesis. Next-generation sequencing techniques identified other susceptibility genes with moderate-to-high penetrance, including *HOXB13*, *BRCA1/2*, *PALB2*, *ATM*, *ELAC2*, *CHEK2*, *NBN*, *OGG1*, *MSR1*, *GDF15*, and *PON1*. Some of these genes encode proteins governing internal defense against oxidative stress and inflammation; therefore, functional anomalies in these proteins accelerate carcinogenesis.[18]

Modifiable risk factors

Dietary intake

According to multiple studies on migrants shifting from low-risk developing nations to high-risk Western nations, dietary intake is integral in PC risk. These studies demonstrate that dietary enculturation provokes dormant tumors into clinically palpable ones. For instance, the National Institutes of Health-AARP diet and health study showed that consumption of fats, particularly polyunsaturated fats, including meat and dairy products, are positively correlated with global incidence and mortality of PC.[19] It successively triggers serum androgen levels, and insulin resistance associated oxidative stress thereby increasing the levels of inflammatory components, including interleukin 6, tumor necrosis factor, and leptin, which significantly augments obesity-induced carcinogenesis. Minimized consumption of fat has been demonstrated to prevent prostate tumor progress in both *in vitro* and *in vivo* models.[20] In the setting of vegetables and fruits, although there have been ambivalent reports, interim analysis with crucifers (broccoli, cauliflower, Brussels sprouts, and cabbage) and lycopene (tomatoes) showed diminished PC incidence. Furthermore, the selenium and vitamin E cancer prevention trial aimed at averting PC corroborated the declined incidence in patients who ingested lycopene with Selenium and Vitamin E.[21]

Lifestyle

Several epidemiological studies reveal that there is no conclusive evidence of a dose-responsive association between smoking and PC risk. Smoking, however, ignites exposure to cadmium, boosting oxidative stress and serum androgen levels, which may augment PC onset. Similarly, cohort studies found no association between alcohol and increased risk, although some discovered a marginal correlation between excessive alcohol consumption and lethal PC.[22]

On the other hand, sexual interactions might lead to pathogenic exposure, and research has indicated a potential link between early sexual activity, multiple sexual partners, and a higher PC risk. Surprisingly, frequent ejaculation has been claimed to have a prophylactic effect on PC, although the underlying basis is uncertain.[23]

Prostatitis

Prostatitis, or inflammation of the prostate gland, is generally asymptomatic, complicating diagnosis. Men with prostatitis symptoms are more prone to be diagnosed with PC due to increased frequencies of biopsies. Acute and chronic prostatitis can be spurred by non-sexually transmitted infections (STIs), including *Propionibacterium acnes* and *Escherichia coli.* Furthermore, some sexually transmitted species, such as *Neisseria gonorrhoeae* and *Chlamydia trachomatis,* can cause inflammation and infection, which may add to PC risk. Prostatic intraepithelial neoplasia, an established pre-cursor to PC, can evolve as a result of proliferative inflammatory atrophy, which is sparked by chronic inflammation. Eventually, numerous pathways mediating inflammatory events influencing prostate microcosm, and the intricacy of biological events connecting inflammation to PC and its dissemination can be explored as promising targets for treatments.[24]

Sexually transmitted diseases (STDs)

Multiple case–control studies stipulated connections between PC and STDs. It indicated that males with a previous record of syphilis or gonorrhea had a greater chance of developing PC through initial phases of prostatitis and prostate atrophy. A Finnish cohort study revealed the transforming properties of HPV in prostate cells *in vitro* and is identified in benign prostatic tissue and PC. Also, human papillomaviruses (HPV)-18 and HPV-16 seropositivity have been implicated in PCs. Ultimately, the cumulative PC risk is greater with patients possessing multiple STI episodes and longer-lasting infections.[25]

Environmental and occupational exposures

The gradual onset of prostate carcinogenesis is attributable to certain environmental and occupational factors, such as synthetic and organic compounds, herbicides, and insecticides. According to the International Agency for Research on Cancer and a meta-analysis, exposure to cadmium has been linked to an increase in PC risk. In the context of toxicity, PC has been shown to have higher tissular levels of Cd than benign prostatic hypertrophy, with larger concentrations observed in tumors with higher histological grades.[26]

