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REVIEW

Advancement and Future Perspectives of Prostate Cancer Treatment by Using Plant Bio-actives: A Review

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Abstract

Prostate cancer (PCa) is the world's second most lethal and hateful disease in people. Even while chemotherapy medications have made considerable progress against cancer disease, the body still has to deal with their toxic side effects. In order to produce anticancer medicines with the lowest cost and treatment time, mostly people are using mechanistic techniques. In addition to chemotherapy advanced treatment techniques are also used in clinical practices, and they have an excellent healing results by enhancing patient survival rates. The social care net faces serious challenges because of the lack and high cost of modern therapeutic techniques. The side effects of chemotherapeutic drugs and expensive advance techniques triggered the patient interest towards phytochemicals drugs which indicate that nature always attracts human to fulfill their medical needs at very low cost.

The pharmaceutical industries are showing strong interest in recent research, which has led to the addition of a quite large number of phyto-medicines in PCa therapeutic practices. Currently, several experimental epidemiological and clinical research reports confirmed that plant bio-actives play a significant role in PCa prevention by using different mechanistic ways such as suppressing adhesion, anti-angiogenesis, pro-apoptosis, anti-proliferation, invasion and migration. This review systematically highlighted various strategies to treat PCa and advances in research by using different bioactive plant extracts and isolated components that have been tested for PCa therapy along with corresponding clinical and epidemiological studies.

Keywords: Prostate Cancer, Phytochemicals, Bio-actives, Treatment, Radiotherapy.

1. Introduction

The prostate is the glandular organ composed of epithelial cells found under the bladder in a fibro-muscular network [1]. Globally, prostate cancer (PCa) is a common fatal disease in men, and the second lethal disease in western countries. It may be asymptotic in the early stages of PCa [2, 3]. It is a complex and heterogeneous type of malignancy that can be aggressive or non-aggressive early-onset or indolent, high or low grade PCa [4]. However, in Asian countries the relative ratio of PCa is less than the western countries, but its occurrence and mortality rate is rapidly increasing by adopting the western life style and the exchange in the socio-cultural life [5]. The PCa treatment includes many different methods such as chemotherapy, radiotherapy and surgery. The chemotherapy is more effective at the early stage of tumor development which induces side effects. When the tumor is spread from their original site to the other body parts, all the treatment is ineffective and form some metastatic tumors in the body. The metastasis stage is highly resistant to treatment tactics as a result death ratio increases among

the patients [6, 7]. However, PCa can be treated via radiotherapy define as the treatment through x-ray's or similar form of radiations and can be applied either external or internal, but ensure that the method is complex and highly expensive [8]. Although, advancement in the radiotherapy leads to many of the targeted radionuclide such as Lutetium 177 (Lu) labelled PSMA peptides (a molecular biomarker) that exhibits the high tolerance in men with prostate-cancer and low toxicity profile [9-11]. Meanwhile, surgery is the only effective method when PCa tumor is localized in early diagnosis.

Epidemiological studies show that cancer can be controlled by intake of more fruits and vegetables. Several reports highlighted that the chances of death occur due to cancer is reduced up to 75% by taking nutrients rich food and drinks (Figure 1). Why fruits and vegetables is essential for the control and treatment of cancer? The fruits and vegetables consists of several biomolecules known as phytochemicals (i.e. polyphenolics, terpenes, carotenoids, alkaloids, anthocyanin's etc), they shows simultaneous targeting multiple neoplastic eventuality by preventing the damage of DNA, inhibiting proliferation of malignant cells, modulation inflammation, so that reducing the overall risk of cancer [6, 12]. Scientific community are now moving towards the herbal or natural treatment strategies for the development of safe and effective treating ways of malignancy, due to the adverse side-effects of the chemotherapy and the other treating methods. Ancient literature studies and current epidemiological review are directed the researchers to focus on the treating ways by using phytochemicals, because these are natural, easily acceptable and have minimum side effects [13]. Further, it is estimated that over 60% anti-cancer agents currently used are extracted from natural sources [14]. The increasing attention for chemoprevention by phytochemicals is just because that they have chemical diversity, essential biological activity, easily available, affordable, and less toxic effects [15]. Meanwhile, with the development of technology it is estimated that many novel natural components from the medicinal plants will be recognized and developed as anti-cancer agents [16, 17]. This review highlights the advances in PCa treatment by using plant bio-actives as the chemo-preventive and anti-inflammatory agents. We mainly focus and analyzed the past ten years' work that was reported on the treatment of the PCa by bioactive components (i.e. tanshinones, biochanin-A, oleuropein, anthocyanins) from different medicinal plants.

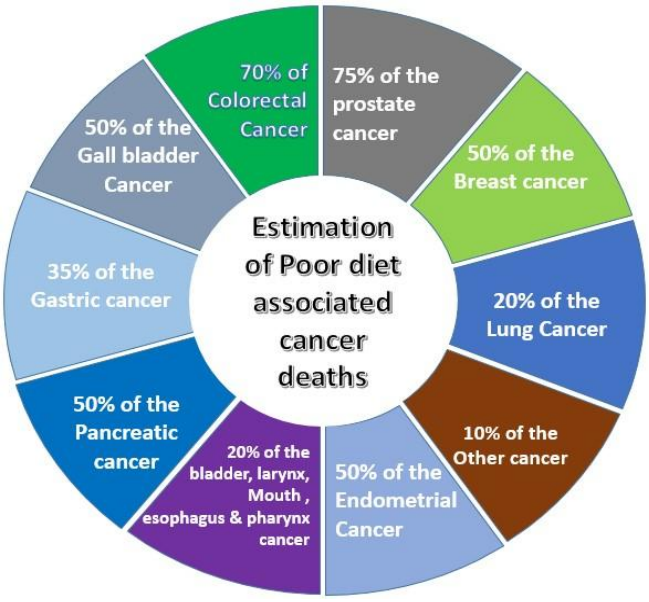

Figure1: Estimation of poor diet associated with cancer deaths. Intake of natural plant based diet (fruits, vegetables etc.) has been proved to significantly reduce the cancer risk. Reproduced with permission: Copyright 2019, MDPI [6].

2. Prostate Cancer (PCa) Treatment

Prostate cancer is the most commonly occurring cancer in men. It is the most lethal malignant disease in people whose symptoms started at the base of the bladder in prostate gland. It surround the proximal part of the urethra that brings the urine from bladder [18]. Geographically, the disease does not show the same symptoms and affects in people across the world, but it shows variation among patients based on their regions or continents. For example,

Asian cancer effected person having less incidence rate of PCa than white and black of Americans. In America and Africa it is reported that 37% of the death occur due to cancer in 2013 [19]. According to UK researchers, approximately and above 40,000 people are effected with this lethal disease every year. National Institute for Health and Care Excellence (NICE) describes PCa as slow growing disease, and hence many of the person may not die due to this disease in their lifespan. In spite of the slow growing localized PCa that is not prove to be fatal, metastatic PCa after multimodal therapy largely remains incurable. About 80% of the newly diagnosed PCa cases are localized, while remaining are the adversely metastatic or advanced. There are various treatment strategies are applying for the treatment of PCa including active surveillance, surgery, radiation therapy, high intensity focused ultrasound, immunotherapy, vaccine treatment, targeted therapy and bone directed treatments etc. [20-23].

2.1 Risk factors of PCa

As PCa is a heterogeneous malignant disease that's why its causality varied from patient to patient even when they have the same type of tumor [24]. Main risk factors that may become the reason of PCa occurrence and associated with treatment, mortality or survival are mainly divided into two categories that is adaptable and non-adaptable risk factors [25]. Some of the main non adaptable risk factors for the PCa to be occur are age, race, ethnicity, geography, positive family history (for example one's first degree relatives) and genetics. Meanwhile, several of other adaptable risk factors such as obesity, smoking, may not the reason of its incidence but may become the booster of PCa mortality. Epigenetic changes i.e. life style ascribe approximately 90%, while somatic or epigenetic changes may attribute 10% or less for the cause of PCa. Similarly, inflammation is the evident process that associates cancer with the main risk factors [26-29]. Physical activities, infectious diseases, external and occupational exposure, endogenous hormones are also some of the adaptable PCa risk factors[30].

2.1.1 Age

PCa possibly occurs among the older men with the age of about 66 years old. Probability of PCa occurrence is increasing with the age, 5% men with age 60-69 years and 7.69% men with age ≥70 years are diagnosed. PCa is the third leading cause of death in men with the age 60-79, and at second with the men age ≥80 years [31, 32]. It has been observed that over the age of 50 years risk factors increases in white men with no PCa family history, and in black men over the age of 50 having PCa family history [33].

