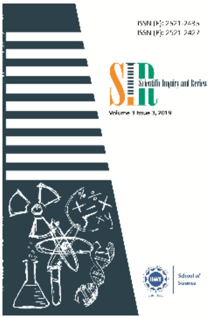

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Article: **Role of Polyphenols in Preventing Prostate Cancer Cell Growth through Calcium Channel Blockers: An Overview**

Author(s): Shazia Perveen[1], Sumaira Kanwal[2], Rehmana Rashid[3], Shafia Arshad[4]

Affiliation:
[1]Department of Zoology, The Women University Multan, Pakistan
[2]Department of Biosciences, COMSATS University Islamabad Sahiwal Campus, Pakistan
[3]Department of Pharmacy, The Women University Multan, Pakistan
[4]Faculty of Medicine and Allied Health Sciences, Islamia University Bahawalpur, Pakistan

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Role of Polyphenols in Preventing Prostate Cancer Cell Growth through Calcium Channel Blockers: An Overview

Shazia Perveen[1], Sumaira Kanwal[2], Rehmana Rashid[3], Shafia Arshad[4*]

[1]Department of Zoology, The Women University Multan, Pakistan
[2]Department of Biosciences,
COMSATS University Islamabad Sahiwal Campus, Pakistan
[3]Department of Pharmacy, The Women University Multan, Pakistan
[4]Faculty of Medicine and Allied Health Sciences,
Islamia University Bahawalpur, Pakistan

*shafia.arshad@iub.edu.pk

Abstract

Prostate cancer (PCa) is the second most widely diagnosed cancer in men and the sixth leading cause of death among them due to cancer. Phytochemicals play a significant role in chemo preventions. Recently, an increasing number of studies have looked into the role of polyphenols with regard to prostate cancer cell growth, highlighting their ability to target various cellular mechanisms. For this reason, we specifically focused on the studies published in the last twenty years by using different search engines including Google Scholar, PubMed, Web of Sciences, and Scopus in order to select and identify the potential role of polyphenols in targeting prostate cancer through calcium channel blockers. We concluded that polyphenols are the primary chemopreventive agents for prostate cancer.

Keywords: calcium channel blocker, cancer, chemopreventive, polyphenols, prostate cancer

Introduction

Prostate cancer is among the second most leading reasons for cancer death within men. It is also the second leading cause of internal malignancy in males. Furthermore, from about 6, 00,000 cases of prostate cancer per annum, 220,000 deaths occur each year. Prostate malignancy is the sixth most primary cause of death in males around the globe. Due to environmental and lifestyle factors, the highest prostate cancer rate was observed among the population of North America and Western Europe, while the lowest rates was observed in Asian populations [1].

Chemoprevention is defined as the use of artificial and natural substances that may gradually inhibit or alter the process of carcinogenesis. It is usually achieved by changing the regulatory and genetic system of the cell that has been altered by a carcinogen. Some strategies play a pivotal role in chemoprevention including anti-initiating, anti-promoting, and anti-progressive free radical scavenging, intensive detoxification of the carcinogens, and stimulating DNA repair mechanisms [2]. Additionally, dietary agents play an important role in the chemoprevention of prostate cancer [1]. An unhealthy diet is one of the foremost reasons for few types of cancer, such as the consumption of tea at high temperatures, alcohol, red meat, salt, a diet with low whole grains, fresh vegetables, and green tea. Prostate cancer is also prevented by the use of green tea polyphenols, namely epigallocatechin gallate. It reduces prostate cancer if consumed regularly [3]. Plant polyphenols attained significant consideration due to their antitumor as well as their anticarcinogenic characteristics. These characteristics are particular to those species of plant that produce green and black tea (-epigallocatechin-3-gallate) [4, 5]. Countries with high consumption of plant polyphenols, such as green tea and soya been foods, have a low morbidity rate of prostate cancer in the countries. [6]. Anti-oxidation characteristic of plant polyphenols stems from their capability to trap peroxyl and hydroxyl radicals. Furthermore, forage reactive oxygen species (ROS) is a well-known antioxidant property of tea catechins, it also inhibits angiogenesis [6]. Rosehip is the pseudo fruit of the rose plant, specifically *Rosa canica L*. (dog rose). It is also considered a valuable source of polyphenols and vitamin C [7]. Vitamin C can inhibit the development of carcinogens such as nitrosamines, modulate the immune response, and might promote oxidative damage (antioxidant function), resulting in cancer [8-11].

Resveratrol is a polyphenol that also acts as a cancer preventive due to its antioxidant, anti-proliferative, pro-apoptotic, anti-inflammatory, and anti-invasive properties [12, 13]. Family history, race, and age are currently the established risk factors for prostate cancer. Hence, environmental and hereditary factors may also be risk factors [14].