Bisphenol A (BPA) is another hazardous substance affiliated with lethal PC onset. It is a polymerizing agent that is utilized to harden epoxy resins and polycarbonate plastic, including food containers. These containers may release BPA into food and drink, which is how most humans are exposed to it. Based on *in vitro* and *in vivo* experimental studies, US research teams highlighted the probable mechanisms of small quantities of BPA and its equivalents in inducing anomalies of the centrosome, which may contribute to PC initiation. In addition, epidemiological data relate the Chinese population's cumulative exposure to BPA to an increased risk of PC.[27]

National Institute for Occupational Safety and Health has identified methyl bromide, an alkylating agent, as a possible occupational carcinogen. Furthermore, individuals above 50 years showed a clear correlation with exposure to organochlorine pesticides, such as dichlorodiphenyltrichloroethane and heptachlor. Men having a family history of PC were the only ones who showed a statistically significant correlation with the usage of different pesticides. Surprisingly, intense heat processing of food generates ample amounts of heterocyclic amines along with other mutagens and carcinogens, such as acrylamide and polycyclic aromatic hydrocarbons, which may be cytotoxic to prostate cells.[28]

SCREENING AND GRADING OF PC

Accurate and reliable grading of prostate tumors is indispensable to establish a patient's prognosis and therapeutic recourse. Currently, Urological guidelines prioritize risk segregation through digital rectal examination (DRE), prostate-specific markers, Gleason grade grouping (GG), tumor mass, as well as imaging techniques.[29]

DRE

DRE is a clinical technique for initial assessment of prostate deformities. It involves the evaluation of the size, shape, symmetry, and consistency of the prostate gland. The detection of an enlarged prostate with solid consistency, lobar asymmetry, atypical nodule(s), induration of a lobe or the entire prostate, and palpable seminal vesicles are among the variables that may evoke the speculation of PC. However, due to the low specificity, sensitivity, and staging error rate, palpation of any of these anomalies during DRE often requires follow-up with a prostate biopsy and evaluation of other diagnostic biomarkers.[30,31]

Prostate-specific biomarkers

Prostate-specific antigen (PSA)

PSA testing is a preliminary screening technique to aid in the diagnosis of PC. PSA is a serine protease synthesized by prostatic epithelial cells. Its physiological function is to hydrate the seminal fluid for the liberation of spermatozoa.[32] Clinically, the PSA levels in the bloodstream are elevated up to 10^5 times in PC cases. However, benign prostate disorders can also be the source of elevated PSA values. Hence, it is usually coupled with DRE to minimize ambiguity and strengthen prognosis. In addition, PSA velocity, free-to-total PSA ratio, and PSA density are recommended to optimize the specificity of the PSA test.[33] The serum PSA concentrations and their interpretations are portrayed in [Figure 2].

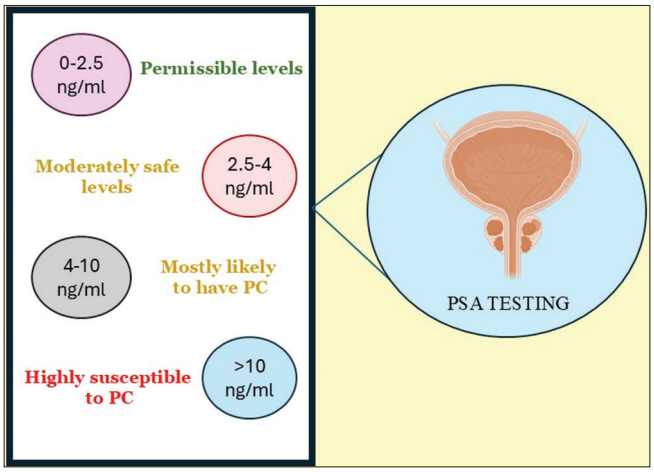


Figure 2: Prostate-specific antigen levels and their implications

Prostate-specific membrane antigen levels (PSMA)

PSMA is a membrane-bound glycoprotein that possesses folate hydrolase activity. In most cases, PSMA expressions have a positive relationship with the Gleason Pattern. Moreover, PSMA is significantly expressed in the neovasculature of prostate cancer (PC) tumors but not in normal or benign lesions.[34] Consequently, monoclonal antibodies are developed for PSMA to facilitate screening and treatment of PC. ProstaScint™ is a 111 In-labeled PSMA monoclonal antibody that has been utilized as a diagnostic tool and earned approval from the Food and Drug Administration for metastatic conditions.[35]

Prostate-specific acid phosphatase (PAP)