2.1.2 Race, Ethnicity and Geography

Globally, the occurrence of PCa is vary on the basis of geography. In developed countries of the world such as Western and North Europe, North America and Australia, the rate of PCa is more than the rest of the world. The developed counties have the facilities for its early detection, screening and medical cares. In contrast death rate associated with PCa is highest in ancient African. Based on population it was reported i.e., GLOBOCAN, 2012, Sub-Saharan African (SSA) and Afro-Caribbean (AC) people are suffered from the world highest death rate due to PCa with the rate 18.7-29.3 deaths per 100,000 [29]. Main reason of these differences of PCa between the countries has not clear entirely. It may have attributed to prostate specific antigen (PSA) testing the main reason of the worldwide variations of PCa incidence. Recent research demonstrated that approximately 20-40% of the PCa cases in Europe and USA may because of the over diagnosis via extensive PSA testing [3].

However, race is actually not associated with the survival after local treatment in metastatic PCa patients. The radiotherapy treated patients of Caucasian race are more associated with the higher cancer-specific mortality and overall mortality than that of the African American race. In the study 2004-2014, people with newly diagnosed metastatic PCa 408 (77.2%) Caucasians and 121 (22.8%) Africa-American's were treated with local-therapy: radiotherapy (n=357) or (n=172). When local therapy

includes radical prostatectomy then the Caucasian race patients demonstrates comparatively higher survival vs. African American's: cancer specific mortality free survival 123 vs. 63 months (p=0.004) and overall mortality free survival were 108 vs 46 months (p=0.002). Thus, it is evident from the foregoing details that when radical prostatectomy is used as local therapy, there will be no racial differences in cancer-specific mortality or total mortality [34].

2.1.3 Family history and Genetics

Family history of PCa is strongly associated with the increased risk of PCa incidence and also the higher mortality rate. A recent analytical study reveals the relationship between the PCa incidence and that of the positive family history of PCa are highly associated with the increased risk of PCa in overall cohort of PCa patients and also the PCa risk in non-screened sub-cohort. From the total 74,781participants, 5281 participants were having the first degree relative (FDR) positive family history and 69,500 participants was without any positive family history. From the participants having no family history of PCa in FDR, PCa were to be diagnosed in the total of 7540 participants' (10.5%). However, the patients having the family history of PCa in FDR are 889(16.5%) from the total are diagnosed [35].

Mutations play a major role in PCa carcinogenesis, as family history and race are linked to PCa incidence and mortality. Family history helps identify PCa-prone genes. Many of studies have identified some of the susceptible genes that are RNASEL, ELAC2, MSR1 and HOXB13. Among them HOXB13 found to be the gene play significant role in the PCa development that is actually the homeo-box transcription factor gene [36]. Increased risk factors for PCa has been notably demonstrated by the BRCA2 and HOXB13 mutations and observed more commonly in early onset PCa diagnosis among the patients. It has been shown that HOXB13 recurrent mutation leads to the hereditary PCa [37].

2.1.4 Obesity

Weight gain or obesity is highly associated with the increased risk of fatal and advanced level of PCa. Metabolic changes that are concerned with obesity or weight gain may become the reason for PCa development [38]. Obesity may play its role as a factor that leads to the less likely early stage PCa diagnosis in the obese patients. Physical examination, laboratory test and imaging process may hindered due to the adiposity [39]. A quantitative study on the relationship between obesity and PCa had done. In cohort studies total of the 3,569,926 individuals were selected in 17 studies takes up to the result that obesity was not as such associated with the PCa incidence. However, further analysis provides with the evidences that obesity were significantly associated with the high risk of PCa aggressiveness [40, 41].

2.1.5 Smoking

Smoking increases PCa incidence and death. Cigarettes' mutagens may induce prostate tumorigenesis [42]. Smokers PCa risk factors rise, leading to PCa-related death. Many studies have linked aggressive-violent PCa to smoking at diagnosis [43]. A quantitative cohort study elaborated the PCa specific mortality associated with smoking, leading to the results that PCa patients with current smoking are at high risk of PCa specific mortality compared to non-smokers, and this increased risk was also partially attributable to tumor characteristics [44]. Recent studies also provides with the evidence that smoking at the time of diagnosis enhance the risk for PCa specific and all-cause mortality [45].

3. PCa therapeutic strategies: A brief summary

PCa treatment includes many different methods such as chemotherapy, radiotherapy, immunotherapy, hormone therapy, and surgery. In the following sections we briefly explain all these types of clinically practiced strategies.

3.1 Chemotherapy

Chemotherapy kills cancerous cells by stopping their replication. Chemotherapeutic agents may cause cell death by producing reactive oxygen species, necrosis or apoptosis of malignant cells, or influencing cell proliferation enzymes. Chemotherapeutic agents are

categorized by their chemical structure, mode of action, and interaction with other drugs, such as alkylating, cross-linking, intercalating, DNA cleaving, and anti-tubulin agents. Treatment by chemotherapy has been used by targeting the escalation potential and metastatic ability of the cancerous tumor cells. Present use of chemotherapy involves DNA interactive agents (doxorubicin, cisplatin), anti-tubulin agents (taxanes), antimetabolite (i.e. methotrexate), molecular targeting agents and hormones [46, 47].

In an analytical study exhibits the results that N-acetylated α-linked acidic dipeptides (NAALADase) activity of PSMA expressing cells can be inhibited by the nanoparticle conjugate forming a dendrimer G5 PAMAM while they bind specifically to these cells. In nanoparticle conjugate the drug methotrexate and a small targeting agent molecule glutamate urea conjugated through the serum stable amide links to a dendrimer G5 PAMAM. In vitro study of this target showed the more cytotoxic behavior towards LNCap cells as compared to PC-3 cells. Maximum of the inhibition of cell growth was reached approximately at 300nM that was about 50% for the conjugate and 70% for the free methotrexate [48]. Despite progress in developing strong chemotherapeutic drugs, their toxic effect on normal body cells (such as hair loss) and adverse concomitant in multiple organ systems (i.e. gastrointestinal lesions, neurological dysfunction, bone-marrow suppression) are major impediments to their successful clinical use. Cytotoxic agents decrease the life of cancer patients, resulting in dire complaints and long-term effects on survivors. Toxicity limits the usefulness of anti-cancer agents, which is why patients stop treatment [13, 47].

3.2 Radiotherapy

Radiotherapy is a physical process in which ionizing radiations are used for the destruction of cancerous cells. Energy from the ionizing radiations passing through the cancerous cells in turn alters the genetic structure and hence blocking their ability to proliferate. In radiotherapy the main goal is to maximally destroy the cancerous cells by the high energy radiation without affecting the adjacent normal cells. Despite of all the development in radiation therapy, the main drawback of it that normal cells are also damaged along with the cancerous cells. Prostate cancerous cells may develop the radiation resistance because of some unknown factors. Hence making radiotherapy an ineffective strategy and causing cancer metastasis. Many of the combination procedures are going through the clinical trials for finding new ways for the effective radiotherapy. Radiotherapy mainly exercised by the two ways describes below.

3.2.1 External beam radiation therapy (EBRT)

External radiotherapy is the grade level strategy which can be opted for the localized PCa. It is the process in which high energy radiation are externally aimed at the location of cancer and destroy them by different way of actions such as apoptosis, autophagy, necrosis or mitotic cell death. Many of the technological advancements in external beam radiation therapy such as 3D conformal radiotherapy, Intensity modulated radiation therapy, and Image guided radiotherapy, stereotactic body radiation therapy are developing in order to decrease the toxic effects of EBRT and making them more effective against PCa [49-51]. External radiation therapy varies in effect as different radiations/particles (photon or proton) and protocols are uses accordingly for the treatment of PCa. Patients recovered from PCa by external beam radiation therapy have 72% increased risk of acquiring second primary bladder cancer than that of the surgical strategy [52].

3.2.2 Internal Radiotherapy

Internal radiotherapy is described as the brachytherapy in which sealed radionuclide (a source of radiation) is introducing into tumor or next to it for treating it directly or by means of catheters. These radionuclides emit a range of radiations including auger electrons, alpha, beta, gamma and x-rays. Most commonly used radionuclides (Yttrium-90, Lutetium-177, and Iodine-131) emits beta rays while others are less common [53-55]. Brachytherapy provides

with a significant good option treatment for the PCa and more advancement in this therapy provides with the marvelous oncological outcomes, limited toxicity rate and also increased life expectancy of PCa patients [56].

