

Quercetin in Prostate Cancer Therapy

Subjects: Urology & Nephrology

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Prostate cancer is the second most leading and prevalent malignancy around the world, following lung cancer. Prostate cancer is characterized by the uncontrolled growth of cells in the prostate gland. Prostate cancer morbidity and mortality have grown drastically, and intensive prostate cancer care is unlikely to produce adequate outcomes. The synthetic drugs for the treatment of prostate cancer in clinical practice face several challenges. Quercetin is a natural flavonoid found in fruits and vegetables. Apart from its beneficial effects, it plays a key role as an anti-cancer agent. Quercetin has shown anticancer potential, both alone and in combination.

Keywords: quercetin ; chemotherapeutic ; chemo resistance ; mechanisms ; nano scale delivery

1. Quercetin in Oncology

In recent decades, the scientific community has uncovered the enormous potential role for natural compounds in the therapy and management of terrible diseases such as cancer. Despite the availability of a wide range of natural therapeutic agents, the creation of a definitive treatment for cancer is still pending. Therefore, it is important to understand the relationships between natural molecules and their respective cellular targets to devise an efficient cancer treatment strategy. This would involve numerous intracellular targets, which include apoptosis, cell cycle, detoxification, replication of antioxidants, and angiogenesis. The scope of the synergistic studies available strongly reinforces the use of quercetin as a medication for chemoprevention [1].

Apoptosis is characterized by specific cellular events such as blebbing, failure of cell adhesion, cytoplasmic expansion, fragmentation of DNA, and caspase activation via external and internal pathways. Research indicates that quercetin can induce apoptosis through the mitochondrial pathway involving activation of caspase-3 and 9, accompanied by liberation of cytochrome C and poly-ADP-ribose polymerase cleavage [2][3][4]. This induction of apoptosis by quercetin through mitochondrial pathways and the caspase cascade has been documented in various cancer cell lines including MCF-7 cells of breast cancer, HK1 cells of nasopharyngeal carcinoma, HL60 cells of leukemia, and SCC-9 cells of oral squamous cell carcinoma [5][6][7][8]. Induction of apoptosis via cellular signaling protein modulation, upregulation of Bax (Bcl2 associated X protein), Cox-2, and downregulation of Bcl-2 proteins is also triggered by quercetin [9][10].

Normally, cyclin and cyclin dependent kinases regulate the cell cycle. Conversely, cyclin dependent kinase inhibitor regulates cyclin dependent kinases [11][12]. Quercetin induces S phase cell cycle arrest and subsequently leads to the inhibition of DNA synthesis in SCC-9 cells [6]. During the S-phase of MCF-7 breast cancer cells, quercetin induces cell arrest, which leads to downregulation of cyclin dependent kinases-2 and p53, and p57 upregulation in a dose-time dependent manner [7]. By inhibiting cell cycle progression, quercetin prevents the proliferation of ovarian cancer cells and promotes cell apoptosis [13]. Quercetin anticancer potential evaluated in multiple cancers is briefly shown in [Table 1](#).

Table 1. Effect of quercetin on multiple cancers.

Cancer Type	Cell Line	Observed Effects	References
Breast cancer	MCF-7 cells	Apoptosis induction, cell cycle arrest	[5][7]
Nasopharyngeal carcinoma	HK-1 cells	Cell cycle arrest and apoptosis induction	[7]
Leukemia	HL-60 cells	Apoptosis induction, detoxification	[8]
oral squamous cell carcinoma	SCC-9 cells	Necrosis and apoptosis induction, cell cycle arrest during S-phase	[6]

Cancer Type	Cell Line	Observed Effects	References
Ovarian cancer	SKOV-3 cells	Promotes cell apoptosis, prevents cancer cells proliferation	[13]
Lung cancer	A549 cells	inhibition of CYP1A2 activity	[14]
Gastric cancer	GC 1401	Suppression of gastric cancer cell growth, apoptosis modulation	[15]
Colorectal cancer	HT-229	Apoptosis promotion, provoke cell cycle arrest, proliferation inhibition	[16][17]
Oral cancer	SAS cells	Repression of invasion, migration and cell viability, decrease tumor rate and enhanced apoptosis	[18][19]
Liver cancer	SMMC7721, QGY7701	Antitumor effect via apoptosis induction	[20]
Thyroid cancer	B-CPAP, K1	Promote apoptosis, reduce cell proliferation.	[21][22][23]
Pancreatic cancer	MIA PaCa-2	Apoptosis induction, reduced cell proliferation, apoptosis induction	[24][25]

