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Research Article

Phytochemicals a Noval Approach as Therapeutic in Prostate Cancer Treatment

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ABSTRACT

Prostate cancer stands as prominent reason for death along with men globally.The escalating challenges of resistance, toxicity, and side effects associated with traditional treatments have propelled a shift toward more intensive and aggressive approaches in prostate cancer treatment. The persistent rise in incidence coupled with the scantiness of standard treatment in managing intricate cancer of prostate necessitates exploration and advancement of contemporary agents involved in both treatment and prevention of this malignancy. Utilization of compounds that occur naturally in chemoprevention has become a viable and affordable strategy in recent decades. This approach aims to decrease the frequency and severity of prostate cancer by preventing precancerous processes before the onset of symptoms (Surh, 2003). Prostate cancer presents substantial chance for intervention to stop it from progressing or to obstruct it. With elevated occurrence as well as extended dormancy, PCa remains a perfect fit for chemotherapy prevention. The search for agents that provide substantial defense besides the onset of this illness is crucial. The discovery of effective chemotherapeutic drugs may significantly affect the costs, morbidity, and mortality associated with disease for a sizable segment of the population (Adhami & Mukthar, 2007; Bommareddy et al., 2009; Bommareddy et al., 2012; Klein, 2005; Powolny et al., 2011; Singh et al., 2009). Phytochemicals, bioactive substances that are not nutrients inherent in a diet high in plants, hold promise for both illness prevention and treatment. Numerous phytochemicals isolated from plants exhibit cytotoxic effects on tumors. Laboratory in vitro investigations encompass demonstrations of these compounds which occur in nature and can impact via affecting important biological signaling pathways, cancer cell proliferates commonly prostatic carcinoma is dysregulated. A variety of compounds that occur naturally are identified as capable of inducing cell cycle termination, fostering apoptosis, impeding development of cancer cells, as well as angiogenesis suppression.

Keywords: Prostate Cancer, Apoptosis, Angiogenesis, Phytochemicals, Metastasis, Cell Cycle.

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INTRODUCTION

Prostate cancer stands as major prevalent non-skin cancer as well as holds position of the second most common reason of mortality for men in the US (Lynn et al., 1995). Cancer of prostate occurrence demonstrates a notable rise with advancing age, and A complex interaction of various genetic and epigenetic

start, development, and metastasis of this malignancy.Despite this, our scientific understanding there are still few known biological processes behind the illness. Prostate malignancy stands as the second most fatal and widespread cancer type in men globally. ROS (Reactive oxygen species) excessive production led to extensive as well as irreparable damage to cells by oxidizing RNA, DNA, carbohydrates, lipids, and proteins (Castañeda-Ovando *et al*., 2009). Many oxidative stress factors in the extracellular and intracellular environment, that as androgen imbalance, aging, dietary fats, antioxidant system, as well as premalignant lesions, are the causes of increased ROS in cells, thus causing prostate cell dysfunction (Khandrika et al., 2009; Khandrika et al., 2021). Uncontrolled cell cycle, metastasis, aggression, and cladogenesis are phenotypic properties of cells caused due to prostate cells oxidative stress. Furthermore, ROS increased production may be caused due to promotion maintenance, as well as prostate cancer initiation (Khandrika et al., 2009). ROS is known to be a double-edged sword in cells, which explains why there is such a high concentration of it in cells. Apoptosis is caused by excessive ROS, Modest ROS can encourage the formation of cells. (Ray *et al*., 2012; Liu *et al*., 2023).

The challenge frequently encountered clinically is often caused by more than just the absence of a single gene or protein that can function as a trustworthy marker (Zhau *et al*., 2009; Webber *et al*., 2012). Furthermore, the absence of an effective therapeutic regimen is compounded by the fact that there are still no available options without serious, and at times fatal, side effects.

Table 1. Factors Influencing Prostate Cancer Risk

Factors	***Influence on prostate cancer risk***
Advanced age	Increased risk; >66% of all PC diagnoses in men over 65 years
Positive family history	Increased risk; 1 in 7 patients diagnosed with PC has a relative with the disease
Genetic associations	Mutations in several genes increase risk; BRCA2 mutations increase PC risk by 25%
Serum androgens	Increased risk, clear evidence lacking
AR gene polymorphism	Increased risk; short CAG repeat length in AR gene is linked to an increased PC risk
Dietary factors	Red meat, alcohol and dairy products increase PC risk, fresh fruits and vegetables reduce PC risk
Lycopene intake	Decreased risk; high intake of tomatoes (rich source lycopene) and overall lycopene intake are linked to a reduced PC risk
Allium vegetables	Decreased risk; high intake of allium vegetables (e.g. garlic, onion) Is linked to reduced PC risk
Vasectomy	Increased risk,
Body weight	Increased risk
Minerals	Increased risk seen with high intakes and/or elevated serum concentrations of copper, calcium, iron and cadmium

Prostate cancer (PC) is not fully understood to have a cellular genesis, but evidence suggests a multistep histological transformation process involving molecular changes that PC develops from normal prostate epithelium. Receptors of androgen (AR), the PI3K trail and retinoblastomas (RB) signaling system are the main signaling pathways that are commonly changed in prostate cancer. (Figure 1). The AR, responsible for regulating the prostate gland's distinctive growth and development, becomes overexpressed to some extent in PC, leading to elevated serum PSA levels.

In prostate cancer, alterations in the AR signaling pathway occur through various mechanisms, such as AR mutation or amplification, intratumoral testosterone synthesis and the existence of AR receptor splice variants. In brief, dihydrotestosterone binding results in start transcription, AR homodimerizes, moves toward the nucleus. The objective of present study is to compile preclinical as well as clinical research assessing the efficacy of phytochemicals in management and avoidance of this particular disease, marking initiative comprehensive examination of their potential in this context.

Several cellular activities are regulated by the various intracellular cascade known as PI3K/Akt signaling system, including metastasis, metabolism, propagation as well as cytoskeletal remodeling of tumors. The pathway, which starts downstream of the activation of receptor tyrosine kinases (RTKs), involves production of phosphatidylinositol 3,4,5-trisphosphate (PIP3) by PI3K. PIP3 works through PDK1 and Akt, leading to the phosphorylation of Akt by PDK1. Phosphorylated Akt activates numerous pathways, notably including the protein called mammalian target for

rapamycin (mTOR) is a serine/threonine kinase, that is essential for the development, growth, survival, and division of tumors. The interaction between Akt and the androgen receptor (AR) can activate the AR in a ligand-independent (androgen-independent) way, which in turn can up-regulate genes implicated in castration-resistant prostate cancer (CRPC) tumorigenesis.