PAP is a secreted glycoprotein and a recognized tumor biomarker synthesized by differentiated epithelial cells of the prostate gland. The physiological role of PAP is unclear. Regardless, PAP is extensively found in human seminal ejaculate, implying its role in fertilization.[36] The serum enzymatic activity is significantly elevated in PC patients and correlates with tumor progression. In particular, 60% of the metastasized PCs have the highest PAP levels.[37] However, the PAP levels are normal or marginally elevated in benign tumors, benign prostatic hyperplasia (BPH), and osteoporosis.[38]

Gleason GG

In 1966, Donald F. Gleason proposed a novel prostatic carcinoma grading system exclusively based on the tumor's histopathological architectural pattern. This approach employs the core biopsy specimens and is graded by summing up the two (prevalent + minor) grade patterns and presented as the Gleason score.[29] This grading system underwent significant updates in 2005 and 2014 during two consensus conferences of the International Society of Urological Pathologists. In this pursuit, prostatic neoplasia can typically be graded into five distinct grades from 1 to 5. The lowest grade, well-differentiated dysplastic tissue is designated to Grade 1, and the most aberrant dysplastic tissue is designated to Grade 5. The aggregate score, usually ranging from 2 to 10, is derived from the sum of scores obtained from the most distinctive pathological samples. Despite major differences between the original Gleason grading system and its current implementation, it remains an extremely reliable indicator of the prognosis for PC and guides clinical care.[39,40] [Figure 3] illustrates the stratification of PCs based on Gleason scores and grade groups.

CURRENT THERAPEUTIC CHOICES

The gold standard treatment for patients afflicted with

localized tumors is primarily surgery and radiotherapy. In contrast, patients with recurrent or metastatic disease receive androgen deprivation therapy, androgen signaling inhibition chemotherapy, and other adjunct therapy.[41]

SIGNIFICANCE OF PLANTS AND THEIR BIOACTIVE COMPOUNDS FOR PC TREATMENT

Numerous cell and animal-based investigations employ plants and phytochemicals inspired by folk medicinal wisdom, especially from China and India. They are proven to have preferential toxicity toward PC inadvertently, with negligible toxicity to normal cells, highlighting intriguing therapeutic potential against malignancies [Figure 4]. Therefore, we have reviewed the literature on different classes of phytochemicals against PC.

Triterpenoids

Triterpenoids, derived from isopentenyl pyrophosphate oligomers, form a diverse group of over 20,000 natural plant compounds. Found in plants, seaweeds, and various fruits and herbs, such as apples, cranberries, and lavender, triterpenoids are also present in invertebrates and fungi. These compounds regulate diverse cellular processes involved in cancer, including proliferation, apoptosis, and angiogenesis, making them promising candidates for cancer research, including PC.[42] A few of the studies on triterpenoids are as follows.

Ursolic acid (UA)

Certain phytochemicals in combination with UA, such as UA with curcumin and UA with resveratrol, resulted in lower adenosine triphosphate levels and impeded the growth and survival of both mouse (HMVP2) and

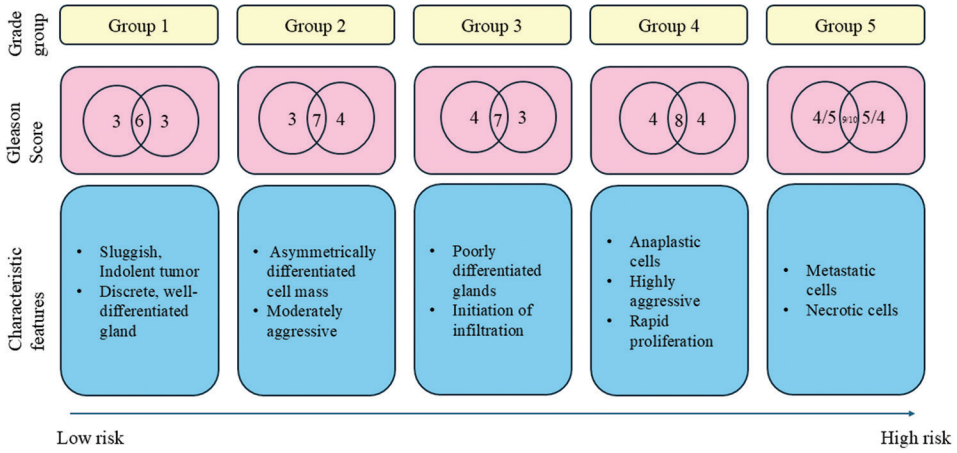


Figure 3: Gleason group grading of histological specimens of prostate cancer and risk stratification