Evidence indicates that quercetin deregulates multiple CYP enzyme isoforms in tumor cells [26]. In vitro studies have demonstrated quercetin induced inhibition of CYP1A2 activity in human lung carcinoma A549 cells, HepG2 cells, and human hepatocytes [14]. Apart from CYP enzyme modulation, quercetin follows the mechanism of Nrf2 (nuclear erythroid factor 2-cognate factor 2) mediated enzyme induction, contributing to its anti-cancer potential. When phase II enzymes like heme oxygenase-1, UDP-glucuronosyl, and glutathione S transferases pose any carcinogens, quercetin causes their suppression. The genes of these enzymes involve antioxidant replication components that are rigorously regulated by nuclear erythroid factor 2-cognate factor 2. This, as a consequence, is correlated with another protein known as the Kelch-like ECH-associated protein-1, a Nrf2 repressor, and further reinforces its deterioration via the ubiquitin-dependent proteasome pathway [27][28][29].

In the treatment of ARE-mediated inducer cells, quercetin facilitates the detachment of the Nrf2-Keap1 complex, resulting in the translocation of Nrf2 to the nucleus, where it composes heterodimers with other transcription factors, binds to ARE, and activates phase II enzyme gene transcription [30]. The molecular target pathway is shown in [Figure 4](#).

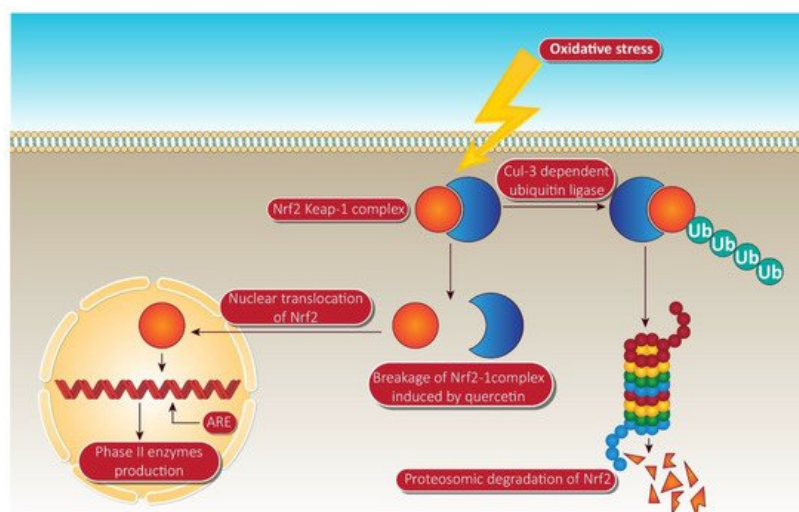


Figure 4. Quercetin targeting via phase II enzyme pathway mediated through Nrf-2. When the cells are unstimulated under stress conditions, Keap-1 isolates Nrf-2 and exposes it to cul-e dependent ubiquitin ligase. This enzyme leads to the proteasomal cleavage of Nrf-2. In the meantime, quercetin degrades the Nrf-2 keap-1 complex and shifts the Nrf2 to the nucleus. Inside the nucleus, Nrf-2 binds to ARE, resulting in the production of phase II enzymes via Nrf-2 associated expression. Nrf-2, nuclear factor erythroid 2 related factor-2; Ub, ubiquitin; ARE, anti-oxidant response element. Human colorectal adenocarcinoma cells and duodenal adenocarcinoma HuTu 80 cells were further identified as receiving a quercetin triggered boost in phase II oxidative stress (detoxification enzymes). Additionally, the time-dependent influence of quercetin on the transcriptional regulation of Nrf2 and its increased mRNA and protein expression was consistently observed in HepG2 and malignant mesothelioma cells [31].