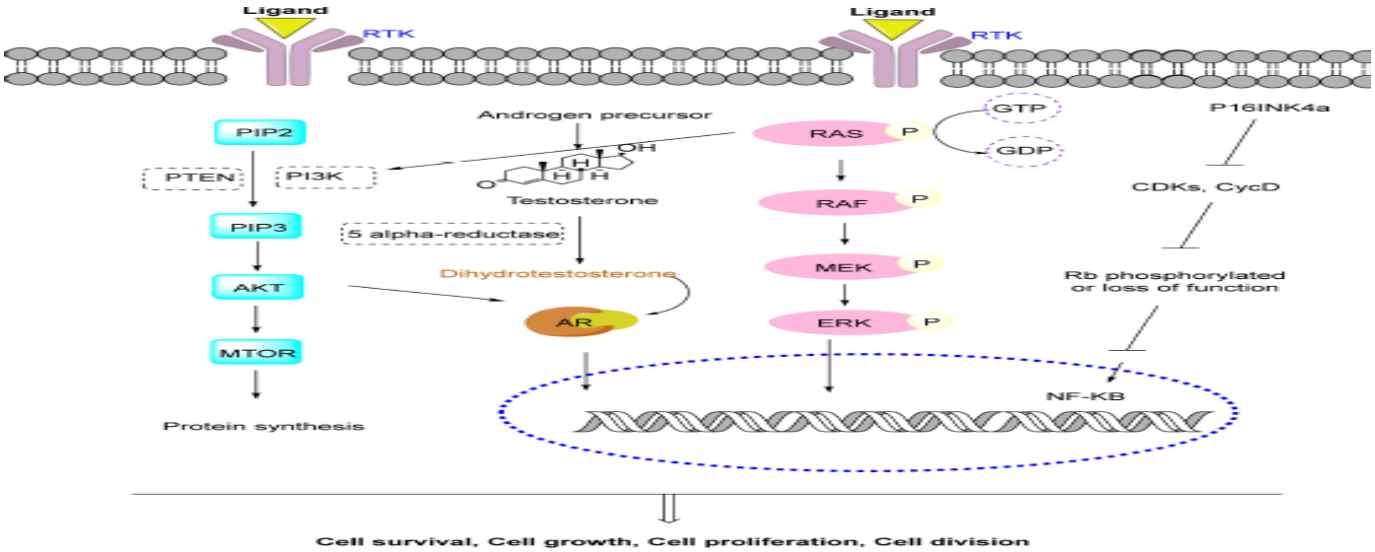

Figure 1. Diagram showing some of the molecular mechanisms involved in prostate cancer.

Indeed, activated Akt exerts its influence on downstream effectors, including PRAS40, TSC2, BAD, and GSK3β. This regulation of downstream effectors by Akt is essential for regulating several biological functions, such as protein synthesis, cell division, growth, as well as survival (Toren *et al*., 2014; Basnet *et al*., 2020).

PHYTOCHEMICALS

Phytochemicals, which are nutrients-free bioactive substances found in plant-based diets, exhibit possibility of both the management and avoidance of illnesses. A noteworthy statistic from September 2019 indicates that natural products and their derivatives provide the basis for 32% of all approved small molecule medications (Newman *et al*., 2020). Current Evidence suggests that phytochemicals effects on animal models and cells health may vary, contingent upon the dosage administered.

Numerous valuable phytochemicals, such as Texans *(paclitaxel, docetaxel)* and derivatives of camptothecin *(topotecan as well as irinotecan)*, have demonstrated efficacy in cancer treatment (Newman *et al*., 2020; Asma *et al*., 2022). The distinctive phytochemical structures and novel methods of action

have garnered increasing attention. Remarkably, numerous reports highlight the function of phytochemistry in prostate cancer prevention and therapy as well (Singla *et al*., 2021; Fontana *et al*., 2020).

Oxidative stress holds significance in the pathogenesis of cancer of the prostate (PCa), with reactive oxygen species (ROS) being implicated in PCa through initiation of various signaling systems. These systems are the hypoxia-inducible factor (HIF-1) signaling pathway, and the cyclooxygenase-2 (COX-2) signaling system (Mirzoeva *et al*., 2013; Mousavi *et al*.,1993).

Phytochemicals as Curative Agent in Prostate Cancer

Phytochemicals with antioxidant properties have demonstrated a noteworthy part in both chemoprevention then chemotherapy for PCa. Numerous beneficial properties of these phytochemicals have been documented, with their notable capacity to suppress tumor cells emerging as a promising therapeutic attribute that has recently garnered significant attention. With the growing body of data highlighting the interference of phytochemicals with various This review explores and highlights the molecular processes involving cell propagation, regulation of the cycle of cells and programmed cell death in prostate cancer. Unraveling anti-cancer mechanisms based on the chemical structures of natural compounds holds the potential to streamline drug development. Utilizing phytochemicals in curing prostate cancer has the potential to yield substantial health benefits for humans. The isoflavonoid family of phytochemicals,

including genistein, shares similarities with estrogen steroidal (Dixon *et al*., 2002). Various clinical investigations suggest genistein exhibits chemotherapeutic against several cancers. This is attributed to various ways of acting i.e. apoptosis induction (Matsukawa *et al*.,1993). Genistein's potential in cancer treatment involves inhibiting DNA topoisomerase-II, acting as a competitive ATP-inhibiting agent as well as tyrosine protein kinase (Akiyama *et al*., 1987). The latter effect might lower the amount of free and active hormones to lower the risk of malignancies linked to hormones in the bloodstream. (Messina *et al*., 1994). Exploration of substances and the molecules they target in prostate cancer chemotherapy relies on information from various origins (Adhami *et al*., 2007). PCa, like different cancers, is believed to evolve through alterations in diverse molecular events. Thus, targeting or it may not be possible to stop or postpone the start of a disease by suppressing just one event. Continuing investigation is crucial for enhancing our understanding of the development of disease. The potential of naturally occurring compounds as chemotherapeutic agents is now being investigated.

Hence, this research aims to examine the biological processes that underlie oxidative stress in the development of prostate cancer as well as to assess antioxidant phytochemicals' potential for the management of PCa.

Mechanism Of Phytochemicals

Induction of Apoptosis

Quercetin

Quercetin, a phytochemical, has demonstrated its potential in enhancing TRAIL-mediated prostate cancer (PCa) cell apoptosis. It has been observed to interfere with various cancer-causing genes as well as genes that suppress tumors, exhibiting tumor-protective properties. It induces programmed cell death in cancer of prostate, and prostate cells by downregulating Hsp90 and inhibiting fatty acid synthase (*FA synthase*) (Aalinkeel *et al*., 2008).

Baicalin

Baicalin, a flavone extracted from various species in the genus Scutellaria, such as Scutellariabaicalensis and Scutellarialateriflora, has exhibited noteworthy properties in prostate cancer (PCa) intervention. Baicalein, derived from baicalin, induces apoptosis and hinders metastasis (Guo *et al*., 2015). Moreover, it efficiently restrains developing androgen receptors through impeding AR N/C dimerization. Additionally, this phytochemical inhibits proliferative activity in PC-3 cells by downregulating Ezrin (Ma *et al*., 2020).

Delphinidin

Delphinidin is demonstrated as having inhibitory effects on NF-κB gesturing as well as a subsequent initiation for caspases. This inhibition results in the dose-dependent suppression of cell growth and then induction of programmed cell death in LNCaP and PC-3 cells (Bin Hafeez *et al*., 2008).

