Cancer Cell Research 20 (2018) 489-495

Available at http:// www.cancercellresearch.org ISSN 2161-2609

Mechanisms of anti-prostate cancer by Polyphenols compounds

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Abstract: **Prostate cancer (PCa) is the most common cancer in the world, it is greatly affected by lifestyle, particularly diet, and is more prevalent in US and European countries compared with South and East Asia. Among several known causes and risk factors, nutrition plays an important role in PCa pathogenesis. And the relationship between dietary polyphenols and the treatment of PCa has been examined previously. There is a general agreement that polyphenols compounds hold great promise for the future management of PCa. Generally considered as non-toxic, polyphenols compounds act as key modulators of signaling pathways and are therefore considered ideal chemopreventive agents. Besides possessing various anti-tumor properties polyphenols compounds also contribute to epigenetic changes associated with the fate of cancer cells and have emerged as potential drugs for therapeutic intervention. This report reviews current knowledge on the anti-prostate cancer effects of several polyphenols compounds, with a focus on their ability to modulate multiple signaling transduction pathways involved in cancer.**

Keywords: Polyphenol; Flavonoid; Anti-Tumor; Prostate cancer

Received 16 July 2018, Revised 28 August 2018, Accepted 30 August 2018

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1. Introduction

Prostate cancer (PCa) is an epithelial malignancy that occurs in the prostate and is a hormone-driven cancer[1]. It is the most common cancer in the world. According to statistics, there were 1.6 million incident cases of PCa and 366 000 deaths in 2015[2]. It is the fifth leading cause of cancer deaths worldwide. The highest incidence of PCa in developed countries such as Europe and the United States[3]. Current methods of treating PCa include radical prostatectomy, chemotherapy, local radiotherapy and hormonal therapy[4-6]. Taking into consideration that chemotherapy and radiotherapy have severe side effects and usually a poor outcome, there is an intensive need for the development of safer and more effective agents.

Prevention of cancer through dietary intervention recently has received an increasing interest, and dietary polyphenols have become not only important potential chemopreventive, but also therapeutic, natural agents. Phenolic acids and flavonoids are the most abundantly occurring polyphenols in plants. And polyphenols compounds have been reported to interfere at the initiation, promotion and progression of cancer[7].

Most of the chemotherapy drugs used to treat cancer have been rooted in natural products for the past 40 years. Furthermore, natural products may provide many lead structures that can be used as templates to design novel compounds with better bioactivity[8,9]. Therefore the present review summarized the anti-prostate cancer characteristics of several promising natural polyphenolic compounds, and discussed the mechanisms of action based on laboratory experiments and clinical trials.

2. Polyphenols compounds and anticancer mechanisms

2.1. Quercetin

Quercetin is one of the most often studied natural flavonoid compound and is ubiquitous in foods such as vegetables, fruits, tea and wine[10]. At present, quercetin is mainly used as nutritional supplement and phytochemical remedy for many diseases, such as diabetes, cancer and so on[11]. Many researchers have studied the role of quercetin in the treatment and prevention of PCa, and elaborated its mechanisms of action from various aspects.

Apoptosis is divided into mitochondrial-mediated intrinsic and death receptor-mediated extrinsic pathways. The intrinsic pathway induces apoptosis mainly by up-regulating the pro-apoptotic protein Bax and down-regulating the anti-apoptotic protein Bcl-2, which leads to the increase in the ratio of Bax/Bcl-2[12]. After quercetin treatment of PC-3 cell lines, endoplasmic reticulum (ER) stress-related proteins such as GRP78 and ATF-4α were also increased, and then the caspase cascade reaction was activated directly, resulting in subsequent cell apoptosis[13]. Quercetin mediated extrinsic apoptosis, one was the up-regulation of DR5 or down-regulation of survivin by extracellular regulated protein kinases (ERK) mediated deacetylation of histone H-3[14], the other was the dephosphorylation of Akt[15]. Finally, tumor necrosis factor-related apoptosis-inducing ligand

(TRAIL) was also associated with extrinsic apoptosis[16].