Internal radiotherapy is actually the targeted treatment strategy, a lot of development and new radionuclides are formed specifically for the treatment of PCa. An alpha-emitter radionuclide ^{225}Ac complexed with PSMA forms the ligand ^{225}Ac-PSMA-617 for the PCa treatment although still in clinical trials however also demonstrating the strong potential toward the advanced stage PCa. The other most efficient therapeutic radionuclide that are also in practice to label PSMA is β-emitter Lu-177 – which required one or two more cycles of therapy to eradicate the PCa as compared to 225Ac-PSMA [57, 58]. ^{177}Lu labelled PSMA which demonstrating strong efficacy in short period of time due to which patient quickly recover from the PCa [59]. Two main factor are big barrier to adopt this therapy; one is the high cost and second is the establishment of 225Ac/177Lu-PSMA therapy.

3.3 Immunotherapy

Immunotherapy plays a consequential role in recent years for the PCa treatment by triggering the immune system of patient's to kill the PCa [22]. A noteworthy reduction in T-cells (immune responsive lymphocytes) are detected in the high risk PCa as compared to the benign nodular hyperplasia of the prostate. Several of the immunologic therapies for the castrateresistant PCa includes antibodies, adoptive T cell therapy, vaccines or targeting the immune function by chemical compounds and the most successful immunotherapy from all of them is the vaccinated immunotherapy while others exhibits less activity comparatively. One of the FDA (Food and drug administration) approved vaccine Sipuleucel-T as the first successful vaccine for PCa immune therapy [60-62]. Despite of the extensive research towards the immunotherapeutic treatment of PCa as monotherapy are not exhibiting the satisfying results. Much more of the further researches are needed in this regard as not all PCa tumors exhibiting the immune-sensitive behavior. For the purpose of more improvements, Combination immunotherapies (immunotherapy with other therapies such as chemotherapy, radiotherapy, hormonal therapy or surgery) shows some positive response, hence paving the way for immunotherapy as a revolutionized PCa treatment strategy [63, 64].

3.4 Hormonal therapy

Hormonal therapy is also regarded as the androgen deprivation therapy. Androgen receptors are the steroidal transcriptional factor for dihydro-testosterone and testosterone PCa growth is triggered by the increased level of androgens, hence provided the basis for androgen deprivation therapy. Androgen deprivation therapy suppresses the androgens and in turn suppresses the growth of PCa. This therapy may also result in the high risk PCa to castrate resistant PCa [65, 66]. Androgen deprivation therapy may also leads to many other diseases involving cerebrovascular disease, cardiovascular disease, Alzheimer's disease and osteoporosis [67, 68].

3.5 Surgery

Surgery is not considered as the only treatment option for the PCa treatment, instead it's the part of multimodal approaches for treatment. Surgery is mostly suggested for the treatment of localized PCa in which tumor is surgically removed from the body and in turn provides with the survival benefits. Surgery may become the protocol for localized PCa treatment and more favorable than watchful waiting of impermanence, risk of metastatic and localized proliferation. Most commonly applicable surgery types for the PCa are pelvic lymphadenectomy and radical prostatectomy (RP). However, RP is generally not preferred for the high risk PCa due to the adverse side effects such as metastasis of lymph nodes, elevated positive surgical margins and PSA recurrence. RP increases the life expectancy of patient with high risk of PCa. While patients having intermediate risk disease gained high benefits by RP, with 24% reduction in PCa specific death, 15% reduction in overall death and 20%

reduction in metastatic disease development. RP may lead to the poorer sexual and urinary function, while leading to the much better execution in bowel domain. However, surgery is not the only and complete treatment option for cancer, as it's just the first mechanistic approach to remove maximum tumor cells/tissues hence surgery is followed by the other treatment options such as radiation therapy or chemotherapy to dead the remaining cancerous cells [69-71].

4. PCa treatment by natural product

Various plant bioactive chemo-preventive compounds target signaling pathways and cellular molecules. These include reactive oxygen species (ROS) formation and signaling, cyclooxygenase-2 (COX-2), xenobiotic metabolizing enzyme (XME), lipo-oxygenase pathways, cell cycle proteins, transcription factors, apoptosis, angiogenesis, invasion, and epigenetic enzyme alterations [15]. PCa treatment with a plant-based extract containing bioactive components reduces the incidence rate of this malignant disease and kills prostate cells through many different pathways (cell cycle arrest, inhibiting cancer cell growth, inducing apoptosis, anti-angiogenesis or anti-proliferation activity, etc.).

In the next sections, we describe all these criteria to update our knowledge of PCa origination, primary risk factors, natural product therapy processes, and screening the remainder of the flora for PCa treatment. Different prostate cell lines (i.e. LNCaP, DU145 or PC-3 cell lines) are used by in vivo, in vitro, or animal model to find the exact pathways of treating PCa by the specific bioactive in specific efficacious concentration from the specific plants, which may be traditional herbal medicine plants or dietary plants etc. These natural chemicals originating from plants are bioactives exhibit their potential anti-cancerous activity within days or months. For better treatment of PCa by plant extracts, more clinical trials and research are needed to obtain viable, less costly, and easily available cancer treatment procedures.

4.1 Plant derived bioactive phytochemicals and PCa

Commonly, it was believed that the chemo-preventive drugs from the last 40 years are used for the treatment of cancer a natural products extracted from plant roots. These natural products are many different types of bioactive components that are present in different parts of the plant i.e. leaves, flowers, fruits, seeds, bark, and roots etc. These bioactive components may have anti-cancer effects used for multiple purposes such as by inducing apoptosis, altering the cell cycle, or inhibiting cancer cell growth and by scavenging free radicals etc. [16].

Researchers have found many plants derivative bioactive components that show the anti-PCa activities in vivo or in vitro, such as *Psoralea corylifolia,* Danshen, American cranberry, olive oil,*Salvia miltiorrhiza* Bunge, black pepper, *O. gratissimum* etc.and many of other plants are describe below **(Table 1)**.

Table 1: List of plants from which phytochemicals have been extracted and are used to treat prostate cancer.

Plant	Used phytochemicals	Efficacy	Prostate target cell lines	Analysis time (Hours, days)	Model of PCa	Result of the used model	References
Psoralea corylifolia	Neobava-isoflavone and psoralidin	Cause apoptosis in the PCa cells.	LNCaP cells	48-h	In vivo & In vitro	Causes increased Percentage apoptosis 77.5 ± 0.5% or 64.4 ± 0.5%,	[2]
Danshen (*Salvia miltiorrhiza Bunge*)	Diterpene compounds (Cryptotanshinone (CT), Tanshinone IIA (T2A) and Tanshinone I (T1))	Anti-angiogenesis activity, anti-growth, anti-invasion	PC-3, LNCaP, and DU145 cell lines(in vitro) Bax and Bcl-2 proteins(in vivo)	7 days (In vivo), 5h (In vitro),	In vivo (in mice) & in vitro	T1 shows IC_{50}'s around 3-6.5 µM, IC_{50}'s of CT and T2A are around 10–25 µM and 8–15 µM, respectively	[72]
American cranberry (*Vaccinium macrocarpon*)	Anthocyanin glycosides (cyanidin-3-galactoside, cyanidin-3-arabinoside, peonidin-3-galactoside, and peonidin-3-arabinoside)	Cell cycle arrest	DU145 human PCa cells.	6-h	In vitro (human PCa cells)	Viability decreased by 26%, 32% and 46% at 10, 25 and 50 mgml_1 of WCE	[73]
Olive leaves	Oleuropein	Antiangiogenic	LNCaP & DU145 PCa cell lines & on BPH-1 non-malignant cells	72 h	*In vivo* and *in vitro* studies	100-500 µM oleuropein causes significant reduction in cell viability (Particularly in LNCaP & DU145 cells)	[74]
Chinese medicinal herbs(*Salvia miltiorrhiza Bunge)*	Tanshinones	Inhibitory potency to the PCa cell lines.	PCa cells	24 h	In vitro, in vivo(mice)	For androgen-dependent LNCaP cells, Shows strong inhibitory potency having order of TIIA≈cryptotanshinone>tanshinone I	[75]
Tomato Powder and Soy Germ	Lycopene (tomatoes) & Parent Isoflavones ,isoflavone metabolites(soy germ)	Reduces prostate carcinogenesis	mouse prostate (TRAMP)model	14 week	In mice	Mice consuming TP (61%, $P < 0.001$), SG (66%, $P < 0.001$), and TPþSG (45%, $P < 0.001$) Having lower incidences of PCa.	[76]
Black pepper	Piperine	Reduces tumor growth, anti-migratory effects.	LNCaP, PC-3 and DU-145 PCa cells	24 h, 48h,& 72 h.	In vivo(in mice) and in vitro	LNCaP (AD), PC3, 22Rv1 & DU-145 (AI) cell lines shows reduction of proliferation with an IC_{50} value of 60µm, 75µm, 110µm and 160µm	[77]