2. Chemopreventive Polyphenols

The term chemoprevention is used to denote a reversion or a decrease in carcinogenesis when it is in its early stages. This treatment reduces the development of invasive cancer by natural or synthetic compounds. In the last ten years, certain factors have increased the use of chemoprevention to treat prostate cancer. These factors include elevated prevalence, gradual nature of progression as well as considerable latency period [1]. Recent experiments demonstrated that a mixture of green tea and quercetin may inhibit methylation, which consequently improves the success rate for prostate cancer chemoprevention and exhibits zero practical demerits [15]. The utilization of tea, mainly green tea, has also been reported to be linked with cancer prevention [16]. The role of epigenetic factors in chemoprevention is also getting attention. The re-expression of DNA methylation-silenced tumor suppressor genes mediated by DNA methyltransferase enzymes (DNMTs) is a novel approach in chemoprevention [17]. Flavonoid and curcumin are used to develop therapeutic drugs used in chemoprevention of various types of cancer [18]. Several studies have investigated how produce could be used to create therapeutic drugs to treat cancer [19, 20, 21]. For example, pomegranate, rich in ellagic acid, inhibits markers involving migration and proliferation and initiates apoptosis and adhesion of cells within prostate cancer cell lines [22]. Tomatoes, products of tomatoes, and soy might also prove to be preventive in the initial stages of prostate cancer [23].

Hence, polyphenols are anticarcinogenic due to their antioxidant properties, which act as a safeguard against oxidative damage for DNA. Many antioxidants, such as polyphenols, restrict the initiation of redox-sensitive signals in the cell and play an essential role in chemoprevention [24]. Polyphenols manipulate the expression of several cancer-linked genes [25]. Genistein is an isoflavone abundant in soybeans. It is chemopreventive against hormone-responsive prostate malignancies and act as a radical scavenger [26]. Curcumin is also a well-known polyphenol with chemopreventive activity [27].

2.1. The Anti-Inflammatory Action of Polyphenols

Inflammation is a physical condition where the affected area experiences elevated temperature, swelling, redness, and pain as a reaction towards an infection or injury. When there is excessive inflammation, it may cause other diseases such as prostate cancer. Polyphenols have been reported to display significant anti-inflammatory characteristics [28]. Virgin olive oil also contains polyphenol content and is anti-inflammatory [29]. Similarly, intake of green tea polyphenols has also been reported to display reduced inflammation levels [30]. Catechins are also present in green tea. They act as anti-inflammatory agents by using different pathways such as modulation of NO synthase isoforms [31].

Quince peel also has several plant flavonoids. Numerous topical applications of plant extracts have been reported to contain flavonoids, which are anti-inflammatory compounds [32]. As described earlier, quercetin is a type of flavonoid that might have a vital role in reducing the threat of atherosclerosis by activating inflammatory signalling [33]. Polyphenol-rich foods, including grapes or their derivative that have anti-inflammatory characteristics, could be utilized to reduce inflammation. Grape products have also been known to lessen inflammation in several mechanisms. For instance, it might block pro-inflammatory cytokines, restrain the inflammatory expression of genes, and trigger transcription factors that provoke chronic inflammation. Hence, grape products are polyphenol-rich and can reduce chronic inflammation that is caused by obesity [34, 35].

Polyphenols could affect vascular inflammation and injury as antioxidants and modulators of signaling pathways as inflammatory redox [36]. Dietary polyphenols could also modulate signal transduction to extract their advantageous effects [6]. Polyphenols can modify the immune reaction by inducing prospective anti-inflammation activity [37].

The constituent polyphenolics of sweet potato greens are highly nutritious and show anti-inflammatory and anticancer activity [38, 39].

2.2. Antioxidant Role of Polyphenol

Epigallocatechin-3-gallate (EGCG) has a significant effect on prostate cancer. In prostate cancer cells, EGCG initiates apoptosis and growth is captured initially through p53-dependent pathways. In androgen-sensitive

LNCaP cells and PC-3 that are insensate cancer cells of the prostate, it restricts COX-2, exclusive of disturbing expression of COX-1, at both the protein and mRNA levels [40].

Polyphenols also affect the modulation of the enzymes of cytochrome P450 expression that are engaged in carcinogen initiation. They ease the emission of cytochrome P450 by raising conjugating enzymes of phase II expression. This initiation of enzymes of phase II may have its basis in polyphenol toxicity. In the body, toxic quinones can be formed by polyphenols, which act as enzyme substrates. The consumption of polyphenols might later initiate these enzymes for detoxification of cells. This enhances body's protective machinery against toxic xenobiotics. The abundant polyphenols that are present in black tea are thearubigins. Polyphenols restrict proliferation and enhance apoptosis in Du 145 carcinoma cells of the prostate [41].