Quercetin can down-regulate cyclin D and E, Cdk2, Cdc25C in PCAp cells, and resulting in G_0/G_1 and sub-G_1 cell cycle arrest[13]. Moreover, it also can increase G_2/M phase population of PC-3 and LNCaP cells, and the number of cells in the S phase of PC-3 cells[17].

Xing. et al found that quercetin can inhibit the secretion of androgen-regulated tumor markers prostate specific antigen (PSA) and HK2, and also reduce the mRNA levels of androgen-regulating genes include PSA, NKX3.1 and ornithine decarboxylase (ODC). This indicates that quercetin can inhibit the expression of androgen receptor (AR) gene at the transcriptional level, thereby attenuating the function of AR[18].

It can be seen from published studies that quercetin can increase in expression of c-Jun and its phosphorylated form in a dose-dependent manner in PCa cell lines, which makes c-Jun play an important role in inhibiting the expression and activity of AR[19]. The combination of the quercetin-induced c-Jun/Sp1/AR protein complex also down-regulates the AR function of PCa[20].

Vascular endothelial growth factor (VEGF) is mainly regulated by hypoxia-inducible factor-1α (HIF-1α) at the transcriptional level, which plays a key role in tumor angiogenesis[21.22]. Quercetin inhibits angiogenesis by reducing the accumulation of HIF-1α and the secretion of VEGF[23]. Similarly, a study by Pratheeshkumar et al. demonstrated that quercetin inhibits VEGF-R2 activation, thereby inhibiting angiogenesis signaling pathway mediated by Akt/mTOR/P70S6K[24].

2.2. Silibinin

Silibinin is a flavonoid extracted from milk thistle and has strong liver protection activity[25]. In recent years, silibinin has shown extensive anti-tumor effects in various cancer models, such as breast cancer, lung cancer, skin cancer, PCa and so on[26].

It can be seen from related studies based on PCa model that silibinin targets insulin-like growth factor-1 receptor (IGF-1R), nuclear factor-kappa B (NF-κB) and ataxia telangiectasia mutated kinase (ATM) pathways to inhibit the proliferation and induce apoptosis of PCa cells. It also reduces the expression of cell-cycle regulators such as cyclin-dependent kinases (CDKs) and cyclins, and induces CDK inhibitors for cell-cycle arrest in PCa cells[27]. The study by Deep et al. also confirmed that silibinin treatment caused cytoplasmic sequestration of cyclin D1 and CDK2, resulting in G_1 arrest. And the G_2-M phase arrest is associated with decreased cyclin B1, cyclin A, pCdc2 (Tyr15), Cdc2 levels, and inhibition of Cdc2 kinase activity[28].

Silibinin can induce apoptosis in PCa cells. The mechanisms of action is that silibinin inhibits the activity of STAT3 and caspase-3, thereby inducing apoptosis of Du145 cells[29]. Another study has also demonstrated its role in inducing apoptosis. At the molecular level, silibinin can increase the levels of insulin-like growth factor-binding protein-3 (IGFBP-3), $p21^{Cip1}$, $p27^{Kip1}$ and ERK1/2 activation, and decrease Bcl-2, survivin and VEGF levels in tumors and induce apoptosis[30].

Under hypoxic conditions, lipogenesis or lipid accumulation may result in androgen production and activation of the AR signaling. Silibinin treatment decreased the level of HIF-1α and several lipid metabolites, and the AR signal associated with inhibition of 22Rv1 xenograft growth. This clearly shows that silibinin treatment can destroy this relationship and prevent PCa progression[31].

Silibinin can also be used as a radiation sensitizer in combination with radiotherapy for PCa. It inhibits ionizing radiation (IR) induced prosurvival signaling and double-stranded breaks (DSB) repair by inhibiting nuclear translocation of epidermal growth factor receptor (EGFR) and DNA-dependent protein kinase (DNA-PK), thereby enhancing radiotherapy response[32].

2.3. Curcumin

Curcumin is a polyphenols compound extracted from turmeric, which has various pharmacological effects such as anti-inflammatory, anti-oxidation and anti-proliferation[33].