						respectively.	
O. gratissimum leaf	Ethanolic extracts (anti-oxidants)	Anti-inflammatory and anti-angiogenesis properties	PC3•AR cells	24, 48, & 72 hours.	In-vitro	The three extracts P2,P3-2 and PS/PT1 in a dose dependent way(P2>P3–2>PS/PT1), inhibits proliferation of PC3•AR cells	[78]
Turmeric and Chinese goldthread	Curcumin and *ar*-turmerone, berberine and coptisine	Induce cell-cycle arrest, inhibition of cell invasion ,cellular apoptosis and metastasis	CWR22Rv1 and HEK293 cells	24h	In-vitro	IC_{50} value of bioactives (combined phytochemical), inhibited the cell proliferation in PCa cell lines that are studied.	[79]
Dried ginger (*Zingiber officinale* Roscoe)	6-Shogaol, 6-paradol (6-PAR) & 6-GIN.	Cause apoptosis	DU145, LNCaP, and PC3 (human) & mouse (HMVP2) PCa cell lines.	24h (human prostate cells) , 32 days (mice)	In vitro (human cultured cells), in vivo (in mouse)	6-SHO was the most chmopreventive than other two bioactives in inhibiting PCa cells (in vivo & in vitro) by apoptosis.	[80]
Cucumber	Cucurbitacin B	Inhibits cell growth, induces apoptosis.	LNCaP and PC-3	24h(in vitro), 30 days (in vivo)	In-vitro , in vivo(mouse)	IC_{50} of CuB results in inhibiting cell viability of prostate cncer cells; also (0.1 µmol/day of CuB) inhibits the growth in athymic mice PC-3 xenografts.	[81]
Alnus japonica (bark)	Hirsutenone	Induce apoptosis	PC3 and LNCaP PCa cells	72h	in silico, in vitro (human PCa cells)	Hirsutenone induces apoptosis by targeting Akt1 and 2 in human PCa cells.	[82]
Cruciferous vegetables	Erucin (isothiocyanates)	induce a proliferation- arrest state	prostate adenocarcinoma cells (PC3)	24 h	In vitro	ER concentration up to 15 μM caused a significant decrease in proliferation of PC3 cell at 25 μM($P \leq 0.01$)	[83]
Arctium lappa (seed), green tea,Curcuma longa (root)	Arctigenin (Arctium lappa), epigallocatechin gallate(green tea), curcumin	Cell cycle arrest, apoptosis	LNCaP PCa	48 h	In vitro	IC_{50} values of EGCG, curcumin, arctigen induces antiproliferative effect in combination &individually induces apoptosis LNCaP cells.	[84]
Salvia triloba (Lamiaceae)	1,8- cineole, β –pinene, β-caryophyllene , camphor	Induced cytotoxicity, apoptosis, angiogensis	PC-3, DU-145 & HUVEC cells	72 h	In vitro	IC_{50} values of extract was 287±8 & 456±15 µg/ml in PC-3& DU-145 cells shows that it induces apoptosis to them and no cyto-toxic affect to normal cells.	[85]

Hedyotis diffusa (Leaves & root)	Diffusa cyclotide 1 to 3 (DC1-3)	Induces cytotoxicity, hepatoprotective, neuroprotective activities inhibited cell migration	PC3, LNCap and DU145(in vitro) Mouse xenograft model (in vivo)	72 h	In vitro and In vivo	IC_{50} value of bioactives is shown at the level below 10 µM for three cancer cell lines. These bioactives shows anticancer affects in vivo and in vitro.	[86]
Milk thistle	Silibinin	Induces autophagy	PC-3 cells	48 h.	In vitro	Silibin induces autophagy (apoptosis) in PC-3 cells by the production of Reactive Oxygen Species.	[87]
Eurycoma longifolia	Quassinoids	Induced cytotoxicity, anti-tumorigenic activity, inhibition of LNCaP cells,	LNCaP cancer cells.	72 h(in vitro, in vitro (6 week)	In vitro(human) , In vivo (mice)	IC_{50} value of SQ40 at level of 5.97 µg/mL inhibits growth of LNCaP while the injecton of 5 and 10 mg/kg of SQ40 inhibits LNCaP tumor growth in mice xenograft.	[88]
Carica Papaya	Crude flavnoid extract (CFE), ELE & MLE	Anti-cancer activity, Induces inhibition of cancer cell growth.	DU-145	48-72h	In vitro	Growth inhibition of DU-145 cancer cells induced at IC_{50} of CFE, ELE and MLE at the level of 2.2 µg/ml, 2.4 µg/ml & 2.6 µg/ml respectively.	[89]
Pumpkin (seed)	Cucurbitin	Inhibiting cell growth	DU145 (androgen insensitive) & LNCaP (androgen sensitive)		In vitro	The considered curcurbitin is not the component that causes the Inhibition of cancerous cells. Although the seed extract are considered safe for the PCa.	[90]
Luobuma (leaves)	Sterols (Sitgmasterol, sitosterol) , Triterpenoid (Lupeol) , Flavonoids (Kaempferol, Isorhamnetin)	Inhibits cell proliferation, induce apoptosis, augment cell cytotoxicity	PC3 cells	24h	In vitro	Lupeol accounted for (w/w) 19.3% of F8 and inhibits proliferation of androgen-insensitive-prostate-cancer cells. Other bioactives also exerts anti-cancer effects by different mechanisms.	[91]
Ginger	6-shogaol, 10-shogaol 6-gingerol, & 10-gingerol,	Inhibit proliferation, induce apoptosis	PC3R, PC3 cells	24h	in vitro	6-shogaol, 10-shogaol 6-gingerol, & 10-gingerol at 100µM inhibits proliferation in PC3R, while same results also observe in PC3 by 6-gingerol, 6-shogaol and 10-shogaol.	[92]

Salvia miltiorrhiza Bunge (Danshen)	dihydroisotanshinone I (DT)	Increases survival rate of patients, inhibits cancer migration.	PC3, DU145 ,22Rv1 cells	15year (in vivo), 24h (in vitro)	in vivo (human), In vitro,	Danshen induces in vivo protective effect on the patients that survival rate increases. While in-vitro DT inhibits the migration ability of PCa by different mechanisms.	[93]
Soybean (seed)	Bioactive peptides	Inhibits cancerous cells	PC-3 cells	48–60 h	In vitro	Different soybean lines shows different inhibitory percentage .S03-543CR soybean line shows highest (63%) inhibitory effect to PCa cells.	[94]
Scutellaria altissima L.	Scutellarin (flavon)	Induces G2/M arrest, apoptosis, inhibits proliferation	PC-3 cells	24h	In vitro	Scutellarin induces apoptosis, G2/M arrest, and inhibits the proliferation of PCa. Sensitized the PC-3 cells to chemotherapy.	[95]
Solanum nigrum L.	Solanine	Reduces tumor growth, induce apoptosis	DU145 cells(human ,in vitro), DU145 cell (mouse xenograft, in vivo)	30 days(In vivo), 24h (invitro)	In vivo, in vitro	Solanine in vivo and in vitro regulated the cell cycle proteins i.e. Cyclin E1, P21, Cyclin D1, CDK4, CDK2, CDK6. IC_{50} of solaline at level32.18 μmol/L causes apotosis. Decrease in tumor in mouse xenograft was observed.	[96, 97]
Citrus aurantium L. (stem bark)	acridone alkaloids (citrusinine-I, citracridone-I, 5-hydroxynoracronycin, natsucitrine-I, glycofolinine, citracridone-III)	Induces cyto-toxicity	PC3 cells	72 h	In vitro	IC_{50} of Citracridone-I shows more antiproliferative activity at the level of 12.5 – 14.8 µM than the other alkaloids.	[98]
Plagiochila disticha (Plagiochilaceae)	plagiochiline A	Induces Cell cycle arrest &cancer cell death	DU145 cell	24 h	In vitro	1.75 µg/mL of plagiochiline A causes cell cycle arrest and cell death in DU145 cell.	[99]
Erythrina Excels (stem bark)	Excelsanone	Induces cyto-toxicity , inhibits cell growth	PC3 & DU145 cell lines	24, 48 and 72 h	In vitro	IC_{50} of 1.31mg/ml of Excelsanone together with 6, 8-diprenylgenistein has moderate potential toward cyto-toxicity & also Inhibits cell growth in DU145 cell lines.	[100]
Punica granatum (juice and peel extract)	Ellagic acid and its derivatives, α & β-punicalagin(juice), punicalagin, ellagic acid and its derivatives (peel extract)	Inhibits migration, proliferation and colony formation	PC3 & DU145 cell lines	24 h or 48 h	In vitro	Pomegranate juice and peel extract both shows the antiproliferative effect for PCa cells. But peel extract show more robust result towards cancer than juice at similar concentration.	[101]

