



Flavonoids and Prostate Cancer

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Abstract: Flavonoids are polyphenols that are ubiquitously present in plants and are categorized into flavones, flavanols, isoflavols, Flavonols, flavanonols, flavanones and chalcones. These are known to exhibit an array of biological activities such as anti-cancerous, anti-inflammatory, anti-thrombogenic, anti-angiogenic as well as anti-oxidant activity. Flavonoids are found to have an inverse association with certain cancers such as lung, digestive tract and hormone-related cancers such as breast and prostate cancer. Various epidemiological studies have shown a reduced risk of Prostate cancer with intake of flavonoids. The East Asian countries diet comprises very high content of flavonoids and consequently has lesser incidences of Prostate cancer. Further flavonoids with a broad spectrum of pharmacological activity are also reported to impair metastasis in Prostate cancer and were found to interfere with initiation, promotion and progression of cancer by different receptor signaling pathways and enzymes. This review is a summary of work done on the role of Flavonols and flavones specifically on prostate cancer metastasis with the main molecular mechanism underling the anti-cancerous activity for their potential application as cancer therapeutic.

Keywords: Flavonoid, Prostate cancer, Castration Resistant Prostate cancer (CRPC), Flavonols, Flavones.

I. Introduction

Prostate cancer (PCa) is one of the major medical burdens in males and is the most commonly diagnosed cancer in men in western countries. The estimated number of new cases and deaths from PCa in United States in 2015 are 220,800 and 27,540 respectively [1]. It has been seen that diets rich in flavonoid have an inverse association with PCa risk. Thus the population that consumes the largest amount of flavonoid has a lower incidence of PCa [2]. The East Asian countries, China and Japan, has an incidence of PCa that is 60- to 80- fold lower than compared to North America [3] indicating the impact of environmental, lifestyle and dietary factors on PCa risk. The incidence rate of PCa is lowest in Asian countries and in India it is the sixth most commonly diagnosed cancer among men [4]. Although Prostate-specific antigen (PSA) detection in serum has facilitated the early detection of Prostate cancer, there are limitations to this as elevated serum PSA is not specific to malignant disease and it gives a high false-positive and a false-negative rate of approximately 15%. In addition, PSA as prognostic marker also has detrimental effects as screening detects indolent tumors as well as that can become life threatening over a period of time. The currently available treatments for PCa includes: surgery, radiation therapy, hormone therapy, chemotherapy, vaccine therapy and bone-directed treatment. Moreover, PCa patients treated for localized prostate cancer shows relapse within 5 years [5] and develops into Castration Resistant Prostate Cancer (CRPC). Although new drugs, such as gonadotropin-releasing hormone (GnRH) agonists and anti-androgens, has been introduced in the market in the last few years (Table 1), however the toxicity associated with the current chemotherapeutic and the positive correlation with flavonoids intake and reduced risk of Prostate cancer has attracted interest and attention of researches on flavanoids as chemotherapeutic agents in Prostate cancer.

Table 1 List of recently approved drugs for Castration Resistant Prostate Cancer (CRPC) by FDA

Drug	FDA approval	Mechanism of Action	PCa state	Reference
Sipuleucel-T	April 2010	Ex-vivo processing of patient's dendritic cells with PA2024	CRPC, metastatic	[6]
Cabazitaxel	June 2010	Non-cross resisted microtubule agent, promotes tubulin assembly, stabilizing the microtubule.	CRPC, metastatic	[7][8], [9]
Abiraterone acetate	April 2011	Suppresses extragonadal testosterone production	CRPC, metastatic	[10]–[15]
Denosumab (Xgeva)	November 2010	Human monoclonal antibody against RANK ligand inhibiting bone-resorption activity of osteoblasts.	CRPC, bone metastatic	[16]
Denosumab (Prolia)	September 2011	Human monoclonal antibody against RANK ligand inhibiting bone-resorption activity of osteoblasts.	High risk Prostate cancer subjects treated with ADT.	[17]

Flavonoids are polyphenolic compounds, ubiquitous in food and beverages of plant origin [17]. Structurally flavonoids are categorized into flavones, flavanols, isoflavones, flavonols, flavanones, flavanonols and chalcones [18]. (Figure 1)