2. Quercetin and Prostate Cancer

Recently, morbidity and mortality of prostate cancer have risen, and systematic cures for prostate are unable to produce sufficient results. Quercetin is a naturally occurring flavonoid compound that has gained immense attention and focus because of its effectiveness against cancer. Both in vitro and in vivo studies have confirmed that quercetin effectively inhibits prostate cancer via different pathways.

2.1. Quercetin and Cell Death

Despite the dismal situation in prostate cancer care, the findings of the anticancer effects of quercetin are promising, having been used in a variety of human prostate cancer trials with beneficial effects. During the progression of prostate cancer, quercetin suppresses the epithelial-to-mesenchymal transition process, promoting apoptosis via deactivation of the PI3K/Akt signaling pathway [32]. Additionally, quercetin has been shown to decrease the ratio of Bcl-xL to Bcl-xS and in contrast, maximize the efflux of Bax to the mitochondrial matrix in human prostate cancer cells [10]. Apart from this, quercetin promotes apoptosis of cancer cells by downregulation of heat shock protein-90 levels. Quercetin depletion of heat shock protein-90 results in reduced cell viability, inhibition of surrogate markers, mediated apoptosis, and activation of caspases [4].

A research study on the correlation between quercetin and prostate cancer indicates that quercetin reduces the viability of androgen-independent prostate cancer cells by regulating the expression of system components of insulin-like growth factors (IGF), signal transduction, and inducing apoptosis, which could be very beneficial for the treatment of androgen-independent prostate cancer [33]. There is no study to discuss the role of endoplasmic reticulum stress in quercetin-induced apoptosis in prostate cancer cells. Multiple pieces of evidence indicate several potential signaling pathways for quercetin in apoptosis. In this regard, Liu et al. demonstrated that quercetin decreases the expression of Bcl-2 protein and activates the caspase cascade via mitochondrial and endoplasmic reticulum stress, subsequently leading to apoptosis in prostate cancer cells [34].

Quercetin downregulated the Notch/AKT/mTOR, a fundamental signaling pathway in tumor progression, which leads significantly to apoptosis of U937 leukemia cells [11]. Targeting extrinsic domains, quercetin has been found to boost tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) mediated apoptosis in DU-145 cells (human prostate cancer cell line) via overexpression of death receptor-5 (DR5) [35]. Downregulation of survivin through histone (H-3 regulated) deacetylation and AKT dephosphorylation in prostate cancer-3 and DU-145 cell line also leads to apoptosis by quercetin due to its anti-prostate cancer potential [36][37]. Apart from apoptosis induced by the caspase cascade, quercetin also triggers other apoptosis pathways, which are schematically shown in Figure 5. Apoptosis induction by quercetin, which could be the significant parameter for its anti-prostate cancer effectiveness, has been extensively explored in numerous types of prostate cancer cell and is attracting ever more attention.