Formononetin

Formononetin (FN), originated from Trifolium pretense, has been linked to the induction of apoptosis. In an additional study, formononetin was found to cause programmed cell death (Huang *et al*., 2013). This effect is associated with modifying the p38/Akt signaling pathways and the Bax /Bcl-2 ratio (Zhang *et al*., 2014). Furthermore, formononetin was observed to trigger the mitochondrial apoptotic pathway in DU 145 cells, following the upregulation of RASD1 (Liu *et al*., 2023).

Genistein

Genistein has been documented to trigger cell death via a mechanism involving the loosening of restrictions of miR-1260b, which in turn leads to the downregulation of Smad4 and sRRP1 (Hirata *et al*., 2014).

Glycyrrhiza Compounds

Two active ingredients in the hexane/ethanol extracted from Glycyrrhiza uralensis (HEGU) are licoricidin and isoangustone A. An active flavonoid isoangustone A, has been found to induce apoptosis. This induction of apoptosis is associated with an increase in cleaved caspases (Seon *et al*., 2010).

Licochalcone

Licochalcone, an estrogenic flavonoid derived from licorice root, has been found to induce G2/M phase arrest in PC-3 cells. This effect is attributed to the suppression of cyclin B1 and cdc2 (Fu *et al*., 2004). Additionally, licochalcone also induces autophagic death of LNCaP cells (Yo *et al*., 2009).

Curcumin

Curcumin, at a concentration of 30μM, was shown to elevate sensitivity for PC-3 cells towards TRAIL. Moreover, it is demonstrated to increase TRAIL's capacity to induce apoptosis in PC-3 and LNCaP cells. Curcumin therapy in concentrations ranging from 20–40μM resulted in the suppression of survivin, Bcl-2, and XIAP. Furthermore, curcumin activated caspases and induced a decrease in the potential of the mitochondrial membrane. When

combined through TRAIL, these effects were more intensified. In addition, a study reported that Combining the administration of 10μM of phenethyl isothiocyanate (PEITC) and 25μM of curcumin resulted in a considerable increase in PARP activity, indicating apoptotic cell death. This combination treatment also led to a notable reduction in IκBα and Akt phosphorylations. The combined administration of curcumin and TRAIL has been demonstrated to trigger programmed cell death, indicated through the aggregation of sub-G1 phase in cells of hypodiploid.

Obovatol

Obovatol, a source through Magnolia obovata, has been shown to induce death via apoptosis. This is accomplished by blocking NF-κBaction, which in turn strengthens the medicines' ability to suppress the proliferation in cells of prostate cancer (Lee *et al*., 2008).

Silibinin

Silibinin, has been reported to induce G1 phase arrest in DU 145 cells (Roy *et al*., 2007). Furthermore, silibinin causes apoptosis by limiting Wnt/LRp6 signaling as well as suppressing active Stat3 (Agarwal *et al*., 2006). It has been shown to inhibit cells of prostate cancer epithelial-to-mesenchymal transition (EMT). Thus, inhibition is attributed to its interference with NF-κB signaling, leading to a subsequent reduction in the transcription factors ZEB1 and SLUG (Wu *et al*., 2010).

Sparstolonin B

Sparstolonin B (SsnB), has demonstrated inhibitory impacts on the development, and progression of the cell cycle as well as apoptosis induction for various cell lines of neuroblastoma. Thus, the planned mechanism for its impact on apoptosis is associated with the production of reactive oxygen species (ROS), particularly in neuroblastoma cells with different genetic backgrounds (Kumar *et al*., 2014). Sparstolonin B (SsnB) exhibits anti-cancer properties by disrupting the supply of blood to cells of cancer. Additionally, it can reduce the appearance of various cytokines. SsnB exerts anti-angiogenic effects by down-regulating the mRNA levels of cell cycle regulatory proteins, including Bateman (Bateman et al., 2013). Recently, Sparstolonin B (SsnB) has been identified as a potent antagonist of Toll-like receptor 2 (TLR2) and Toll-like receptor 4 (TLR4). Consequently, it can mitigate hypoxia-reoxygenation-induced inflammation by inhibiting the ERK1/2 and JNK signaling pathways (Liu *et al*., 2014).

Phytochemicals Playing Role in The Mechanism of Cell Cycle Arrest

Daidzein

Daidzein, is found in beans of soya, through arrest of cell cycles for PC-3, LNCaP, and DU 145 (Ma *et al*., 2016). The addition of Daidzein was observed to inducing modifications for epigenetic in genes which suppresses tumors (Vardi et al., 2010).

Isoangustone A

Isoangustone A was found to reduce CDK2 activity by inhibiting the synthesis of DNA. It induces arrest in G1 phase of DU 145 cells (Seon *et al*., 2012).

Licochalcone

Licochalcone, derived from roots of licorice, was observed to cause the arrest of PC-3 cells during G2/M stage. This effect was achieved by suppressing the B1 as well as cdc2 cyclins expressions (Fu *et al*., 2004).

Honokiol

Honokiol, has been shown to induce arrest of G0-G1 phase for LNCaP as well as cells of C4-2. This effect is attributed to its ability to trigger apoptotic DNA fragmentation (Hahm *et al*., 2007).

Silibinin

Silibinin, also known as silybin, causes induction of arrest for the G1 phase in cells of DU 145 (Roy *et al*., 2007).

Ellagitannins

Ellagitannins, a type of polyphenol, have been associated with apoptosis induction as well as the arrest of cell cycles during S phase. It is achieved by decreasing the expression of D1 as well as B1 cyclins through the caspase system (Naiki-Ito *et al*., 2015).

Gallic acid

Gallic acid (GA), has been reported to induce damage to DNA by elevating phosphorylation of cdc25A/C-cdc2. This mechanism leads to inhibition of growth for cells of DU 145 (Agarwal *et al*., 2006).

Gossypol

Gossypol, derived from seeds of cotton, has been shown to modulate expressions for cyclin Cdk4, D1, signaling pathways. This modulation results in G0/G1 stage arrest (Jiang *et al*., 2009).

Artemisinin

Artemisinin has been observed to transcriptionally downregulate CDK4 expression. This downregulation is achieved by interfering with Sp1's connections through CDK4 promoter, which causes LNCaP cells to enter the arrest of G1 cell cycle (Willoughby *et al*., 2009).

Oridonin

Oridonin demonstrates multifaceted effects on cell regulation. In LNCaP cells, oridonin elicits programmed cell death as well as arrest of the cell cycle (G0/G1) through upregulation of p53 then Bax (Li *et al*., 2012).

Berberine

Berberine has been observed to induce G1 arrest in RM-1 cells. This effect is achieved when p53-p21 cascade is activated, particularly at low amounts of berberine (Wang *et al*., 2012).

Piperine

Piperine exhibits diverse effects in cells of prostate cancer. They are reported for apoptosis induction, trigger arrest of cell cycle at G0/G1 (Ouyang *et al*., 2013).

Sulforaphane

Sulforaphane (SFN), has demonstrated potential to lessen the occurrence and advancement of prostate cancer through PCa cells metabolic regulation (Tan *et al*., 2015). It has been found to induce arrest of cell cycle during G2/M stage by disrupting signaling pathways (Atwell *et al*., 2015).