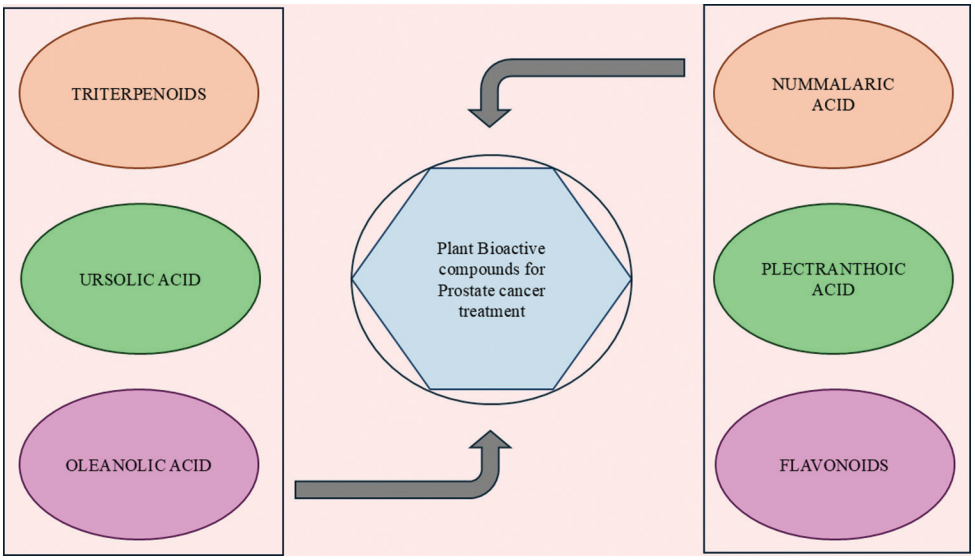


Figure 4: Plant bioactive compounds for the treatment of prostate cancer

human (PC-3 and Lymph node carcinoma of the prostate [LNCaP]) PC cell lines. In terms of mechanisms, the combined treatments involving UA with either curcumin or resveratrol resulted in an elevation of AMP-activated protein kinase (AMPK) activity and a concurrent reduction in mTORC1 activity.

Oleanolic acid (OA)

Research on OA, a natural triterpenoid, reveals therapeutic potential in PC through multiple mechanistic pathways. OA interferes with aerobic glycolysis in PC-3 cells by redesigning pyruvate kinase isoforms, switching toward the less proliferative PKM1. In addition, OA suppresses mTOR activation through AMPK activation and minimizes lipid production, thereby recommending its ability as a therapeutic drug in PC by targeting vital metabolic pathways.

Nummalaric acid (NA)

In 2007, researchers discovered a compound called NA in a plant called *Evolvulus nummularius*. When tested on PC cells (DU145 and C4-2), NA showed promising effects. The treatment with NA significantly slowed down the growth and movement of these PC cells in a manner that depended on both time and dosage. It also triggered a process called apoptosis, which is a natural way for the body to eliminate unhealthy cells. This was evident from the activation of Poly(ADP-ribose) polymerase and Caspase 3 cleavage. In simpler terms, NA appears to disrupt the energy production process in PC cells by activating AMPK.

Plectranthoic Acid (PA)

In a study by[43] discovered a compound called PA from the *Ficus microcarpa* plant, known for its anti-diabetic properties. PA showed significant anti-cancer effects on PC cell lines, such as PC-3, DU145, and CW22RV1. The treatment with PA hindered a signaling pathway called mTOR/S6K and triggered a process called apoptosis, which is a natural way for the body to eliminate unwanted cells in PC.

Flavonoids

Flavonoids are natural compounds with antioxidant properties found in a variety of plant-based foods. Their potential role in preventing or treating PC is an active area of research, and incorporating a diet rich in flavonoid-containing foods may contribute to overall prostate health. In this context,[44] have elaborated about quercetin, an active and potent flavonoid that can prevent PC by *in vitro* and *in vivo* studies.

Quercetin

The androgen receptor (AR) plays a crucial part in the growth and functioning of male reproductive tissues, as well as in the progression of certain diseases. In the *in vitro* studies, quercetin proved the following anti-PC effects.