Green tea, along with constituents like EGCG, initiate apoptosis, restricts cell growth, and inhibits the progression of the cell cycle. It is also reported to limit the invasion of tumour cells as well as matrix metalloprotease expression that is over-expressed in angiogenesis.It is also important in invading the basement membrane ionic barriers. In plasma, among the elevated stages of a matrix metalloprotease, two are related to metastasis in patients of prostate cancer and high Gleason score. Polyphenols in green tea restricts prostate carcinogenesis [42]. The development of PCa is a resulting process of epigenetic and genetic alterationswhich changes the normal glandular epithelium of prostrate into the preneoplastic lesions. It later mutates into invasive carcinoma.

In contrast, insulin-like growth factor I (IGF-I) occurs more than the formation of constant chromosomal defects in specific levels of CaP. NKX3.1 is a gene that is found near 8p21.2 and is engaged in the activation stage of prostatic tumour formation [43]. Curcumin has chemopreventive potential in opposition to prostate cancer. It is a specified inhibitor of nuclear factor-kappaB (NF-kB) and also an initiator of apoptosis. It has a restricted effect on EGFR phosphorylation within cells of PC-3 b-phenylethyl isothiocyanate (PEITC) taken from cruciferous vegetables. These vegetables are an extremely potent chemopreventive agent and initiate apoptosis in cancer cells of the prostate and other cell types [44].

Phenolic acids and anthocyanins have anticancer effects. Anthocyanins possess chemopreventive mechanisms, such as hunting free radicals, decreasing proliferation of the cell, initiating apoptosis, and modifying activities of MAPK. Speciality (coloured) potato (Solanum tuberosum L.) is also reported to have multiple levels of anthocyanins and phenolic acids. Little knowledge is accessible on the molecular mechanisms of the pro-apoptotic and anti-proliferative characteristics of potato polyphenols for treating prostate cancer [45].

Free radical harms the DNA, lipids, and proteins; however, they can be removed using antioxidants and the system of enzymes related to antioxidants. Flavonoids possess several biological functions. They are anti-inflammatory, have antioxidant activity, and possess several other cancer prevention functions [46].

A rate-limiting enzyme of the polyamine pathway, known as ornithine decarboxylase (ODC), plays a vital role as a target in preventing and treating prostate cancer in humans. The activity of ODC is synchronized using the specific androgens. Considerable elevation in the level of ODC enzyme activity has been observed when LNCaP cells are treated with testosterone [47]. Resveratrol, a polyphenol found abundantly in grapes, causes a decline in proliferation and an elevation in apoptosis in cancer cells [48].

Epigallocatechin gallate is the active constituent of tea polyphenols. It has a protective effect, which is mediated via radical scavenging, inhibiting the accumulation of reactive oxygen species (ROS) and blocking the activators of specific intracellular signaling pathways. It ultimately modulates apoptosis and cell cycle. It also blocks an enzyme known as ornithine decarboxylase, which triggers the proliferation of cells and avoids apoptosis. Additionally, it is known to reduce several growth factors that block angiogenesis and de-differentiation. It also initiates cell line growth [49]. Curcumin, DIM, EGCG, lycopene, and soy isoflavones all target several pathways that help prevent tumour progression [50].

Lycopene, present among all species of tomatoes, is responsible for reducing prostate cancer. It has the same properties as an antioxidant and enhances communication with cells by uplifting the gap junctions among cells and altering the cell cycle progression [51].

Abundant polyphenols found in PJ are Ellagitannins (ETs). ETs restrict the growth of the cell of PCa cells by arresting the cell cycle and initiating apoptosis. They inhibit PCa growth in vitro [52].

2.3. Calcium Channel Blocker Activity of Polyphenols

Ca^{2+} signalling is utilized in cell apoptosis, differentiation, proliferation, phenotypes, cell excitability, secretion, and contraction activities. Each cell phenotype is known to be characterized by specific action of Ca^{2+} irrespective of the cell's phenotype whether it is pathological or normal. This property has been revealed through localization, amplitude, and kinetics of signals of Ca^{2+} [53].