Phenethyl-isothiocyanate

Phenethyl-isothiocyanate (PEITC), induces arrest of cell cycle during G2/M phase. This effect is achieved through preventing the production of α- and β-tubulin as well as promoting the production of reactive oxygen species (Yin et al., 2014).

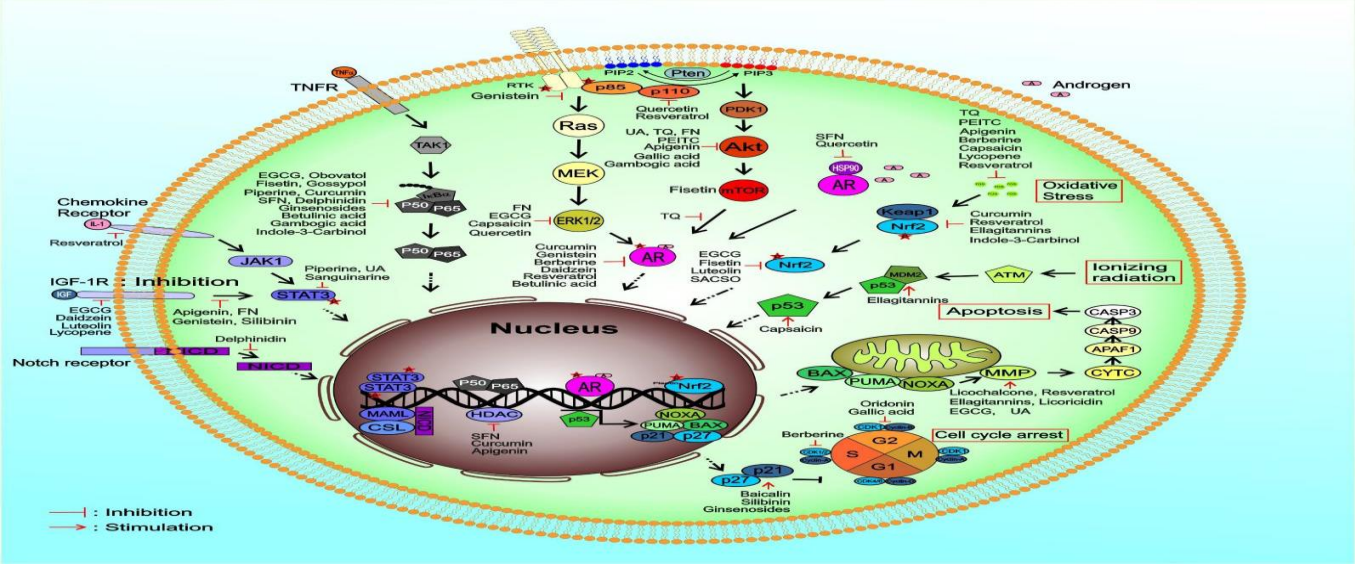

Figure 2. Role of phytochemicals in several pathways of prostate cancer

Unfortunately, during medical analysis, human cancers of the prostate commonly manifest as a diverse entity. Re-growth of tumors following remission of post-treatment is often attributed to the transformation of cells of cancer from androgen-dependent towards androgen-independent as well as transitions to proliferating cells of tumor. Consequently, effective chemotherapy should aim to eliminate all tumors, regardless of their growth. It necessitates the exploration of drug combination

treatments that act through diverse mechanisms of action. Given that cells of prostate cancer inherently possess machinery for apoptosis, they may be susceptible to appropriate and effective chemotherapeutic interventions.

The molecular pathways responsible for PCa's beginning then progression remain incompletely understood (Whittemore *et al*., 1995; Ross & Henderson, 1994). While there are various options for managing localized illness, such as hormonal therapy, radiation therapy, as well as surgery, managing advanced PCa remains challenging (Walsh *et al*., 2007). Androgen ablation is frequently recommended for PCa treatment, yet it is only partially effective as well as palliative for cancer that is hormone-refractory (Laufer *et al*., 2000).

In our review of the latest advancements in prostate cancer studies, we focused on phytochemicals and their mechanisms of action. Our particular interest lies in demonstrating the efficacy of these phytochemicals in primary signaling trials in cancer of prostate.

CONCLUSION

This study encompasses the up-to-dated discoveries regarding phytochemicals sourced from edible green plants, tea and fruits which are demonstrated to have impacts as anti-cancer in cells of prostate cancer through using multi-modals. These effects include arrest of cell cycle, induction of apoptosis then metastasis suppression, all elucidating its fundamental molecular processes (Figure 2). Thus, the ability of phytochemicals to target multiple pathways is advantageous against cancer cells, which often exhibit numerous dysregulated signals that have mutual interactions. Additionally, several phytochemicals exhibit selectivity in concentrating on cells of cancer while sparing healthy cells, rendering phytochemicals as therapeutic mediators. Moreover, a growing body of research from lab experiments suggests that phytochemicals have the potential to enhance the chemotherapeutic efficacy of medicines in less-toxic way when curing various tumors, including cancer of the prostate.

REFERENCES

Aalinkeel, R.; Bindukumar, B.; Reynolds, J.L.; Sykes, D.E.; Mahajan, S.D.; Chadha, K.C.; Schwartz, S.A. The dietary bioflavonoid,quercetin, selectively induces apoptosis of prostate cancer cells by down-regulating the expression of heat shock protein 90. Prostate 2008, 68, 1773–1789. [CrossRef] **https://doi.org/10.1002/pros.20845**

Adhami VM, Mukthar H: Antioxidants from Green Tea and Pomegranate for Chemoprevention of Prostate Cancer. Mol Biotechnol*37*: 52-57, 2007. DOI 10.1007/s12033-007-0047-

Akiyama T, Ishida J, Nakagawa S, Ogawara H, Watanabe S, Itoh N, Shibuya M, Fukami Y: Genistein, a specific inhibitor of tyrosinespecific protein kinases. *J Biol Chem* 1987, 262:5592-5595. https://doi.org/10.1016/S0021-9258(18) 45614-1

Bin Hafeez, B.; Asim, M.; Siddiqui, I.A.; Adhami, V.M.; Murtaza, I.; Mukhtar, H. Delphinidin, a dietary anthocyanidin in pigmented fruits and vegetables, 2008. DOI 10.4161/cc.7.21.6969

Bommareddy A, Hahm ER, Xiao D, Powolny AA, Fisher A, Jiang Y and Singh SV: ATG5 Regulates phenethyl isothiocyanateinduced autophagic and apoptotic cell death in human prostate cancer cells. Cancer Res *69(8)*: 3704-3712, 2009. https://doi.org/10.1158/0008-5472.CAN-08-4344

Bommareddy A, Rule B, VanWert AL, Santha S and Dwivedi C: Alpha-santalol, a chemopreventive agent induces apoptosis in human prostate cancer cells by causing caspase-3 activation. https://doi.org/10.1158/1538-7445.AM2012-611

Dixon RA, Daneel Ferreira: Genistein. *Phytochemistry* 2002, 60:205-211.