1. Quercetin has inhibited the release of tumor biomarkers, PSA, and hK2, which are regulated by androgens. It has also established its potential to suppress the expression of the *AR* gene.
2. It has demonstrated its capability to inhibit the expression of the *AR* gene.
3. The dosage-dependent modification of cell apoptosis has been observed, attributed to the suppression of the key survival protein AK.
4. Its potential has been shown to reduce the proportion of primary prostate epithelial cells.
5. Quercetin can hinder the cancer stem cell (CSC) characteristics and metastatic potential of isolated PC cells by influencing the Jun N-terminal kinases signaling pathway.

In *in vivo* studies, it has demonstrated the following potential

1. Green tea + quercetin + low-dose docetaxel reduced tumor growth and improved anticancer effects.
2. Quercetin enhanced paclitaxel's impact without side effects in PC models.
3. It effectively suppresses PC growth, reducing angiogenesis.
4. Quercetin with 2-methoxyestradiol suppressed cell growth in xenograft models.
5. Quercetin-loaded nano micelles showed promise in reducing growth in castration-resistant PC in xenograft models.

Rutin

Rutin is a flavonoid found in various plants, particularly citrus fruits and buckwheat. Studies indicate that rutin can interfere with the growth and progression of PC cells, potentially inhibiting tumor development. Rutin exerts its anti-cancer potential in various ways as follows:

1. The expression of mutant p53 protein is downregulated in human PCa cell lines (DU-145, PC-3, and LNCaP by arresting the cell cycle
2. It demonstrates cytotoxic effects on PC cells in laboratory settings by enhancing caspase activity and promoting apoptosis.[45]
3. Combining 5-fluorouracil and rutin synergistically serves as a promising cytotoxic agent targeting PC3 PC cells.[46]

Apigenin

Apigenin, a natural flavonoid commonly found in parsley, celery, and chamomile tea, has garnered attention for its potential anti-cancer properties, particularly in PC. Research suggests that apigenin exhibits inhibitory effects on the proliferation of PC cells.

The following are the effects shown by apigenin against PC through various studies

1. In a dose-dependent manner, apigenin hindered the

survival of CSCs, including those from human PC (PC-3), by increasing the levels of p27 and p21.
2. Within PC cell lines, apigenin lowered the levels of anti-apoptotic proteins, resulting in an elevated apoptosis rate.
3. It has demonstrated a notable decrease in IGF-I-stimulated cell proliferation and an increase in apoptosis in DU145 cells, which are human PC cells.[47]

Carotenoids

The vivid colors of almost all fruits and vegetables are due to the presence of carotenoids. Lycopene, lutein, β-carotene, zeaxanthin, α-carotene, and β-cryptoxanthin are some of the carotenoids.

Lycopene

Lycopene is a natural carotenoid pigment that imparts characteristic hues of red in many fruits and vegetables, including tomatoes, watermelon, and grapefruit. Meticulously researched for its prospective health impacts, lycopene has garnered the spotlight for its application in combatting PC. Based on existing research, lycopene might reveal inhibitory effects toward PC by serving as a powerful antioxidant and neutralizing hazardous free radicals.

In vitro studies

1. Reduction in the proliferation of androgen-dependent or independent PC.
2. It controls the metastatic phase of PC.
3. The growth and proliferation of cancer cells were decreased in the cell culture medium where the LnCaP is seeded with different concentrations of lycopene.
4. Treating human PC cells with 5 mg/mL of cis-lycopene for 96 h inhibited cancer cell viability. This effect was followed by a rise in apoptosis, evidenced by the over-expression of TP53 and Bax, and a down-regulation of Bcl_2.

In vivo studies

1. Consumption of lycopene juice for about 28 days increased the level of lycopene in serum by about 80.2%,

Table 1: Plant-derived bioactive compounds for PC treatment and its mechanism of action