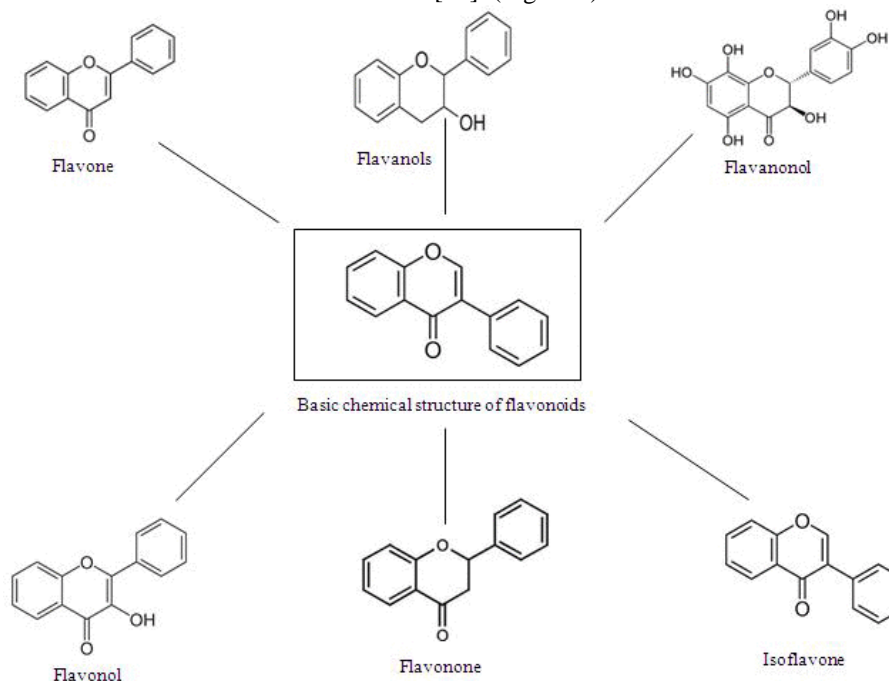


Figure 1: Classification of flavonoids based on structure

These compounds have a wide range of pharmacological activities such as antioxidant, antimutagenic, antibacterial, anti-inflammatory, antiangiogenic, antithrombogenic, antiallergic and anticancer activity [19]–[21]. Out of their remarkable spectrum of biological activities, the ability of flavonoid to arrest cell cycle, induce apoptosis [22] disrupt mitotic spindle formation, [23] and angiogenesis inhibition [24] makes them versatile source of anticancer drug. Flavonoids as potential anti cancer agents are being demonstrated in a variety of cell types both *in vitro* and *in vivo* [25].

II. Flavonoids and Prostate cancer (PCa)

Prostate cancer is an ageing disease. Dietary habits and lifestyle are identified as two most important factors for PCa occurrence and progression [26]. Thus use of flavonoids as chemo-preventive agents for PCa is of great interest. Despite the large number of available flavonoids, very few have been intensively studied in PCa. Table II summarizes the flavonoids being studied in Prostate cancer and the molecular mechanism underlying their important role in cancer pathology.

Flavonoids, at molecular level, are found to regulate various protein kinases viz., protein –kinase C [27], cyclin-dependent kinases [28] and phosphatidylinositol 3-kinase [29]. Protein kinases have important role in various signal transduction pathways, catalysis various cellular substrates and regulating various cellular functions and maintaining homeostasis [30]. Deregulation of PKs are associated with various abnormalities including cancer [31], [32]

Flavonoids have been shown to arrest cell cycle in a time and dose dependent manner. Depending on their structure and the type of cancer, flavonoids block cell cycle at either G0/G1 or G2/M. For instance, flovones such as leutolin blocks cell cycle in G0/G1 phase whereas flavonols such as quercetin can block cell cycle both at G0/G1 and G2/M depending on the cell line being studied [28].

Table 2 List of flavonoids being studied in PCa.

Flavonoid	Subgroup	IC50 (µM) In PC3	IC50 (µM) In LNCaP	Arrest stage of cell cycle	CDK1 inhibition	CDK2 inhibition	PKC inhibition	PI-3-kinase inhibition
Quercetin	Flavonols	33.41	19.44	G1 & G2/M	√	-	√	√
Luteolin	Flavones	28.84	18.22	G1	√	-	√	√
Myricetin	Flavonols	>100	>100	-	-	-	√	√
Morin	Flavonols	>100	>100	-	-	-	-	-
Kaempferol	Flavonols	41.98	52.24	G2/M	-	√	-	-
Fisetin	Flavonols	32.50	22.65	-	-	-	√	-
Chrysin	Flavones	>100	56.81	-	-	-	-	-

III. Flavonols and Prostate Cancer

The flavonols are polyphenols which are the largest category of phytochemicals and they are mostly found in the plant kingdom including foods such as onions, olives, cranberries and kale [33]. Quercetin, Myricetin, Kaempferol, Fisetin and Morin are the most studied flavonols. In recent years, the inspiring anticancer effects of flavonols have drawn the interest of a number of researches in a variety of cancers including Prostate cancer [34]–[41].

Flavonols have a structural similarity to testosterone (Figure 2) and thus they are hypothesized to have an interaction with androgen (AR) receptors, which might be the mechanism behind their anticarcinogenic activity in PCa.