3. The Effect of Polyphenols on ER Calcium Homeostasis and Role in Prostate Cancer

Antitumor activity is reportedly present in polyphenols due to the consequence of pro or antioxidant stimulation in cancer cells, which advance priming of defensive tumour-suppressing immunity. In murine melanoma cells, The role of severe endoplasmic reticulum (ER) stress in apoptosis mediated by a polyphenol-rich extract of Caesalpinia spinosa (P2Et) and ICD (immunogenic cancer death of cells) was discovered. When B16-F10 cells of melanoma are examined with P2Et, considerable discrimination in the initiation of particular ER-stress mediators was demonstrated. In cells of melanoma, the initiation of PERK that is driven by P2Et was reported to improve the release of ER calcium and cause disturbance in mitochondrial membrane potential. It also enhances the up-regulation of drivers of ICD, expression of surface calreticulin, and extracellular discharge of HMGB1 and ATP [54].

A lot of research and evidence supports the fact that polyphenols have therapeutic and preventive effects against prostate cancer [55]. Consumption of green tea polyphenols is known to hinder the carcinogen processes in prostate cancer. On the other hand, epidemiological results revealed contradictory consequences of anticancer activity [56].

Cellular senescence is one of the most common issues that occur during cancer therapy. It is reported to promote recurrence, chemoresistance, and cancer relapse and is often developed by the patients undergoing chemotherapy[57]. Docetaxel is a chemotherapy medication that has been FDA-approved, it is used to deal with prostate cancer. It initiates cellular senescence to downgrade the overall survival of patients [58]. DSAs exposure has also been reported to down-regulate and reverse cellular senescence linked with p21/FOXO1/TGFβR1 signalling [59]. DSAs have been reported to induce the death of the cells via the initiation of apoptotic signalling. In the mice with PC-3 xenograft tumours, DSAs revealed targeting behaviour, anticancer activity, and anti-senescence activity by inhibition of TGFβR1 protein and regression of growth tumour. As a whole, DSAs proved to target cancer and help in cellular internalization, which promotes the efficacy of docetaxel [60].

To modulate pathways of signal transduction linked with cancer, dietary phytochemicals play a vital role. They are predominantly used for chemoprevention. The most plentiful source of phenolic compounds is olive oil, which is an essential part of the Mediterranean diet. The extraction of olive oil results in the production of a waste material that reportedly contains water-soluble polyphenols, known as 'olive mill wastewater' (OMWW) [61]. Another study reported that A009 targeted NF-κB also reduces pro-angiogenic growth factors and reduces the production of CXCL12, CXCL8, and VEGF. It also regulates IL-6/STAT3 axis. In a nutshell, these results are in agreement with the notion that food waste can be utilized to produce nutraceutical products. This would be a cost-efficient process that aids the environment as well as the industrial sector [62].

Previous studies revealed that colonic metabolites may help to prostate cancer chemoprevention through a diversified polyphenol-rich diet and the preparation of composite polyphenols. [63].

Endoplasmic reticulum (ER) stress plays a significant part in chemotherapy. Unfolded proteins may accumulate in cells due to the interruption in the endoplasmic reticulum functions, which can be detected by transmembrane sensors. The interruptions lead to the initiation of the unfolded protein response [64]. For that reason, the controlling strategy of unfolded protein response through endoplasmic reticulum stress via the naturally occurring compounds might prove to be a novel approach towards the management of cancer of the prostate. For the treatment of prostate cancer, a naturally occurring polyphenol, Tannic acid, was used to determine the unfolded protein response pathway mediated by the endoplasmic reticulum stress. This treatment restricted the clonogenic, growth, migratory, and invasive potential of prostate cancer cells [65].

Moreover, this treatment also initiates the endoplasmic reticulum stress response to change its regulatory protein expressions, such as ATF4, PDI, and Bip [66]. Moreover, in this treatment, accelerating the regulation of markers and the retardation of the pro-survival proteins, such as Bcl-xL and Bcl-2, have also been reported to be associated with apoptosis, including cleaved PARP, caspase 3, Bim, and Bak. Particular G_1 population, restricted expression of cyclin D1, reduction of MMP9 and MMP2, and restored E-cadherin have also been demonstrated by the results of this treatment [67].

4. Conclusion

This study overviews polyphenols' ability to reduce the incidence of prostate cancer. Polyphenols are widely thought to have significant potential for the treatment of prostate cancer. Polyphenols, among other dietary components, have been demonstrated to have anti-cancer properties. Dietary polyphenols, generally regarded as non-toxic, operate as critical modulators of signalling pathways, and are good chemopreventive agents. Until well-designed clinical trials could confirm their effectiveness in patients, the effect of dietary polyphenols on PCa remains uncertain. Signaling pathways could also be used as a suitable approach to minimize drug resistance. Further research and investigation are needed to determine the exact role of each polyphenol with regards to its anticarcinogenic abilities. Hence, the link between dietary polyphenols and PCa can potentially make dietary polyphenols an appropriate choice for PCa prevention and therapy.

Conflict of Interest

The authors declare no conflict of interest.

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