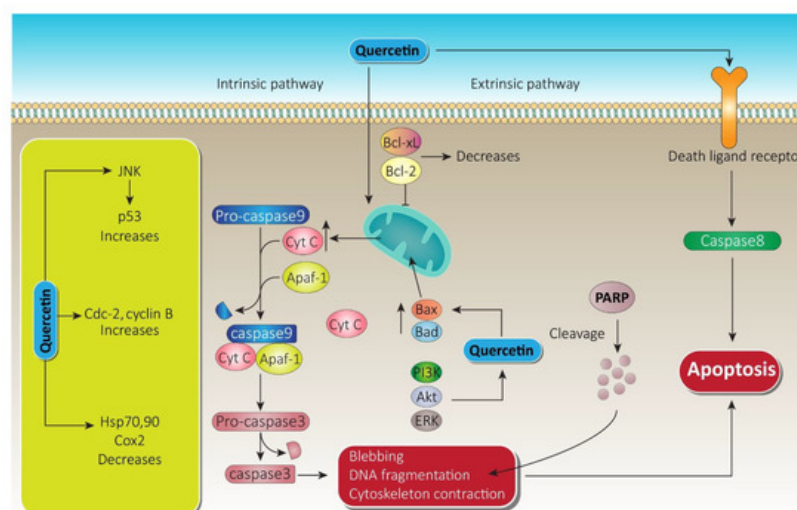


Figure 5. Quercetin apoptotic mechanism via death ligand and mitochondrial membrane. Following the intrinsic pathway, quercetin causes massive release of Cyt-c from the mitochondrial intramembranous space and induces apoptosomes. Furthermore, via blebbing, DNA fragmentation, and cytoskeleton contraction, it paves the way to apoptosis. On the other hand, through the extrinsic pathway, quercetin initiates caspase-8, which leads to apoptosis. A substantial increase in JNK and cdc cyclin B while decreasing heat shock proteins by quercetin also promotes therapy of prostate cancer. Bcl-xL, B-

cell lymphoma extra-large; Bcl-2, B-cell lymphoma-2; Cyt-c, cytochrome c; JNK, c-jun N terminal kinase; ERK, extracellular signal regulated kinase; PARP, poly ADP-ribose polymerase; PI3K, phosphoinositide 3 kinase; Akt, serine/threonine specific protein kinase.

2.2. Quercetin and Metastasis

The epithelial–mesenchymal transition (EMT) is a flexible transition in the progression of tumors, during which cancer cells undergo drastic changes to develop highly invasive properties. Transforming growth factor- β (TGF- β) is an epithelial–mesenchymal transition inducer within epithelial cells, required for the development of the invasive carcinoma phenotype. Transforming growth factor- β plays a critical role in prostate cancer metastasis and tumorigenesis, with mutations in the Wnt signaling pathway being linked to a further variety of cancer types. Quercetin interferes with the Wnt signaling pathway, leading to inhibition of migration and invasion [38].

Urokinase plasminogen activator (uPA) is a serine protease that is associated with the progression of prostate cancer, especially the invasion and metastasis stages. In the prostate cell proliferation stage, urokinase plasminogen activator is regulated by uPA and transactivation of the epidermal growth factor receptor. Cells of prostate cancer (PC-3) are highly invasive when expressing the uPA and uPAR genes. Quercetin downregulates mRNA expressions for uPA, uPAR, and EGF. In addition, quercetin also inhibits β -catenin, NF- κ B, and even proliferative signaling molecules such as p-EGF-R, N-Ras, Raf-1, c. Fos c. Jun, and p-c. Jun protein expressions of the cell survival factor. This whole process leads to the inhibition of invasion and migration phenomena, resulting in inhibition of prostate cancer metastasis [39]. Quercetin also blocks angiogenesis and metastasis by upregulating thrombospondin-1 to suppress in vitro and in vivo growth of PC-3 cells in human prostate cancer [40].

Angiogenesis is a vital step in the invasion and progression of cancer as it helps the expanding tumor to acquire oxygen and nutrients. At non-toxic concentrations, quercetin significantly inhibits the protrusion of micro vessels and shows substantial inhibition of the proliferation, migration, invasion, and tube forming of endothelial cells, which are essential events in the angiogenesis process. The findings of an associated study revealed that quercetin inhibits angiogenesis and cell growth targeting the VEGF-R2 regulated AKT/mTOR/P70S6K signaling pathway, leading to inhibition of prostate cancer metastasis [41]. Another target for quercetin is miR-21, where it significantly suppresses the proliferation and metastasis of prostate cancer cells and decreases the expression of multiple miRNA associated with prostate tumors, particularly miR-21. Such an inhibition of the miR-21 signaling pathway results in the prevention of prostate cancer metastasis [42]. The comparative detail of quercetin on multiple prostate cancer cell lines, along with the observed effects, are shown in Table 2.

Table 2. Comparative details of quercetin on multiple cell lines of prostate cancer.