Curcumin augments TRAIL-mediated apoptosis in androgen-sensitive PCa cells. The induction of apoptosis by combined curcumin and TRAIL treatment involves the activation of initiator/effector caspases (caspase-8, caspase-9, caspase-3), truncation of Bid, and the release of cytochrome c from the mitochondria. Thus, combination of TRAIL with curcumin may provide a more effective adjuvant treatment for PCa[34]. The poptosis of PCa cells is also prompted by curcumin's interference with Bcl proteins, reactive oxygen species (ROS) generation, and the activation of mitochondrial related pathways[35,36].

As inflammation emerges as a risk factor for PCa, there is potential for chemoprevention by anti-inflammatory agents[37]. Mitogen-activated protein kinase phosphatase-5 (MKP5) over-expression decreases cytokine-induced NF-κB activation, COX-2, IL-6 and IL-8 in normal prostatic epithelial cells, suggesting potent anti-inflammatory activity of MKP5. However, curcumin can up-regulate MKP5 in normal prostate epithelial cells, implicating potential utility in management of early or advanced PCa[38].

In terms of radiosensitization, curcumin inhibits NF-κB activation that in turn downregulates endogenous Bcl-2 and Bax protein[39]. And the results of Chendil et al. showed that curcumin in combination

with radiation inhibits TNF-α-mediated NF-κB activity, resulting in Bcl-2 protein downregulation in PC-3 cells. Also, curcumin enhances radiation-induced apoptosis by releasing cytochrome c and activated caspases in combinations with radiation in PC-3 cells[40].

2.4. Resveratrol

Resveratrol is a naturally occurring polyphenols compound in grapes, peanuts and berries that has a exceptional potential as a treatment modality due to its cardioprotective, anti-inflammatory, chemopreventive and anti-angiogenic properties[41].

Resveratrol inhibits growth and induces apoptosis of PCa cells through multiple mechanisms. It regulates Bcl-2 family members, causes translocation of Bax to mitochondria, releases mitochondrial proteins, generates ROS, inhibits surviving, and activates caspases. Furthermore, resveratrol upregulates TRAIL-R1/DR4 and TRAIL-R2/DR5, in turn, enhances the apoptosis-inducing potential of TRAIL. Thus, resveratrol alone or in combination with TRAIL can be used to prevent and/or treat human PCa[42]. And other studies have shown that resveratrol causes down-regulation of metastasis-associated protein 1 (MTA1) protein, leading to destabilization of MTA1/NuRD, which results in p53 acetylation, increased stability and transcriptional activityand lead to apoptosis[43,44].

Kuwajerwala et al. indicated that LNCaP cells treated with resveratrol, are induced to enter into S phase, but subsequent progression through S phase is limited by the inhibitory effect of resveratrol on DNA synthesis, particularly at concentrations above 15 μM. And the resveratrol-induced increase in DNA synthesis is associated with enrichment of LNCaP cells in S phase, and a concurrent decrease in nuclear $p21^{Cipl}$ and $p27^{Kip1}$ levels[45]. Similarly, resveratrol also promotes expression of $p21^{Waf1}$, resulting in cell cycle arrest between the G_1 and S phases[46].

AR mediated signaling is important in the development of PCa. Researchers found that resveratrol represses different classes of androgen up-regulated genes at the protein or mRNA level including prostate-specific antigen, human glandular kallikrein-2, AR-specific coactivator ARA70, and the cyclindependent kinase inhibitor p21[46.47]. This inhibition is likely attributable to a reduction in AR contents at the transcription level, inhibiting androgenstimulated cell growth and gene expression.

2.5. Epigallocatechin-3-gallate

Epigallocatechin-3-gallate (EGCG), a major polyphenolic constituent of green tea, has chemopreventive and chemotherapeutic effects in many tumor models[48,49].