Erdogan, S.; Turkekul, K.; Dibirdik, I.; Doganlar, O.; Doganlar, Z.B.; Bilir, A.; Oktem, G. Midkine downregulation increases the efficacy of quercetin on prostate cancer stem cell survival and migration through PI3K/AKT and MAPK/ERK pathway. Biomed. Pharm. 2018, 107, 793–805. [CrossRef] https://doi.org/10.1016/S0031-9422(02)00116-4

Fu, Y.; Hsieh, T.C.; Guo, J.; Kunicki, J.; Lee, M.Y.; Darzynkiewicz, Z.;Wu, J.M. Licochalcone-A, a novel flavonoid isolated from licorice root (Glycyrrhiza glabra), causes G2 and late-G1 arrests in androgen-independent PC-3 prostate cancer cells. Biochem. Biophys. Res. Commun. 2004, 322, 263–270. [CrossRef] [PubMed https://doi.org/10.1016/j.bbrc.2004.07.094

Guo, Z.; Hu, X.; Xing, Z.; Xing, R.; Lv, R.; Cheng, X.; Su, J.; Zhou, Z.; Xu, Z.; Nilsson, S.; et al. Baicalein inhibits prostate cancer cell growth and metastasis via the caveolin-1/AKT/mTOR pathway. Mol. Cell Biochem. 2015, 406, 111–119. [CrossRef] [PubMed] DOI 10.1007/s11010-015-2429-8

Hirata, H.; Hinoda, Y.; Shahryari, V.; Deng, G.; Tanaka, Y.; Tabatabai, Z.L.; Dahiya, R. Genistein downregulates onco-miR-1260b and upregulates sFRP1 and Smad4 via demethylation and histone modification in prostate cancer cells. Br. J. Cancer2014, 110, 1645–1654. [CrossRef] doi: 10.1038/bjc.2014.48

Huang,W.J.; Bi, L.Y.; Li, Z.Z.; Zhang, X.; Ye, Y. Formononetin induces the mitochondrial apoptosis pathway in prostate cancer cells via downregulation of the IGF-1/IGF-1R signaling pathway. Pharm. Biol. 2013, 52, 466–470. [CrossRef] [PubMed] https://doi.org/10.3109/13880209.2013.842600

Klein EA: Chemoprevention of prostate cancer. Critical Reviews in Oncology and Hematology *54*: 1-10, 2005.

Liu, X.J.; Li, Y.Q.; Chen, Q.Y.; Xiao, S.J.; Zeng, S.E. Up-regulating of RASD1 and apoptosis of DU-145 human prostate cancer cells induced by formononetin in vitro. Asian Pac. J. Cancer Prev. 2014, 15, 2835–2839. [CrossRef] DOI: http://dx.doi.org/10.7314/APJCP.2014.15.6.2835

Lynn AG, Ries MS: Stat Bite: Top 5 cancers for females and males in the U.S. *JNCI* 1995, 87:867.

Ma, S.C.; Chen, R.; Yang, T.N.; Zhang, F.; Zhao, D. Baicalein inhibits the proliferative activity of human prostate cancer cell line PC3 by downregulating Ezrin. J. Biol. Regul. Homeost. Agents 2020, 34, 885–892. [CrossRef] [PubMed] https://doi.org/10.23812/20-145-a-44

Matsukawa Y, Marui N, Sakai T, Satomi Y, Yoshida M, Matsumoto K, Nishino H, Aoike A: Genistein arrests cell cycle progression at G2-M. *Cancer Res* 1993, 53:1328-1331.

Messina MJ, Persky V, Setchell KDR, Barnes S: Soy intake and cancer risk: A review of the in vitro and in vivo data. *Nutr Cancer* 1994, 21:113-131. https://doi.org/10.1080/01635589409514310

Mirzoeva, S.; Franzen, C.A.; Pelling, J.C. Apigenin inhibits TGF-beta-induced VEGF expression in human

https://doi.org/10.1002/mc.22005

Mousavi Y, Adlercreutz H: Genistein is an effective stimulator of sex hormone binding globulin production in hepatocellular human liver cancer cells and suppresses https://doi.org/10.1016/0039-128X(93)90088-5

Pandey, M.; Kaur, P.; Shukla, S.; Abbas, A.; Fu, P.; Gupta, S. Plant flavone apigenin inhibits HDAC and remodels chromatin to induce growth arrest and apoptosis in human prostate cancer cells: In vitro and in vivo study. Mol. Carcinog. 2012, 51, 952–962.[CrossRef] https://doi.org/10.1002/mc.20866

Phytomedicine *19*: 804-811, 2012.pigmented fruits and vegetables: A new weapon to blunt prostate cancer growth. Cell Cycle 2008, 7, 3320–3326. [CrossRef] https://doi.org/10.3390%2Fbiom12091306

Powolny AA, Bommareddy A, Hahm ER, Normolle DP, Beumer JH, Nelson JB and Singh SV: Chemopreventative Potential of the Cruciferous Vegetable Constituent Phenethyl Isothiocyanate in a Mouse Model of Prostate Cancer. J Natl Cancer Inst *103(7)*: 571-584, 201 https://doi.org/10.1093/jnci/djr029

Seon, M.R.; Lim, S.S.; Choi, H.J.; Park, S.Y.; Cho, H.J.; Kim, J.K.; Kim, J.; Kwon, D.Y.; Park, J.H. Isoangustone A present in hexane/ethanol extract of Glycyrrhiza uralensis induces apoptosis in DU145 human prostate cancer cells via the activation of DR4 and intrinsic apoptosis pathway. Mol. Nutr. Food Res. 2010, 54, 1329–1339. [CrossRef] [PubMed] https://doi.org/10.1002/mnfr.200900260

Shukla, S.; Gupta, S. Apigenin suppresses insulin-like growth factor I receptor signaling in human prostate cancer: An in vitro and in vivo study. Mol. Carcinog. 2009, 48, 243–252. [CrossRef] **https://doi.org/10.1002/mc.20475**

Shukla, S.; Gupta, S. Apigenin-induced prostate cancer cell death is initiated by reactive oxygen species and p53 activation. Free Radic. Biol. Med. 2008, 44, 1833–1845. [CrossRef] https://doi.org/10.1016/j.freeradbiomed.2008.02.007

Singh SV, Warin R, Xiao D, Powolny A, Stan SD, Arlotti JA, Zeng Y, Hahm E, Marynowski SW, Bommareddy A, Desai D, Amin S and Chambers WH: Sulforaphane inhibits prostate carcinogenesis and pulmonary metastasis in TRAMP mice in association with increased cytotoxicity of natural killer cells. Cancer Research *69(5)*: 2117-2125, 2009 https://doi.org/10.1158/0008-5472.CAN-08-3502

Surh YJ: Cancer chemoprevention with dietary phytochemicals. Nat Rev Cancer *3*: 768-780, 2003. https://doi.org/10.1038/nrc1189

Umekita Y, Hiipakka RA, Kokontis JM, Liao S: Human prostate tumor growth in athymic mice: Inhibition by androgens and stimulation by finasteride. *Proc Natl Acad Sci USA* 1996, 93:11802-11807. https://doi.org/10.1073/pnas.93.21.11802

Webber MM, Waghray A, Bello D: Prostate-specific antigen, a serine protease, facilitates human prostate cancer cell