Silybum marianum	Silychristine, silibinin & Silymarin-enriched extract (SEE)	G2/M blockade, inhibits anti-proliferative effect	PC-3 cells	24 ,48 and 72h	In vitro	Silychristine, silibinin IC_{50} value of 3–120 µg/mL and SEE have IC50 of 44–52 µg/mL inhibits proliferation in dose dependent way. DXR-SEE co-treatment enhances the cell death than the SEE alone.	[102]
Rooibos (*Aspalathus linearis*)	Flavonoid (aspalathin)	G2/M cell cycle arrest, apoptosis	LNCaP 104-R1 cells xenogafted in mice.	96h	In vivo (mouse xenograft)	GRT extract aspalathin majorly inhibits the proliferation and suppressed the CRPC cells. Causes apoptosis in LNCaP 104-R1 xenografts in mice.	[103]
Paederia foetida (leaf extract)	Lupeol, β-sitosterol and MEPL.	Induces cyto-toxicity,	PC-3 and DU-145, THP-1 cells	24h	In vitro	Lupeol, β-sitosterol and MEPL at their respective IC_{30} values exhibits cyto-toxicity, apoptosis & inhibits proliferation.	[104]
Citrus sinensis L. (peel extract)	Citric acid, narirutin & hesperidin	Suppresses DNA synthesis rate in PC cells,induce apoptosis, inhibits cell cycle re-entry	LNCaP, RWPE-1, GM3348 & PC-3	24h & 48h	In vitro	Narirutin & hesperidin was not the bioactives responsible for inhibiting cell cycle re-entry but it was the citric acid. So, citric acid along other bioactives can be act as chemopreventive.	[105]
Green tea	Epigallocatechin-3-gallate (EGCG)	Inhibits migration and invasiveness of cancer, upregulateTIMP-3 level, decreases class I EZH2 & HDACs.	LNCaP & DUPRO cells	6week (in vivo), 48h (in vitro)	In vivo (human), In vitro	EGCG/GTP inhibits migration & invasive capability of cancer cells. In addition, EGCG in patients increases TIMP-3 levels by balancing MMP: TIMP suppresses PCa.	[106]
Glycyrrhiza glabra	GGE (Glyccyrhiza glabra Extract)	Inhibits proliferation, induce apoptosis	PC-3 cells, WI-38 cells	96h	In vitro	GGE treatment causes proliferation at IC_{50} value of PC-3 and WI-38 cells are at the level of 35.7 ± 2.0 lg/m and 96 ± 1.6 lg/ml. while ADR+GGE causes proliferation at IC50 11.6 ± 0.6nM.	[107]
Rosa canina	Phenolics (ascorbic acid, p-coumaric acid, gallic acid, quercetin, 3, 4- dihydroxy benzoic acid, rutin hydrates and chlorogenic acid).	Induces cyto-toxicity, apoptosis,cell cycle arrest, increases caspase activity.	PC-3 cells	72h	In vitro	Significant increase in M phase cells at observed at IC_{90} of 257 and 378 mg/mL of *Rosa canina* extract. Apoptosis, cell cycle arrest and increase in caspase activity also observed that may be due to phelonic content of extract.	[108]

Cymbopogon citrates (lemon grass)	Citral	Induce apoptosis, inhibits colonogenic formation and proliferation of PCa cells.	PC3 and PC-3M cells	72h	In silico , in vitro	Citral significantly reduces the colonogenic potential, proliferation, cell viability, changes the morphology and inhibits the lipogensis of cancerous cells.	[109]
Rhizoma Curcuma	Germacrone	Reduces the viability, induces apoptosis and autophagy.	PC-3 & 22RV1 human PCa cells	48h	In vitro	Germacrone in dose dependent manner with IC_{50} have the value for PC-3 were 259 μM and for 22RV1 were 396.9 μM induces apoptosis and inhibits cells proliferation.	[110]
Orobanche crenata	Orobanche crenata methalonic extract	Inhibits PCa cells,	PC-3 PCa cells	24h	In vitro	O. crenata extract exhibits the anticancer, cytotoxic and antiproliferative activity due to the bioactive methalonic components present in it.	[111]
Moringa oleifera (Leaves)	Methalonic extract	Induces G0/G1 cell cycle arrest, anti-cancer potential and ROS-mediated apoptosis.	PC-3 cells	24h	In vitro	Moringa oleifera methalonic leaves extract demonstrates ROS-mediated apoptosis and reduction in proliferation by suppressing deregulated Hedgehog signaling in PCa.	[112]
Paris forrestii	Total saponins (polyphillin D, paris saponin Tg).	Induces apoptosis,PCT3 treatment changes mRNA and lncRNA.	LNCAP, DU145, PC3, RWPE	24h	In vitro	PCT3 exhibits the anticancer activity on PCa and also reveals some crucial mRNAs and lncRNAs that take part in the anticancer activity of PCa.	[113]

5. Multi-targeted Chemo-prevention

Assembling evidences describes that a lot of phytochemicals are acting via multiple mechanisms involving modulating pathways of signal transduction, interconnections with receptors and the genes includes in the control of apoptosis, cell cycle, cell proliferation and regulating transcription by exerting their chemotherapeutic and antitumor effects. Some of the potential phytochemicals are described under that are proven to be having the chemo-preventive effects towards the PCa [15].

5.1 Tanshinones

Tanshinones are abietane diterpene compounds found in Salvia miltiorrhiza. They include tanshinone-I "T1" (Compound 1), tanshinone-IIA "T2A" (Compound 2), and cryptotanshinone "CT" (Compound 3). (a traditional Chinese medicine). These bioactive elements are used to cure disorders and display anti-cancerous action by anti-angiogenesis, anti-proliferation, pro-apoptosis, reducing adhesion, metastasis, invasion, and migration, and inducing differentiation, with no negative effects on normal cells. [114, 115].

Tanshinones showed the anti-cancerous results while doing invitro study in the dose dependent manner by inducing apoptosis and cell cycle arrest. Tanshinone-I exhibits the potential activity with IC_{50} value around 3–6 µM. Aurora A kinase were identified as the probable target of these phytochemicals actions (tanshinones), as in the cell lines of PCa. Aurora “A” were over-expressed and hence decreases the PCa cell growth. Its expression was significantly downregulated by tanshinones. Tanshinones especially “T1” exhibits the anti-angiogensis effects in-vivo and in-vitro suggesting that these are the safe anti-cancerous and therapeutic agents against PCa[72] . T1 also increases TRAIL mediated apoptosis through the miR135a-3p arbitrated DR5 up-regulation in the PCa cells as an effective TRAIL sensitizer [116]. In another study tanshinone IIA isolated from Salviae Miltiorrhizae (root extract) exhibits the antiproliferative effects to PCa in a dose dependent way. Tan- IIA causes the cell death and cell cycle arrest in LNCaP cells at G0/G1 phase and correlating it with the enhanced CDK inhibitors levels. These tanshinones induces ER stress, induces the cell death with the blockage of the expression GADD153/CHOP via siRNA reduced tanshinone IIA, increases the expression of down-stream of different molecules and suppresses the tumor growth and reduces tumor volume to 86.4% in xenograft model within the 13 days of treatment. In PC-3, LNCaP cells the IC_{50} value for the bioactives Tanshinone IIA were 2.54µg/mL and 5.77µg/mL[117].Tanshinone IIA also exhibits the inhibitory effects on the proliferation and growth of the LNCaP cells via BrdU incorporation assays and colony formation respectively and induces the cell cycle arrest at G1 phase by the activation of p53 signaling, also the down regulating Cyclin D1, CDK2 and CDK4 and inhibiting androgen receptor (AR) in LNCaP cells [118].