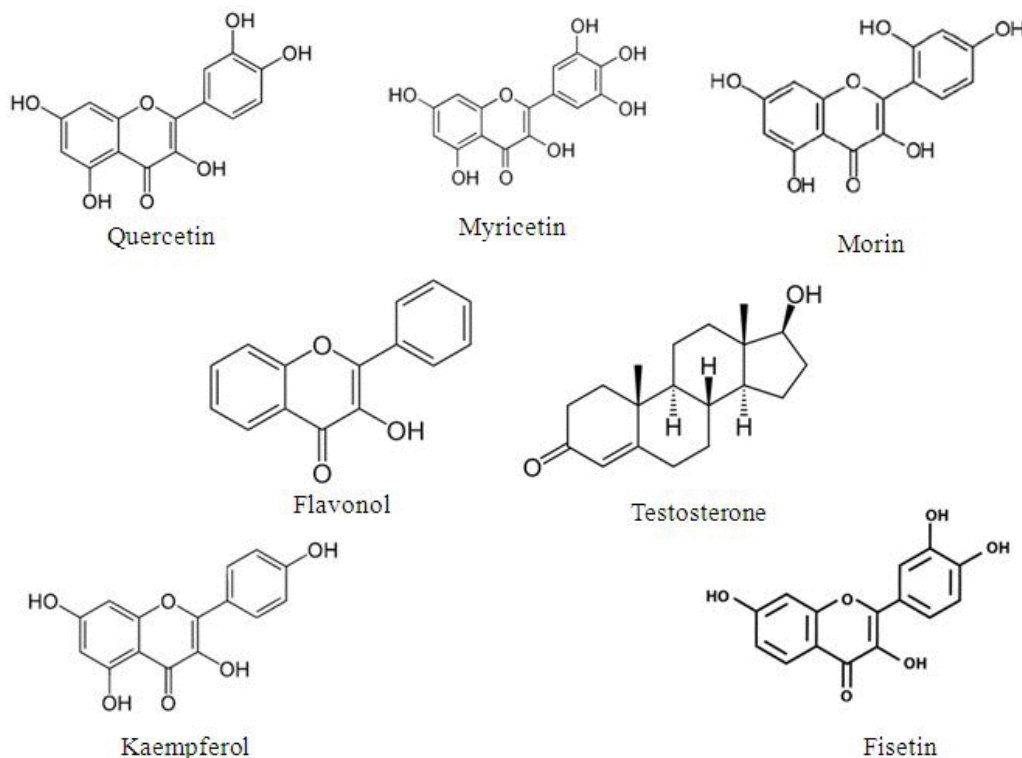


Figure 2: Chemical structure of flavonols

AR receptors are important for the development and maintenance of male organs [42]. AR receptors are expressed in many human tissues, indicating AR-signaling pathway as an important signaling pathway for normal metabolic function, maintenance and homeostasis of cells [43]. AR receptor mutations are associated with PCa pathogenesis and thus more research on AR receptor function is a real need of the time.

The enzyme 5α -reductase is responsible for converting testosterone into dihydrotestosterone (DHT) [44]. Quercetin, Myricetin, Fisetin and Morin inhibits type 1 5α -reductase because of the presence of the catechol group in their structure, and Kaempferol is found to be a better inhibitor of the type2 isoenzyme [45]. This shows that a regular intake of flavonols in the diet may impair DHT levels and consequently the growth of PCa.

Many studies have taken into consideration the effect of flavonols on the expression and activity of AR receptor [46], [47]. The expression AR-dependent genes viz., PSA, 5α -reductase and human kallikrein 2 (KLK2) are considered as markers of AR activity [48]. Quercetin and kaempferol suppresses the gene expression of PSA and KLK2 with the inhibition of AR accumulation in the nucleus [49]–[51]. These studies together show the inhibitory effect of flavonols on AR expression and activity thereby showing a potential for the prevention or treatment of CRPC.

Quercetin is widely available flavonol and most studies on flavonols are inclined to focus on it [52], [53]. Quercetin is a polyphenol (3,3',4',5,7-pentahydroxyflavone) and is available in fruits and vegetables in the form of a glycoside which shows it cannot be easily absorbed. Quercetin is available in extremely high concentration in tea, apples, broccoli, onions and red wine [54]. Like all other flavonoids, quercetin also possesses biological attributes like antioxidative, anti-apoptosis and anti-inflammatory activities

In recent years, the inspiring anticancer effects of quercetin have drawn the interest of a number of researches in a variety of cancers including Prostate cancer [55]–[57]. Results of *in vitro* studies have shown that quercetin, whether used alone or in combination, greatly blocks the cell cycle, reduces cell viability, impairs proliferation and induces apoptosis. Similarly, *in vivo* studies have also shown xenografts tumor growth inhibition in a dose dependent manner (Table 3).