Ye, Y.; Hou, R.; Chen, J.; Mo, L.; Zhang, J.; Huang, Y.; Mo, Z. Formononetin-induced apoptosis of human prostate cancer cells through ERK1/2 mitogen-activated protein kinase inactivation. Horm. Metab. Res. 2012, 44, 263–267. [CrossRef] DOI: 10.1055/s-0032-1301922

Yo, Y.T.; Shieh, G.S.; Hsu, K.F.;Wu, C.L.; Shiau, A.L. Licorice and licochalcone-A induce autophagy in LNCaP prostate cancer cells by suppression of Bcl-2 expression and the mTOR pathway. J. Agric. Food Chem. 2009, 57, 8266–8273. [CrossRef] https://doi.org/10.1021/jf901054c

Zhang, X.; Bi, L.; Ye, Y.; Chen, J. Formononetin induces apoptosis in PC-3 prostate cancer cells through enhancing the Bax/Bcl-2 ratios and regulating the p38/Akt pathway. Nutr. Cancer 2014, 66, 656–661. [CrossRef] https://doi.org/10.1080/01635581.2014.894098

Zhau HE, Pisters LL, Hall MC, Zhao LS, Troncoso P, Pollack A, Chung LWK: Biomarkers associated with prostate cancer https://doi.org/10.1002/pros.21086

Lee, S.Y.; Yuk, D.Y.; Song, H.S.; Yoon, D.Y.; Jung, J.K.; Moon, D.C.; Lee, B.S.; Hong, J.T. Growth inhibitory effects of obovatol through induction of apoptotic cell death in prostate and colon cancer by blocking of NF-kappaB. Eur. J. Pharm. **2008**, 582, 17–25. [CrossRef] https://doi.org/10.1016/j.ejphar.2007.12.027

Roy, S.; Kaur, M.; Agarwal, C.; Tecklenburg, M.; Sclafani, R.A.; Agarwal, R. p21 and p27 induction by silibinin is essential for its cell cycle arrest effect in prostate carcinoma cells. Mol. Cancer Ther. **2007**, 6, 2696–2707. [CrossRef] https://doi.org/10.1158/1535-7163.MCT-07-0104

Agarwal, C.; Tyagi, A.; Kaur, M.; Agarwal, R. Silibinin inhibits constitutive activation of Stat3, and causes caspase activation and apoptotic death of human prostate carcinoma DU145 cells. Carcinogenesis **2007**, 28, 1463–1470. [CrossRef] https://doi.org/10.1093/carcin/bgm042

Wu, K.; Zeng, J.; Li, L.; Fan, J.; Zhang, D.; Xue, Y.; Zhu, G.; Yang, L.; Wang, X.; He, D. Silibinin reverses epithelial-to-mesenchymal transition in metastatic prostate cancer cells by targeting transcription factors. Oncol. Rep. **2010**, 23, 1545–1552. prostate model mice. Clin. Cancer Res. **2008**, 14, 7773–7780. [CrossRef] https://doi.org/10.3892/or_00000794

Kumar, A.; Dhar, S.; Rimando, A.M.; Lage, J.M.; Lewin, J.R.; Zhang, X.; Levenson, A.S. Epigenetic potential of resveratrol and analogs in preclinical models of prostate cancer. Ann. N. Y. Acad. Sci. **2015**, 1348, 1–9. [CrossRef] https://doi.org/10.1111/nyas.12817

Kumar A, Fan D, Dipette DJ, et al. Sparstolonin B, a novel plant derived compound, arrests cell cycle and induces apoptosis in N-myc amplified and N-myc nonamplified neuroblastoma cells. PLoS One, 2014; 9, e96343. https://doi.org/10.1371/journal.pone.0096343

Bateman HR, Liang Q, Fan D, et al. Sparstolonin B inhibits pro-angiogenic functions and blocks cell cycle progression in endothelial cells. PLoS One, 2013; 8, e70500. https://doi.org/10.1371/journal.pone.0070500

NIH. A Story of Discovery: Natural Compound Helps Treat Breast and Ovarian Cancers. Published 31 March 2015. Available online: https://www.cancer.gov/research/progress/discovery/taxol (accessed on 29 December 2021). https://doi.org/10.3390/cells11071070

Kwok, K.K.; Vincent, E.C.; Gibson, J.N. Antineoplastic Drugs. In Pharmacology and Therapeutics for Dentistry; Elsevier: Amsterdam, The Netherlands, 2017; pp. 530–562. https://doi.org/10.3390/biom11050633

Pullaiah, T.; Raveendran, V. Camptothecin: Chemistry, biosynthesis, analogs, and chemical synthesis. In Camptothecin and Camptothecin Producing Plants; Elsevier: Amsterdam, The Netherlands, 2020; pp. 47–101. https://doi.org/10.1016/j.bcab.2023.102846

Dockery, L.; Daniel, M.-C. Dendronized Systems for the Delivery of Chemotherapeutics. Adv. Cancer Res. **2018**, 139, 85–120. https://doi.org/10.1016/bs.acr.2018.04.003

Kumar, S.; Bhandari, C.; Sharma, P.; Agnihotri, N. Role of Piperine in Chemoresistance. In Role of Nutraceuticals in Chemoresistance to Cancer; Elsevier: Amsterdam, The Netherlands, 2018; pp. 259–286. https://doi.org/10.1016/B978-0-12-812373-7.00013-9

Wang, L.S.; Stoner, G.D. Anthocyanins and their role in cancer prevention. Cancer Lett. **2008**, 269, 281–290. [CrossRef] https://doi.org/10.1016/j.canlet.2008.05.020

Lin, B.-W.; Gong, C.-C.; Song, H.-F.; Cui, Y.-Y. Effects of anthocyanins on the prevention and treatment of cancer. Br. J. Pharmacol. **2017**, 174, 1226–1243. [CrossRef] [PubMed] https://doi.org/10.1111/bph.13627

Liu, J.; Zhou, H.; Song, L.; Yang, Z.; Qiu, M.; Wang, J.; Shi, S. Anthocyanins: Promising natural products with diverse pharmacological activities. Molecules **2021**, 26, 3807. [CrossRef] [PubMed] https://doi.org/10.3390/molecules26133807

Mattioli, R.; Francioso, A.; Mosca, L.; Silva, P. Anthocyanins: A Comprehensive Review of Their Chemical Properties and Health Effects on Cardiovascular and Neurodegenerative Diseases. Molecules **2020**, 25, 3809. [CrossRef] https://doi.org/10.3390/molecules25173809

Castañeda-Ovando, A.; de Pacheco-Hernández, M.L.; Páez-Hernández, M.E.; Rodríguez, J.A.; Galán-Vidal, C.A. Chemical studies of anthocyanins: A review. Food Chem. **2009**, 113, 859–871. [CrossRef] https://doi.org/10.1016/j.foodchem.2008.09.001

Salehi, B.; Sharifi-Rad, J.; Cappellini, F.; Reiner, Z.; Zorzan, D.; Imran, M.; Sener, B.; Kilic, M.; El-Shazly, M.; Fahmy, N.M.; et al. The Therapeutic Potential of Anthocyanins: Current Approaches Based on Their Molecular Mechanism of Action. Front. Pharmacol. **2020**, 11, 1300. [CrossRef] https://doi.org/10.3389/fphar.2020.01300

Adhami VM, Mukthar H: Antioxidants from Green Tea and Pomegranate for Chemoprevention of Prostate Cancer. Mol Biotechnol*37*: 52-57, 2007. DOI 10.1007/s12033-007-0047-8

Khandrika L, Kumar B, Koul S, Maroni P, Koul HK. Oxidative stress in prostate cancer. Cancer Lett. 2009;282(2):125–36. https:// doi. org/ 10. 1016/j. canlet. 2008. 12. 011

Tan BL, Norhaizan ME. Oxidative Stress, Diet and Prostate Cancer. World J Mens Health. 2021;39(2):195–207. https:// doi. org/ 10. 5534/ wjmh. 200014.