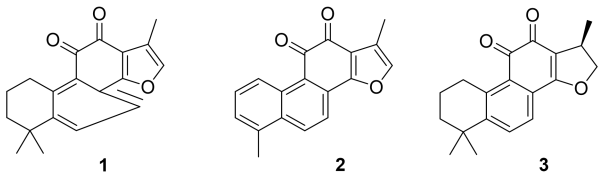

Figure 2: Molecular structures of tanshinone-I (1), tanshinone-IIA (2) and cryptotanshinone (3). Reproduced with permission: Copyright 2015, MDPI [119]

5.2 Biochanin-A

Iso-**flavones** are the most common plant-based bioactive chemicals. Biochanin-A (compound 4) in red clover and soy has chemo-preventive, anti-proliferative, and anti-cancerous activities. Biochanin-A significantly enhances the Trail mediated apoptosis and cytotoxicity in LNCaP and DU145 PCa cell lines. TRAIL is actually the innate potent anti-cancerous agent that inequitably induces the apoptosis in the malignant cells and cause no damage or toxicity to normal cells. In vitro study shows TRAIL cytotoxicity at 50-100ng/mL for 48h was 2.8% -1.4% to 6.2% -1.7% for DU145 and 8.3% -1.2% to 19.6%-1.1% for LNCap. Biochanin-A sensitized the LNCaP cells that are TRAIL-resistant by inhibiting the activity of transcription

factor NF-κB (p65). This compound enhanced the expression of TRAIL-R2 (DR5) a death receptor and disrupted the potential of mitochondrial membrane. Apoptosis is enhanced by inducing the potential of sensitized TRAIL and TRAIL resistant PCa. This isoflavone regulated NF-κB activity and also affected the intrinsic and extrinsic apoptotic pathways [120-122].

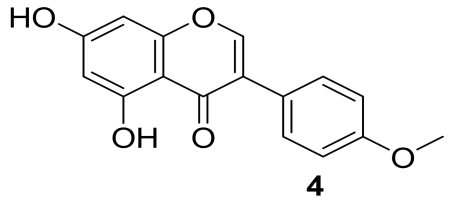

Figure 3: Molecular structure of Biochanin-A (4). Reproduced with permission: Copyright 2014, PLOS [123]

5.3 Oleuropein

Olive leaves, fruits, and oil contribute to the Mediterranean diet's health benefits. Oleuropein (Compound 5) is an anti-tumor polyphenol found in olive leaves. Olive leaves and oil contain polyphenols. Many of the invitro studies demonstrated the apoptotic and anti-proliferative effects in many of the cancer cell lines. In a study using MMT test to assess cell proliferation, 100-500M oleuropein treated over 72 hours on LNCaP, DU145, and non-malignant BPH-1 cells suppressed cell viability, especially in DU145 and LNCap cells. Hydrolysis of oleuropein produces the compounds such as hydroxytyrosol and eleonolic acid that are also the bioactive compounds. This polyphenol induces the decrease in cell viability and modification in the thiol group, ROS (reactive oxygen species), γ-glutamylcysteine synthetase, heme oxygenase-1 and pAkt. Oleuropein induces the antioxidant effect while exposing cell culture on the BPH-1 cells, a non-malignant cell line. Oleuropein proves to be an adjuvant agent while treating the prostasis, so as for preventing the modification of hypertrophic to malignant (cancerous) cell [74, 124-126].

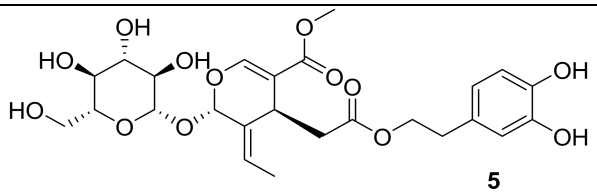

Figure 4: Molecular structure of Oleuropein (5). Reproduced with permission: Copyright 2015, Scientific Research Publishing, Inc. [127]

5.4 Anthocyanins and phenolic acid

Anthocyanins are phenolic pigments found in berries and grapes. Anthocyanins are also found in cereals, tubers, and other plants. These bioactive components have proven to be beneficial for health [128]. Sweet potato leaves contain anthocyanins and phenolic acid. Polyphenol rich sweet potato green extract (SPGE) stimulates anti-proliferative activity in prostate epithelial cells without injuring normal cells, modifies the cell cycle, lowers colonogenic survival, and induces apoptosis in human PCa "PC-3 cell line" in-vivo and in-vitro. Alternations in apoptosis regulatory constituents e.g. Bcl2 inactivation, BAX upregulation, release of cytochrome and the activation of the down-stream apoptotic signaling were observed by the action of SPGE. SPGE also cause the degradation of DNA as obvious via TUNEL (terminal deoxynucleotidyl transferase-mediated dUTP-nick-end labeling) staining of enhanced 3′-DNA ends concentration. In-vivo 400 mg/kg SPGE oral administration show the reticent progression and growth approximately 69% in prostate tumor xenograft model of mice and exhibits that normal tissues are also not affected[129].

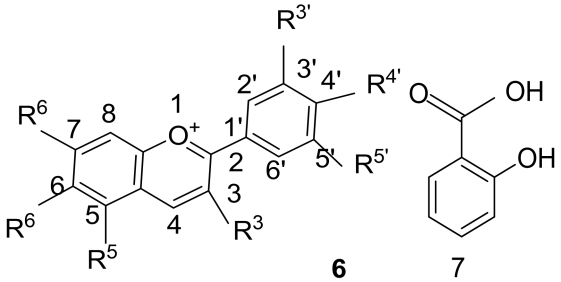

Figure 5: Molecular structure of Anthocyanins (6) and phenolic acid (7). Reproduced with permission: Copyright 2017, MDPI [130]

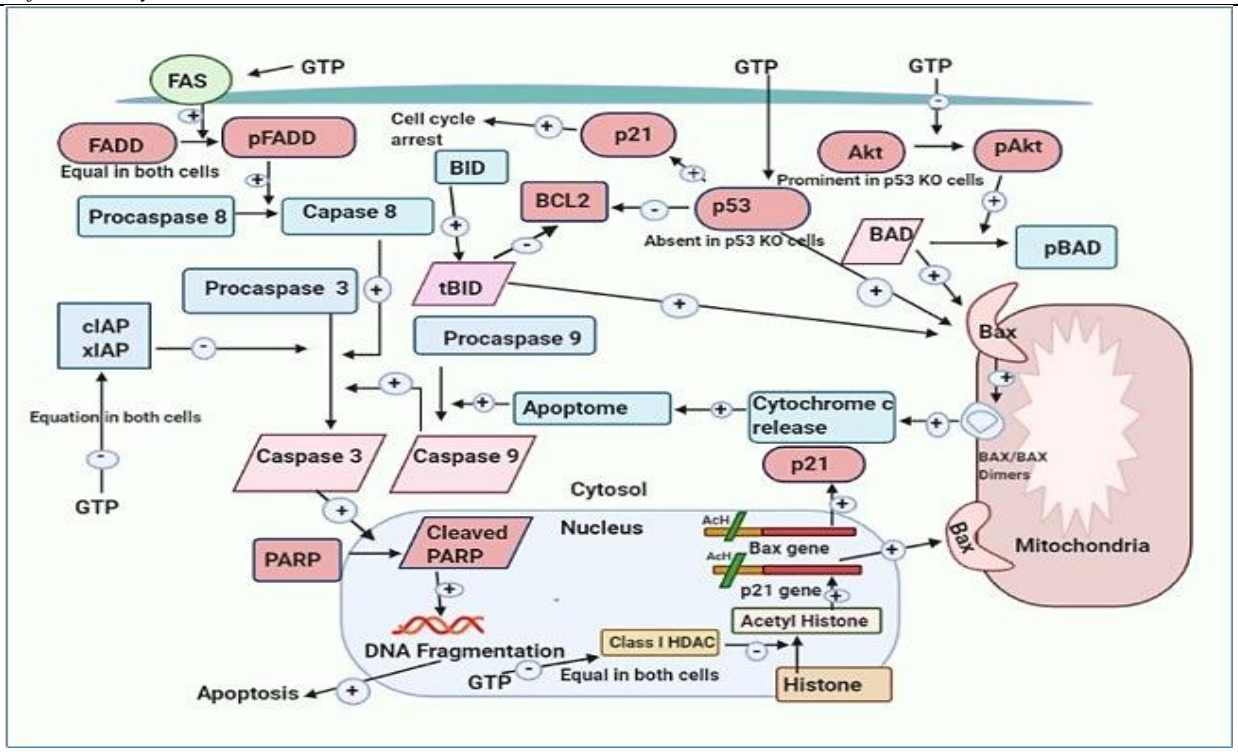

Figure 6: Schematic model illustration of the green tea polyphenol induced activation of intrinsic (death cascade of mitochondria) and extrinsic (death receptor pathways) molecular pathways in the presence and absence of p53. Reproduced with permission: Copyright 2012, PLOS [131].

5.5 Epigallocatechic-3-gallate (EGCG)

Epigallocatechic-3-gallate (EGCG) is the major green tea polyphenol. Green tea polyphenol induced P53 activation and stabilization of down-stream targets Bax and p21/waf1are induced by the GTP treatment in a dose dependent manner especially in LNCaP cells. These polyphenols promotes the apoptosis in cancerous cells effectively both in absence and presence of p53 function via agitation in signaling pathways involving the extrinsic FAS-FADD death receptor and constancy pathways that intersects in the induction of apoptosis via mitochondrial death cascade **(Figure 6)** [132].