Molecular Mechanism	Signaling Pathway	Cell Lines	Observed Effects	References
Apoptosis	PI3K/Akt signaling pathway	PC-3 and its xenograft tumor	Suppression of epithelial to mesenchymal transition	[32]
	Caspase activation, regulation of Bcl-2,	PC-3	Decrease the ratio of Bcl-xL to Bcl-xS and in contrast maximize the efflux of Bax to the mitochondrial matrix	[10]
	Downregulation of heat shock protein-90	PC-3, LNCaP, DU-145	Reduced cell viability, inhibition of surrogate markers, mediated apoptosis and activation of caspases	[4]
	Insulin-like growth factors (IGF), signal transduction both internal and external	PC-3	Reduces the viability of androgen-independent prostate cancer cells	[33]
	Notch/AKT/mTOR, caspase-3, and caspase-9	DU-145	Boost tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), sensitization cancer cells to apoptosis	[35]
Metastasis	Wnt signaling pathway,	PC-3	Inhibition of migration and invasion	[38]
	Inhibition of β -catenin, NF- κ B, p-EGF-R, N-Ras, Raf-1, c. Fos c. Jun and p-c. Jun	PC-3	Inhibition of migration and invasion of prostate cancer cell lines	[39]

Molecular Mechanism	Signaling Pathway	Cell Lines	Observed Effects	References
Angiogenesis and proliferation	Thrombospondin-1	PC-3	Suppress in vitro and in vivo growth of PC-3 cells in human prostate cancer	[40]
	VEGF regulated AKT/mTOR/P70S6K	HUVECs (Human umbilical vein endothelial cells), PC-3	Inhibition of angiogenesis and tumor growth	[41]
	VEGF/PI3k/Akt	LNCap, PC-3	Synergistic inhibition of cell invasion and proliferation	[43]
	capase-3/7, nuclear β -catenin, and TCF-1/LEF	LNCap, PC-3	Inhibition of invasion and proliferation	[44]
	Bcl-2/Bax	LNCap, PC-3	Antiproliferative effect, growing the Stage G2/M	[45]
	PI3K/Akt	LAPC-4 and LNCaP	Inhibition of cell migration, antiprostate cancer potency at lower dose, antiproliferative effect	[46]

Quercetin in combination with metformin targets the VEGF/PI3k/Akt signaling pathway, which synergistically inhibits cell invasion and proliferation in prostate cancer cell lines [43]. In addition, quercetin in combination with epigallocatechin gallate inhibits the invasion and progression of prostate cancer stem cells via activation of X-linked inhibitor of apoptosis protein (XIAP) and survivin, leading to its metastasis inhibition potential in prostate cancer [44]. With regard to this synergy, in PC-3—the cell lines of human prostate cancer—quercetin and 2-methoxyestradiol display antiproliferative and proapoptotic activity by growing the Stage G2/M of the cell population and decreasing Bcl-2/Bax. Thus, promoting the G2/M stage leads to the anti-metastatic potential of prostate cancer [45]. At low physiological doses, the combination of arctigenin and quercetin targeting related pathways (androgen receptor and PI3K/Akt) offers a novel protocol for accelerated chemoprevention in prostate cancer [46].

2.3. Quercetin in Reversing Chemoresistance

Chemotherapy is indeed an indispensable therapy for prostate cancer. The development of chemoresistance, however, is a widespread and crucial issue that requires urgent remedies to be dealt with.

Advanced drug studies have shown that quercetin serves as a potential anti-cancer agent in several types of cancer by regulating multiple pathways. However, current therapies are limited by resistance, which might be reversed by quercetin. In this regard, doxorubicin induced resistance was successfully recovered via quercetin in a research study. A cell line-PC3/R of prostate cancer with acquired doxorubicin resistance was identified. In comparison with normal PC3 cells, a strong drug-resistance to doxorubicin and significant activation of the phosphoinositide 3-kinase/protein kinase-B (PI3K/AKT) pathway was shown in PC3/R cells. Doxorubicin combination therapy with quercetin greatly facilitated the apoptosis induced by doxorubicin in PC3/R cells via the mitochondrial/reaction oxygen species pathway. A major upregulation of tyrosine-protein kinase-met was observed in PC3/R cells as opposed to normal PC3 cells. Furthermore, c-met mediated expression rescued quercetin-promoted apoptosis in doxorubicin treated PC3/R cells [47]. This clearly indicates that quercetin can reverse the resistance of prostate cancer cells to doxorubicin by downregulating the expression of c-met. This might provide a potential strategy to reverse prostate cancer chemoresistance.