Ray PD, Huang BW, Tsuji Y. Reactive oxygen species (ROS) homeostasis and redox regulation in cellular signaling. Cell Signal. 2012;24(5):981–90. https:// doi. org/ 10. 1016/j. cells ig. 2012. 01. 008.

Liu W, Wang B, Zhou M, et al. Redox Dysregulation in the Tumor Microenvironment Contributes to Cancer Metastasis [published online ahead of print, 2023 May 8]. Antioxid Redox Signal. 2023. https:// doi. org/ 10. 1089/ ars. 2023. 0272.

Klein EA: Chemoprevention of prostate cancer. Critical Reviews in Oncology and Hematology *54*: 1-10, 2005.https://doi.org/10.1016/j.critrevonc.2004.11.008

Adhami VM, Mukthar H: Antioxidants from Green Tea and Pomegranate for Chemoprevention of Prostate Cancer. Mol Biotechnol*37*: 52-57, 2007. DOI 10.1007/s12033-007-0047-8

Bommareddy A, Rule B, VanWert AL, Santha S and Dwivedi C: Alpha-santalol, a chemopreventive agent induces apoptosis in human prostate cancer cells by causing caspase-3 activation. Phytomedicine *19*: 804-811, 2012.https://doi.org/10.1158/1538-7445.AM2012-611

Bommareddy A, Hahm ER, Xiao D, Powolny AA, Fisher A, Jiang Y and Singh SV: ATG5 Regulates phenethyl isothiocyanateinduced autophagic and apoptotic cell death in human prostate cancer cells. Cancer Res *69(8)*: 3704-3712, 2009.**https://doi.org/10.1158/1538-7445.AM2012-611**

Powolny AA, Bommareddy A, Hahm ER, Normolle DP, Beumer JH, Nelson JB and Singh SV: Chemopreventative Potential of the Cruciferous Vegetable Constituent Phenethyl Isothiocyanate in a Mouse Model of Prostate Cancer. J Natl Cancer Inst *103(7)*:571-584, 2011.https://doi.org/10.1093/jnci/djr029

Singh SV, Warin R, Xiao D, Powolny A, Stan SD, Arlotti JA, Zeng Y, Hahm E, Marynowski SW, Bommareddy A, Desai D, Amin S and Chambers WH: Sulforaphane inhibits prostate carcinogenesis and pulmonary metastasis in TRAMP mice inassociation with increased cytotoxicity of natural killer cells. Cancer Research *69(5)*: 2117-2125, 2009. https://doi.org/10.1158/0008-5472.CAN-08-3502

Lv, S.; Song, Q.; Chen, G.; Cheng, E.; Chen, W.; Cole, R.; Wu, Z.; Pascal, L.E.; Wang, K.; Wipf, P.; et al. Regulation and targeting of androgen receptor nuclear localization in castration-resistant prostate cancer. J. Clin. Investig. 2021, 131, 141335. [CrossRef] https://doi.org/10.1172/JCI141335

Lonergan, P.; Tindall, D. Androgen receptor signaling in prostate cancer development and progression. J. Carcinog. 2011, 10, 20. [CrossRef] [PubMed] https://doi.org/10.4103%2F1477-3163.83937

Tan, M.E.; Li, J.; Xu, H.E.; Melcher, K.; Yong, E.L. Androgen receptor: Structure, role in prostate cancer and drug discovery. Acta Pharmacol. Sin. 2015, 36, 3–23. [CrossRef] https://doi.org/10.1038/aps.2014.18

Toren, P.; Zoubeidi, A. Targeting the PI3K/Akt pathway in prostate cancer: Challenges and opportunities (Review). Int. J. Oncol. 2014, 45, 1793–1801. [CrossRef] [PubMed] https://doi.org/10.3892/ijo.2014.2601

Phin, S.; Moore, M.W.; Cotter, P.D. Genomic rearrangements of PTEN in prostate cancer. Front. Oncol. 2013, 3, 240. [CrossRef] https://doi.org/10.3389/fonc.2013.00240

Basnet, R.; Basnet, B.B. Overview of Protein Kinase B Enzyme:a Potential Target for breast and Prostate Cancer. Curr. Mol. Pharmacol. 2020, 13, 527–536. [CrossRef] https://doi.org/10.2174/1874467213999201027221759

Whittemore AS, Kolonel LN, Wu AH, John EM, Gallagher RP, Howe GR, Burch JD, Hankin J, Dreon DM, West DW, Teh Chong- Ze and Paffenbarger RS Jr.: Prostate cancer in relation to diet, physical activity, and body size in blacks, whites, and Asians in the

United States and Canada. J. Natl. Cancer Inst *87*: 652-661, 1995. https://doi.org/10.1093/jnci/87.9.652

Nelson WG, De Marzo AM and Isaacs WB: Prostate cancer. N Engl J Med *349*: 366-381, 2003. https://doi.org/10.1038/nrc2090

Ross RK and Henderson BE: Do diet and androgens alter prostate cancer risk *via* a common etiologic pathway? J Natl Cancer Inst *86*: 252-254, 1994. https://doi.org/10.1093/jnci/86.4.252

Walsh PC, De Weese TL and Eisenberger MA: Clinical practice: Localized prostate cancer. N Engl J Med *357*: 2696-2705, 2007. DOI: 10.1056/NEJMcp0706784

Laufer M, Denmeade SR, Sinibaldi VJ, Carducci MA and Eisenberger MA: Complete androgen blockade for prostate cancer: What went wrong? J Urol*164*: 3-9, 2000. https://doi.org/10.1016/S0022-5347(05)67436-8

Newman DJ, Cragg GM. Natural Products as Sources of New Drugs over the Nearly Four Decades from 01/1981 to 09/2019. J Nat Prod. 2020;83(3):770–803. https:// doi. org/ 10. 1021/ acs. Jnatp rod. 9b012 85.

Asma ST, Acaroz U, Imre K, et al. Natural Products/Bioactive Compounds as a Source of Anticancer Drugs. Cancers (Basel). 2022;14(24):6203. Published 2022 Dec 15. https:// doi. org/ 10.3390/ cancers142 46203.