An analytical study reported that EGCG in combination with quercetin induces apoptosis, cell cycle arrest and inhibits the cell proliferation in PCa in vitro by enhancing the EGCG intracellular concentration and lessen the EGCG methylation. As compared to the sum rate of inhibition of EGCG and quercetin individually their combination with 10µM or 20µM respectively enhances the reduction in PC-3 cell proliferation at 24h and 48h by 15% and 20%, or 21% and 19%, respectively. The combined effect of these agents based on the certainty that quercetin decreases the quantity of catechol-*O*-methyl transferase (COMT) activity while EGCG inhibits activity of catechol-*O*-methyl transferase (COMT). EGCG and quercetin leads to the additive effects by executing the strong anti-proliferative effects in LNCaP cells. Combination of these two bioactive molecules proved to be much effective in order to induce chemotherapeutic and chemo-preventive effects towards PCa[133].

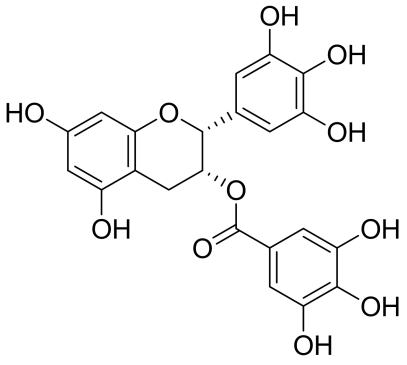

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Figure 7: Molecular structure of Epigallocatechic-3-gallate

(8). Reproduced with permission: Copyright 2006, Elsevier [134]

5.6 Resveratrol

Resveratrol is a natural polyphenol found in peanuts, berries, and grapes. Many pre-clinical investigations suggest resveratrol is a promising natural bioactive anticancer drug [135]. These research showed that resveratrol (Compound-9) shields various biological systems, especially in cancer[136]. By altering androgen receptor signaling in PCa, resveratrol inhibits androgen-regulated gene expression and cell proliferation. Anti-androgenic resveratrol analogues were extracted from plants or semi-synthesized. LNCaP prostate cell lines were seeded in the luciferase assay along with MMTV-luc reporter plasmid for the measurement of androgen dependent (AR) activity. 4′-O-methylresveratrol (3, 5-dihydroxy-49-methoxystilbene) resveratrol analog were proved to be most potent abstractor of AR transcriptional activity as IC_{50} value for the resveratrol and its analogs were to be 5μM and 2μMrespectively. The hydroxyl (OH) in the ring of resveratrol plays the major role in the anti-androgenic effects via modulation of androgen dependent (AR) activity [137]. Peanut stem extract (PSE) contains high content of resveratrol that augments its radio-sensitization affects in PCa which is likely to be mediated through the apoptotic pathway activation, DSB (DNA double-strand break) repair attenuation and the arrest of cell cycle in G2/M phase. Resveratrol and PSE inhibits proliferation in LAPCD-KD cells for 48h treatment with IC_{50} value 25 and 500μg/mL, respectively. In addition, co-administration of PSE or resveratrol and radiation, induced the apoptosis in radio-resistant PCa cells. Radiation therapy were enhances effectively by exploration of PSE and resveratrol in the shDAB2IP PCa mouse xenograft model [138].

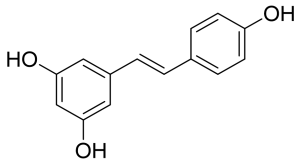

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Figure 8: Molecular structure of resveratrol (9). Reproduced with permission: Copyright 2019, MDPI [139]

5.7 Piperine

Black pepper contains the medicinal alkaloid piperine (*Piper nigrum* Linn.). Pepper has wide-ranging pharmacological effects and is used to treat numerous diseases. Piperine is anti-asthmatic, immune-modulatory, anti-ulcer, anti-oxidant, anti-inflammatory, and anti-carcinogenic, according to human research [140-143]. A study provide evidence that piperine exerts the antitumor activities towards the PCa, in-vivo and in-vitro. Piperine was pre-treated with DU145 cells for 48h and then their viability was examined by the CCK-8 assay. It clearly caused apoptosis and inhibited cell migration and proliferation in DU145 prostate cell lines by downregulating MMP-9 and Akt/mTOR signaling, also Akt/mTOR signalling appears to be MMP-9 protein upstream regulator (**Figure 9**) [144].

Piperine in the dose dependent manner suppresses different metastatic behavior and proliferation of PCa by inducing the G°/G1 phase arrest. The bioactive component piperine shows the IC_{50} value for the PC-3, DU145 and androgen-dependent LNCap cells were 111μM, 226.6μM and 74.4μM respectively106. In another in-vivo and in-vitro studiesthe effectiveness of piperene were examined. It induces apoptosis and inhibits proliferation in both the androgen independent PC-3, 22RV1 and DU145 and the androgen dependent LNCap cells in vitro. PC-3, 22RV1 and DU145 PCa cell line while treating with piperine results in the lessened expression of nuclear factor-kB (NF-kB) and phosphorylated STAT-3 transcription factors. In-vivo study shows that xeno-transplanted model with PCa in mice results in the reduction of androgen dependent (AD) and androgen independent (AI) tumor growth. Significant reduction in viability and proliferation of PC-3 (AI) and LNCaP (AD) cells with piperine were exhibits while assessing as MMT assay with the IC_{50} values of 75μM and 60μM respectively in a dose dependent way [77].

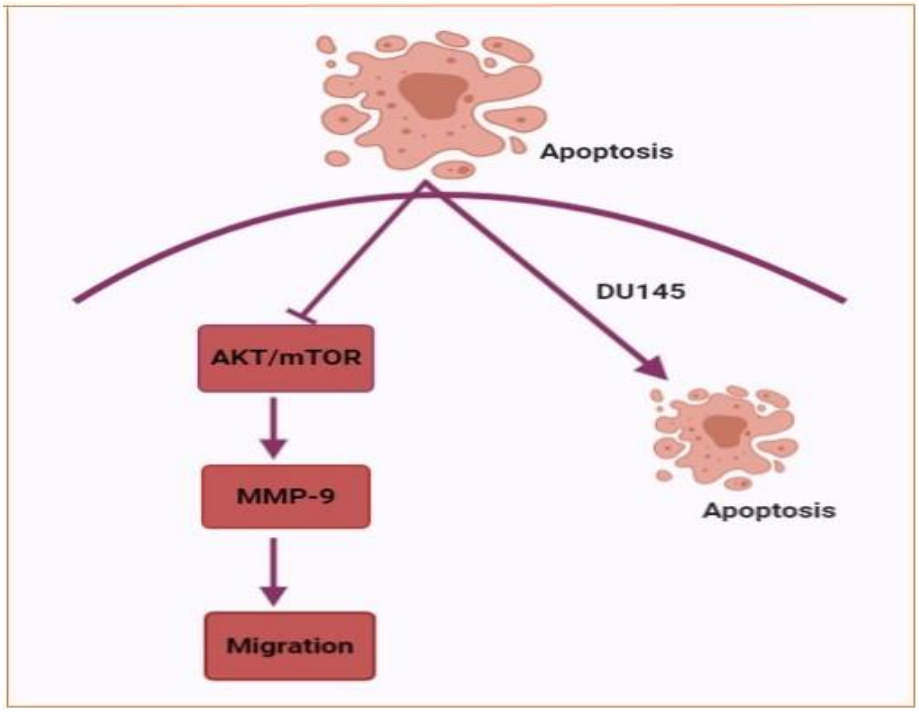

Figure 9: Piperine inhibits the continuation of migration via downregulating signaling pathway Akt/mTOR/MMP-9 in DU145 PCa cells. Reproduced with permission: Copyright 2018, Spandidos publications [145].