Studies in LNCaP and DU145 cells have shown that EGCG negatively modulates PCa cell growth by affecting mitogenesis as well as inducing apoptosis, in cell-type-specific manner which may be mediated by $p21^{WAF1}$-caused G_0/G_1-phase cell-cycle arrest, irrespective of the androgen association or p53 status of the cells[50]. Subsequent research by the same research group demonstrated that EGCG treatment up-regulates the protein expression of $p21^{Waf1}$, $p27^{Kip1}$, $p16^{INK4a}$, and $p18^{INK4c}$, down-regulated the protein expression of cyclin D1, cyclin E, cdk2, cdk4, and cdk6, increased in the binding of cyclin D1 toward $p21^{Waf1}$ and $p27^{Kip1}$, and decreases in the binding of cyclin E toward cdk2[51]. In addition, EGCG inhibits p38 mitogenactivated protein kinase and the proteasome activities, leading to inhibition of Bcl-xl phosphorylation and induction of PCa cell death[52].

EGCG has been shown to inhibit tumour invasion and angiogenesis, crucial steps for the growth and metastasis of all solid tumours. It was proposed that the anticancer activity of EGCG is associated with the inhibition of invasion by inhibiting the activity of urokinase[53] or the matrix metalloproteinases (MMPs)[54], or by the removal of oxygen radicals[55]. And Shaheen et al. suggest that down-regulation of VEGF by EGCG may lead to endothelial cell apoptosis within tumours, which could not only inhibit new blood vessel formation and tumour growth, but could also lead to tumour cell apoptosis[56]. In addition, the inhibition of MMP-2 and MMP-9 in DU145 cells by EGCG is mediated via inhibition of phosphorylation of ERK1/2 and p38 pathways, and inhibition of activation of transcription factors c-jun and NF-κB. EGCG may play a role in prevention of invasive metastatic processes of both androgen-dependent and androgen-independent PCa[57].

2.6. Apigenin

Apigenin is a naturally occurring nontoxic, nonmutagenic plant flavonoid commonly present in fruits and vegetables with proven anti-inflammatory and anticarcinogenic effects in various animal tumor model systems[58].

Apigenin causes a significant decrease in cyclin D1 expression that occurs simultaneously with inhibition of cell cycle progression. The reduce expression of cyclin D1 protein correlated with decrease in expression and phosphorylation of p38 and PI3K-Akt, which are regulators of cyclin D1 protein. Interestingly, apigenin causes a marked reduction in cyclin D1, D2 and E and their regulatory partners CDK 2, 4 and 6, operative in G_0-G_1 phase of the cell cycle[59.60]. Apigenin treatment also results in alteration in Bax/Bcl2 ratio in favor of apoptosis, which is associated with the release of cytochrome c and induction of apoptotic protease-activating factor-1 (Apaf-1). This effect results in a significant increase in cleaved fragments of caspase-9, -3, and poly (ADP-ribose) polymerase. Further, it also results in down-modulation of the constitutive expression of NF-κB/p65[61.62].

Low oxygen (hypoxia) and transforming growth factor-b (TGF-b) are two major factors responsible for increased VEGF secretion, while apigenin blocks TGF-b1 activation of Src and Smad2/3 pathways and inhibits VEGF production[63]. In combination with previous reports that apigenin inhibits expression of HIF-1α by reducing stability of the protein as well as by reducing the level of HIF-1α mRNA[64], indicates that apigenin may represent an attractive candidate compound for prevention of PCa metastasis.

3. Conclusion

The vast majority of laboratory studies supported anticancer activities of natural polyphenols, such as quercetin, resveratrol and curcumin. The mechanisms of action mainly included modulation of molecular events and signaling pathways associated with cell survival, proliferation, migration, angiogenesis, hormone activities, etc. Besides, the anticancer effects of polyphenol varied with cancer types, cell lines and doses.

However, there are still only a few clinical trials regarding the use of polyphenols in combination with conventional therapies for cancer treatment. One probable reason could be the fact that metabolism, stability, interaction with other drugs, side effects and mechanisms of action of these plant derivatives have not been fully elucidated in humans. An incorrect administration of these phytochemicals may interfere with the activity of conventional therapies leading to harmful effects in humans.

We can optimize and design more compounds with polyphenols compounds as the lead structures by computer aided drug design to increase bioavailability and antitumoral activities of polyphenols. And their synergistic and/or additive effects with conventional anticancer therapies may provide the starting point to improve the rationale for designing new clinical trials to be employed in cancer treatment.

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