Docetaxel is a first line therapeutic drug that is used in the treatment of prostate cancer metastasis. Unfortunately, the advent of resistance reduces its effectiveness and restricts its benefits to survival. In prostate cancer cells and xenograft models, quercetin can reverse docetaxel resistance on proliferation, colony formation, migration, invasion, and apoptosis. Combination therapy of quercetin with docetaxel can sufficiently inhibit the PI3K/Akt pathway and promote apoptosis. Subclones susceptible to docetaxel and prone subclones have been treated with quercetin, which showed that docetaxel-resistant subclones had greater androgen receptor and PI3K/Akt pathway activation, more remarkable phenotypes of mesenchymal and stem-like cells, and more expression of P-gp than that of parental cells. All these transformations were interestingly reversed by quercetin [48]. This offers in-depth evidence for the clinical use of quercetin in docetaxel-resistant prostate cancer.

The effect of cancer treatment and ATP-dependent drug efflux pumps may be significantly affected by multidrug resistance to chemotherapy. P-glycoprotein, and midkine (MK) contribute to the resistance of different chemotherapeutic agents. Z—polypeptide 1 is one of the midkine receptors and, in PI3K and MAPK pathways, has been found to be

synergistically active in midkine-mediated cell migration. Consequently, modulation of the PI3K and MAPK signaling pathways by quercetin can cause amplification of gene expression associated with endothelial–mesenchymal transition. Thus, quercetin modulation of the endothelial–mesenchymal transition and drug resistance genes might contribute to the inhibition of CD44⁺/CD133⁺ proliferation and migration ^{[49][50][51]}. In summary, these findings show that MK siRNA coupled with quercetin can inhibit the therapeutic resistance of CD44⁺/CD133⁺ cells. Treatment with quercetin combined with the midkine knockdown strategy could effectively target and facilitate removal of CD44⁺/CD133⁺ cells, thereby preventing chemoresistance.

The splice variant AR-V7 is implicated in resistance not only to enzalutamide, but also to abiraterone and other traditional therapeutics. Clinical evidence indicates that resistance toward the next-generation antiandrogen, enzalutamide, can be largely induced by alternative androgen receptor splicing to establish constitutively active splice variants (AR-V7). Recent studies indicate that fusing factors such as hnRNPA1 promote the production of AR-V7 and thus contribute to the resistance of enzalutamide in cells of prostate cancer. Quercetin decreases hnRNPA1, and subsequently AR-V7 expression. Quercetin suppression of AR-V7 desensitizes enzalutamide-resistant prostate cancer cells to enzalutamide therapy. Altogether, the underlying mechanism involves downregulation of hnRNPA1 expression, downregulation of AR-V7 expression, antagonizes the signaling pathway of androgen receptors, and desensitizes enzalutamide-resistant prostate cancer cells to in vivo treatment with enzalutamide in mouse xenografts ^[52]. These findings indicate that blocking the alternative splicing of the androgen receptor can have major consequences in overwhelming resistance to antiandrogen therapy of the next generation.

Metastatic or locally induced prostate cancer is usually managed with androgen deprivation therapy. Prostate cancer initially reacts to the medication, and then its response begins to revert, gaining tolerance to androgen deprivation and developing toward castrate-resistant prostate cancer—an incurable form. Research using transgenic mouse models shows that modulation of the Wnt/β-Catenin signaling pathway in the prostate cancer is cancerous, allowing for castration-resistant growth of prostate cancer, inducing an epithelial-to-mesenchymal transformation, promoting differentiation of neuroendocrine and giving stem cell-like characteristics to prostate cancer cells ^[53]. These major Wnt/β-Catenin signaling functions in prostate cancer development emphasize the need to establish drugs targeting this pathway for dealing with resistance to prostate cancer therapy.

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