Table 3 Summary of *in-vitro* and *in-vivo* work carried out in Prostate cancer using Quercetin

Cell	In vitro studies		Animal Model	In vivo studies	
	Effect and Mechanism	Reference		Effect and Mechanism	References
PC-3	Inhibits proliferation, cell cycle arrest, induces apoptosis, endoplasmic reticulum stress, mitochondrial apoptosis, modulates NO production, enhances TRAIL-induced apoptosis, downregulates survivin, reduces phosphorylated AKT level, increases p21 and hypophosphorylated retinoblastoma protein, inhibits angiogenesis, increases p38-MAPK, reverses EMT, downregulates MMP-2 and MMP-9.	[40], [58]–[69]	Male BALB/c nude mice	Inhibits angiogenesis	[65]
LNCaP	Inhibits proliferation, cell cycle arrest, induces apoptosis, cell cycle arrest, modulates NO production, induces formation of c-JUN/Sp1/AR protein complex, inhibits expression and function of AR, retards DNA synthesis, decreases HIF-1 α accumulation, inhibits fatty acid synthase activity	[46],[50],[58],[62],[66],[70]–[74]	Male SCID mice	Induces apoptosis, inhibits proliferation, phosphorylated AKT, PSA, and AR.	[75]
DU-145	Inhibits proliferation, modulated NO, upregulates death receptor 5, enhances extrinsic apoptosis mediated by TRAIL, dephosphorylation of AKT, increases tumor suppressor genes, reduces oncogenes and cell cycle genes	[36], [62], [63], [76], [77]	Severe combined immune deficient (SCID) mice	Inhibits proliferation and angiogenesis	[78]
			Male Sprague-Dawley rats	Inhibits proliferation, reduces phospho-MEK1/2 and phospho-MAPK, increases p15, p21 and p27.	[79]
			Male nude mice	Inhibits HSP72	[80]

IV. Flavones and Prostate cancer

Luteolin (3',4',5-7-tetrahydroxyflavone) and chrysin (5,7-dihydroxyflavone) are the two most studied flavones in Prostate cancer. Luteolin is commonly available in many types of plants, fruits, vegetables and medicinal herbs. Chrysin is extracted from honey, plants and propolis.

Recently, a number of researches have focused on the biological activities of Chrysin, such as anti-oxidant, anti-inflammatory and anti-cancer effects [81]. Chrysin reduces proliferation and induces apoptosis in the human prostate cancer cell line PC-3. Chrysin is found to increase the prolyl hydroxylation of hypoxia inducing factor 1 α (HIF1- α) consequently increasing its ubiquitination and degradation in human Prostate cancer DU145 cells [82]. Chrysin inhibits the ubiquitine-proteasome pathway that plays an important role in apoptosis and cell cycle [83]. In a study by Li *et al.* the authors have shown that treatment with chrysin sensitized various human cancer cells to apoptotic cells, induced by tumor necrosis factor alpha (TNF- α) [84]. Such sensitization is associated with the inhibition of NF- κ B activation by chrysin, which consequently leads to the reduced expression of anti-apoptotic gene c-FLIP-L, which has an inhibitory effect on caspase-8 [85]. These studies together show the anti-proliferation and anti-cancerous effects of chrysin through induction of apoptosis in Prostate cancer indicating its promising role in Prostate cancer prevention and treatment.

Compare to quercetin, the concentration of luteolin is generally low in food. Like quercetin, luteolin also has the potential to block various points in the development of cancer, such as inhibition of cell transformation, invasion, metastasis and angiogenesis, regulation of cell cycle and induction of apoptosis. Studies have shown that luteolin impairs proliferation, causes growth arrest and inhibits invasion of Prostate cancer cells (PC-3 and LNCaP) [86]. Luteolin causes a G2/M arrest in both PC-3 and LNCaP cells. Studies on impairment of invasion in PC-3 cells by luteolin have shown that luteolin exerts such anti cancer effects by regulating E-cadherin through AKT/mdm2 pathway.

V. Conclusion and Future Prospects

Flavonoids provide a new horizon for Prostate cancer therapeutics. The positive correlation between flavonoid intake and reduced incidence of Prostate cancer along with no toxicity associated with flavonoid consumption makes them attractive molecules in cancer therapeutics. The *in-vitro* and *in-vivo* research work summarized in table 1 and table 2 shows the potential of flavonoids in interfering with the development and progression of Prostate cancer. By understanding the exact molecular mechanism underlying the potential of flavonoids as anti-cancer agents and with further clinical trials considering the therapeutic and preventive effects of flavonoids in Prostate cancer will provide new insights and reliable evidence in fighting against Prostate cancer.

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