Mottaghipisheh J, Doustimotlagh AH, Irajie C, Tanideh N, Barzegar A, Iraji A. The Promising Therapeutic and Preventive Properties of Anthocyanidins/Anthocyanins on Prostate Cancer. Cells. 2022;11(7):1070. Published 2022 Mar 22. https:// doi. org/10. 3390/ cells 11071 070

Singla RK, Sharma P, Dubey AK, et al. Natural Product-Based Studies for the Management of Castration-Resistant Prostate Cancer: Computational to Clinical Studies. Front Pharmacol. 2021;12:732266. Published 2021 Oct 19. https:// doi. org/ 10. 3389/ fphar. 2021. 732266.

Fontana F, Raimondi M, Marzagalli M, Di Domizio A, Limonta P. Natural Compounds in Prostate Cancer Prevention and Treatment:Mechanisms of Action and Molecular Targets. Cells. https://doi.org/10.3390/cells9020460

Rabiau, N.; Kossai, M.; Braud, M.; Chalabi, N.; Satih, S.; Bignon, Y.J.; Bernard-Gallon, D.J. Genistein and daidzein act on a panel of genes implicated in cell cycle and angiogenesis by polymerase chain reaction arrays in human prostate cancer cell lines. Cancer Epidemiol. 2010, 34, 200–206. [CrossRef] https://doi.org/10.1016/j.canep.2009.12.018

Vardi, A.; Bosviel, R.; Rabiau, N.; Adjakly, M.; Satih, S.; Dechelotte, P.; Boiteux, J.P.; Fontana, L.; Bignon, Y.J.; Guy, L.; et al. Soyphytoestrogens modify DNA methylation of GSTP1, RASSF1A, EPH2 and BRCA1 promoter in prostate cancer cells. In Vivo 2010, 24, 393–400.

Seon, M.R.; Park, S.Y.; Kwon, S.J.; Lim, S.S.; Choi, H.J.; Park, H.; Lim, D.Y.; Kim, J.S.; Lee, C.H.; Kim, J.; et al. Hexane/ethanol extract of Glycyrrhiza uralensis and its active compound isoangustone A induce G1 cycle arrest in DU145 human prostate and 4T1 murine mammary cancer cells. J. Nutr. Biochem. 2012, 23, 85–92.[CrossRef][PubMed] https://doi.org/10.1016/j.jnutbio.2010.11.010

Fu, Y.; Hsieh, T.C.; Guo, J.; Kunicki, J.; Lee, M.Y.; Darzynkiewicz, Z.;Wu, J.M. Licochalcone-A, a novel flavonoid isolated from licorice root (Glycyrrhiza glabra), causes G2 and late-G1 arrests in androgen-independent PC-3 prostate cancer cells. Biochem. Biophys. Res. Commun. 2004, 322, 263–270. [CrossRef] [PubMed] https://doi.org/10.1016/j.bbrc.2004.07.094

Hahm, E.R.; Singh, S.V. Honokiol causes G0-G1 phase cell cycle arrest in human prostate cancer cells in association with suppression of retinoblastoma protein level/phosphorylation and inhibition of E2F1 transcriptional activity. Mol. Cancer Ther. 2007, 6, 2686–2695. [CrossRef] [PubMed] https://doi.org/10.1158/1535-7163.MCT-07-0217

Roy, S.; Kaur, M.; Agarwal, C.; Tecklenburg, M.; Sclafani, R.A.; Agarwal, R. p21 and p27 induction by silibinin is essential for its cell cycle arrest effect in prostate carcinoma cells. Mol. Cancer Ther. 2007, 6, 2696–2707. [CrossRef] https://doi.org/10.1158/1535-7163.MCT-07-0104

Naiki-Ito, A.; Chewonarin, T.; Tang, M.; Pitchakarn, P.; Kuno, T.; Ogawa, K.; Asamoto, M.; Shirai, T.; Takahashi, S. Ellagic acid, a component of pomegranate fruit juice, suppresses androgen-dependent prostate carcinogenesis via induction of apoptosis. Prostate 2015, 75, 151–160. [CrossRef] [PubMed] https://doi.org/10.1002/pros.22900

Agarwal, C.; Tyagi, A.; Agarwal, R. Gallic acid causes inactivating phosphorylation of cdc25A/cdc25C-cdc2 via ATM-Chk2 activation, leading to cell cycle arrest, and induces apoptosis in human prostate carcinoma DU145 cells. Mol. Cancer Ther. 2006, 5, 3294–3302. [CrossRef] https://doi.org/10.1158/1535-7163.MCT-06-0483

Jiang, J.; Ye, W.; Lin, Y.C. Gossypol inhibits the growth of MAT-LyLu prostate cancer cells by modulation of TGFbeta/Akt signaling. Int. J. Mol. Med. **2009**, 24, 69–75. [PubMed] https://doi.org/10.3892/ijmm_00000208

Willoughby, J.A., Sr.; Sundar, S.N.; Cheung, M.; Tin, A.S.; Modiano, J.; Firestone, G.L. Artemisinin blocks prostate cancer growth and cell cycle progression by disrupting Sp1 interactions with the cyclin-dependent kinase-4 (CDK4) promoter and inhibiting CDK4 gene expression. J. Biol. Chem. **2009**, 284, 2203–2213. [CrossRef] https://doi.org/10.1074/jbc.M804491200

Li, X.; Li, X.;Wang, J.; Ye, Z.; Li, J.C. Oridonin up-regulates expression of P21 and induces autophagy and apoptosis in human prostate cancer cells. Int. J. Biol. Sci. **2012**, 8, 901–912. [CrossRef] [PubMed] https://doi.org/10.7150%2Fijbs.4554

Wang, Y.; Liu, Q.; Liu, Z.; Li, B.; Sun, Z.; Zhou, H.; Zhang, X.; Gong, Y.; Shao, C. Berberine, a genotoxic alkaloid, induces ATM-Chk1 mediated G2 arrest in prostate cancer cells. Mutagenesis Res. **2012**, 734, 20–29. [CrossRef] https://doi.org/10.1016/j.mrfmmm.2012.04.005

Ouyang, D.Y.; Zeng, L.H.; Pan, H.; Xu, L.L.H.; Wang, Y.; Liu, K.P.; He, X.H. Piperine inhibits the proliferation of human prostate cancer cells via induction of cell cycle arrest and autophagy. Food Chem. Toxicol. 2013, 60, 424–430. [CrossRef] [PubMed] https://doi.org/10.1016/j.fct.2013.08.007

Yin, P.; Kawamura, T.; He, M.; Vanaja, D.K.; Young, C.Y. Phenethyl isothiocyanate induces cell cycle arrest and reduction of alphaand beta-tubulin isotypes in human prostate cancer cells. Cell Biol. Int. 2009, 33, 57–64. [CrossRef] https://doi.org/10.1016/j.cellbi.2008.09.013

Atwell, L.L.; Beaver, L.M.; Shannon, J.; Williams, D.E.; Dashwood, R.H.; Ho, E. Epigenetic Regulation by Sulforaphane: Opportunities for Breast and Prostate Cancer Chemoprevention. Curr. Pharm. Rep. 2015, 1, 102–111. [CrossRef] [PubMed] https://doi.org/10.1007/s40495-014-0002-x