Sl. No.	Class	Bioactive compounds	Plant	Activity	References
1	Alkaloids	6-Hydroxycrinamine, lycorine, china mine	*Crinum asiaticum*	GLI1-mediated transcriptional inhibitory activity	[50]
		Liriodenineanonaine, caaverine, nuciferine, 7-hydroxydehydronuciferine	*Nelumbo nucifera*	Cytotoxicity in DU145 cells.	[51]
		Emitine	*Carapichea ipecacuanh*	Anti-tumorous actions on DU145, LNCaP and PC-3	[52]
2	Flavonoids	(-)-epicatechin-3-O-gallate and (-)-5,7-difluoro-epicatechin-3-O-gallate	*Camellia sinensis*	Prevents tumor growth across its various stages	[53]
		7-O-galloyl catechin, catechin, methyl gallate, and catechin-3-O-gallate	*Acacia hydaspica*	Cellular apoptosis of PC-3 cell line	[54]
3	Anthocyanidins	Delphinidin	*Vaccinium cyanococcus*	Stops the carcinogenic potential of PC-3 cells in an *in vivo* pre-clinical setting by hindering the NF-κB route of signaling.	[55]
4	Phenols	Dehydrozingerone	*Zingiber officinale*	Potent cytotoxic potential	[56]
		Cinnamaldehyde and eugenol	*Cinnamomum cassia, Laurus nobilis, Syzygium aromaticum.*	Possess 64–75% cytotoxic activity against the PC-3 cell line at 100 μM concentration	[57]
		Garcinol	*Garcinia indica*	Suppressing human autophagy in PC cells at 30 μM	[58]
5	Lignans	Magnolol	*Magnolia officinalis*	Preventing the advancement of the cell cycle of DU145 and PC-3 cells.	[59]
		Peperotetraphin	*Peperomia tetraphylla*	Inhibits the PC-3 cell growth in a dose- and time-dependent fashion	[60]

PC: Prostate cancer

which in turn showed positive effects, such as elevating antioxidant markers in individuals, which in turn can mitigate DNA damage, reduce oxidative stress, and lower the risk of diseases.

2. Three weeks of 30 mg lycopene-rich tomato sauce in localized prostate adenocarcinoma patients increased lycopene levels in prostate tissues and serum. This correlated with lower PSA levels and reduced DNA damage post-prostatectomy.
3. Furthermore, a pilot study involving 40 patients with BPH who received lycopene (15 mg/day for 6 months) demonstrated a decrease in PSA levels, an increase in lycopene levels, a slowed progression of cancer, and a reduction in prostate size.[48]

OTHER UNDEREXPLORED PLANTS WITH ANTI-CANCER POTENTIAL

The listed some remarkable plants belonging to various families that have high anti-cancer potential.[49]

- The compound acetogenins from the plant *Annona muricata*, part of the Annonaceae family, demonstrates the potential to inhibit hypoxia-induced NADPH oxidase (NOX) activity in various PC cells. Specifically, it reduces NOX activity by 39–98% in 22Rv1 cells, 77–91% in LNCaP cells, and 71–75% in PC-3 cells.
- Luobama, a well-known beverage in Asia derived from the plant *Apocynum venetum*, contains bioactive compounds, such as sterols (lupeol, stigmasterol, and β-sitosterol) and polyphenolics (isorhamnetin, kaempferol, and quercetin). These compounds have been identified for their chemopreventive properties, particularly in the context of anti-androgen-insensitive PC.
- The combined action of extracts from *Achillea teretifolia*, *Achillea santolinoides, Sigesbeckia orientalis*, and *Wedelia chinensis*, containing bioactive compounds, such as luteolin, wedelolactone, and apigenin, synergistically inhibits PC cell growth. *Wedelia*, particularly effective, suppresses crosstalk between AR and HER2/3 signaling in a castration-resistant PC model, offering promising therapeutic benefits, even in cases resistant to androgen withdrawal and enzalutamide. This highlights the potential of a single plant-derived extract for enhancing castration's therapeutic efficacy and extending progression-free survival.
- *Anogeissus latifolia* and *Terminalia bellerica of* Combretaceae*, Baliospermum montanum, Cnidoscolus chayamansa, Euphorbia microsciadia and Euphorbia szovitsii of* Euphorbiaceae, *Arachis hypogaea, Acacia catechu, Calliandra portoricensis, Glycyrrhiza uralensis, Leucaena leucocephala, Medicago sativa, Sophora alopecuroides, Sutherlandia frutescens of* Fabaceae, *Nepeta cataria, Mentha arvensis, Mentha spicata, Mentha viridis, Salvia multicaulis, Salvia triloba of* Lamiaceae. The different types and concentrations of extracts from these plants have shown promising effects against PC. A list of some of the bioactive compounds from plants that are very effective against PC is given in [Table 1].

CONCLUSION AND FUTURE PERSPECTIVES

Concisely, this review briefs about the biological background of PC. Despite technological breakthroughs, PC persists as a major global health concern. Comprehension of the molecular characteristics of the disease might facilitate greater clinical efficacy through precision medicine. Hence, this review briefs about the epidemiology, etiological grounds, associated risks, classification and staging of the disease based on tumor traits, and therapeutic modalities in the management of PC. It also gives a detailed overview of the significance of phytomedicinal compounds for combatting the PC burden.

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