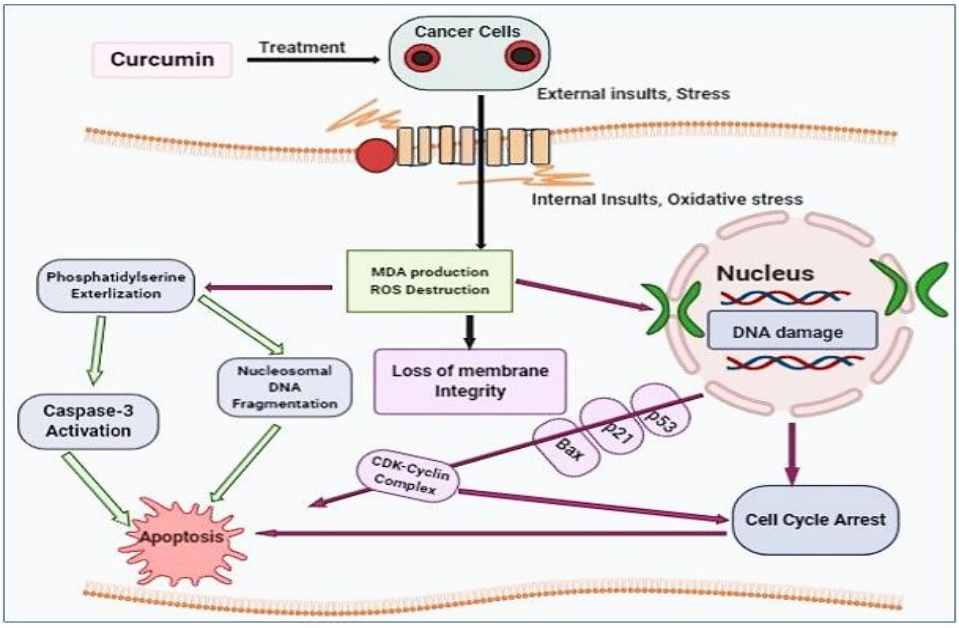

Figure 10: Schematic model representation of curcumin molecular mechanism, in malignancies management as a therapeutic agent. Reproduced with permission: Copyright 2019, MDPI [146].

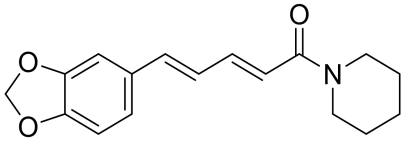

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Figure 11: Molecular structure of piperine (9)Reproduced with permission: Copyright 2022, Springer [147].

5.8 Curcumin

Curcumin a pleiotropic curcuma longa constituent is a polyphenol with therapeutic properties. Curcumin has anti-arthritic, antioxidant, anticancer, and anti-inflammatory properties, according to in-vivo and in-vitro studies. Due to its regulation and efficacy towards multiple targets, as well as its tolerability, safety, and non-toxicity for human use, curcumin is a potential therapeutic agent for the treatment and/or prevention of chronic diseases [148-151]. Curcumin (Curcuma longa) is a potential chemo-preventive for early-stage PCa. It affects cell proliferation by reducing the expression of ß-catenin-targeted genes, which links cell death with autophagy in androgen-dependent prostate cells. Curcumin cell viability were assessed by tryphan-blue exclusion test that reveals that curcumin exhibits cytotoxic effect for the concentration >75µM, both in androgen dependent and independent PCa. Androgen dependent PCa cells were more sensitive for the natural compound curcumin (IC_{50} value were 44 and 48µM for the cells 22rv1 and LNCaP, respectively) than in androgen independent PCa cells (IC_{50} value were 115 and 170µM for PC-3 and DU145 cells respectively) [152]. Curcumin inhibited the cell growth and induces cell growth arrest via DNA damage, cell cycle arrest, stress genes (Bax, p21, p53 and CDK Cyclin complex) expression, and induces apoptosis through the phosphatidylserine externalization modulation, fragmentation of nucleo-somal DNA and caspase-3 activation **(Figure 10)**[146].

In PCa metastasis liable phenotype can be induce as a result of chronic inflammation via sustaining pro-metastatic and a positive pro-inflammatory feedback loop betwixt CXCL1/-2 and NFκB. This feedback loop disrupted from curcumin by suppression of NFκB signaling that leads to the lessened in-vivo metastasis formation [153]. Curcumin's anticancer effects were studied in nude mice. PC-3 cells were subcutaneously injected to the nude mice for establishing the tumor model. Nude mice were divided into different groups, group B (6% polyethylene glycol and 6% anhydrous ethanol, group C (normal saline), and group H, M, L (100 mg/kg, 50 mg/kg, and 25 mg/kg curcumin). Tumor growth were measured every 6th day and after 30 days they were killed to weight the tumor. Cell apoptosis were determined by TUNEL assay. In group H, M, L the volume and weight of tumor was lower remarkably than that of the control groups (C, B) ($P<0.05$), and as the dose for curcumin increases the inhibitor rate were also increases. While comparing with that of the control group, in H, M,L group Bcl-2 gradually decreased and Bax protein expression were enhanced ($p<0.05$). So, this study leads to the result that curcumin have the ability to inhibit PC-3 cells growth, reduces the weight and volume of tumor and also induces apoptosis under the nude mice skin by up regulating Bax and down regulating Bcl-2 [154]. Curcumin repudiate cancer associated fibroblasts (CAF) induced capture/invasion and epithelial to mesenchymal-transition and suppresses CXCR4,IL-6 receptor expression and Reactive oxygen species(ROS)in the PCa cells via suppressing HIF 1α/mTOR/MAOA signaling so that exhibiting the potential therapeutic effects of curcumin in PCa[155].

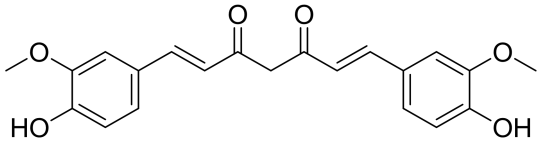

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Figure 12: Molecular structure of Curcumin (9)Reproduced with permission: Copyright 2018, Frontiers [156].

6. Future Prospective

Health claims are highly concerns with the nutrition

regulation in order to protect and inform the public about the fallacious health declarations. Although it's challenging but human intrusion studies are important in supporting the plant derived bio-actives, for the validated scientific findings [157-159]. However, with the advancement in cancer studies, characterization of neoplastic transformations due to the aberration in several signaling pathways arise the need for the identification of chemo-preventives that must be target specific towards the carcinogenesis. Hence, unraveling the bio-actives synergistic interactions and their potential impact on humans would considerably help in attaining success in the chemo-prevention via the plant bio-actives [15]. Pure plant derive bioactive compounds individually are needed for determining their potential chemo-preventive effects from the dietary supplements. However, isolation of the pure bioactive compound is sometime become difficult and challenging because of the stability issue, and missing their potential or in some of the cases unknown constituents may also demonstrate bioactivity either synergistically or additively from the same plant of interest[160].

Nutraceuticals and dietary supplements exert chemo-preventive effects that vary within the populations and also largely rely on microbiota gastro-intestinal composition, which in turn affect the level of anticancer compounds and bio-available nutrients. So, studies that exhibit the distinction in microbiome betwixt high and low risk populations, or in-between patients and healthy person with metastatic or dormant and androgen insensitive disease may lead to the valuable insight into the microbiome role in the progression and development of PCa. Human microbiome modulation may exert beneficial effects in chemoprevention of PCa [161]. Even though unique chemotherapeutic constituents would be more and more efficacious against the cancerous cells, their drug resistance as well as toxicity to normal tissues remain the extensive obstacle for its clinical use. Using various plant derived bio-actives for the personalized approach provides with the new dimensions for the standard cancerous growth therapy for the betterment of its outcome in complementary and complex way [47].

Despite, a lot of the data involvement for the carcinogenic studies and its treatment, only arbitrary controlled trial is able to assess adequate evidences for creating the universal guidelines. Additionally, only a few of the plant derive bio-actives have been taken for the reasonable clinical trials to evaluate their potential anti-PCa activity [162]. Many more efforts are needed in clinical, epidemiological research, as well as in Phyto-biology that must be addressed, before the potential health effect of these phytochemicals on human[163].

7. Conclusion

Finally, many cancer treatment strategies are still in clinical trials, and many are on the way to improvement despite the enormous amount of work that has already gone into them. Because of their proven effectiveness against a wide range of acute diseases, low cost, and widespread availability, the scientific community is also making headway in treating malignant PCa with natural plant sources. Several useful plants, shrubs, and herbs have been shown to have chemo-preventive effects against PCa malignancies due to the presence of novel bioactive components. Being the active constituent bio-actives of the plants act as an agent that distressing the signaling of the prostate cells in several of the pathways, causes blockage of cell cycle at various phases, induces alternations and killing of the PCa cells with the less chances of drug resistance. Numerous in-vivo and in-vitro clinical studies have been conducted to better understand the precise protocol pathway of these bioactives in their interaction with and effect on PCa cells. However, much more of the research and clinical trials are needed for the detection of chemo-preventive effects of different plants bio-actives, while watching towards the future prospective.

Conflict of interest

The authors declare no conflicts of interest.

Authors Contribution

Hira Zulfiqar convinced the main idea and wrote the

manuscript. Hunain Zulfiqar, M. Furqan Farooq, Iqbal Ahmed, Iqra Rani revised the manuscript and prepared figures and references. Farman Ullah helps in scientific writing of the paper.

Data Availability Statement

The data presented in this study are available on request from the corresponding author.

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