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REVIEW ARTICLE

# Polyphenols and cancer: A review

**Soheila Moein** [1]

[1] Biochemistry Department, Molecular Medicine Research Center , Faculty of Medicine, Hormozgan University of Medical Sciences, Banad Abbas, Iran

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## ABSTRACT

**Introduction:** Atherosclerosis, hypertension, ischemic diseases, Alzheimer's disease, Parkinson disease, cancer and inflammation emerge from imbalance between antioxidant and oxidants. Cancer is a most important public health problem in both developed and developing countries. Natural antioxidants such as polyphenols are being used for prevention and treatment cancer. Polyphenols include phenolic acids, flavonoids, stilbenes, lignanas and tannins. This article explains different activities of polyphenols in prevention of cancer and discusses the multiple approach which these phytochemicals merit proper position in therapeutic of cancer. In cancer, these compounds induce apoptosis, reduction the number of tumors, inhibition angiogenesis, modulation of multidrug resistance and antiproliferat- ive activity. In tumor cells, signal transduction cause proliferation in cancer cells. Polyphenols inhibit signal transduction such as protein kinase C, tyrosine kinase and serine/ threonine kinase. Diverse anticancer mechanisms of some polyphenols like resveratol, epigallo catechin gallate, curcumin and genestin are discussed in this article.

**Key words:** Polyphenols; Flavonoids; Anticancer properties; Antiproliferation; Signaling inhibition

*Corresponding author: Telfax: +98-761 6668479

E-mail addres: moein@hums.ac.ir (S. Moein)

## Introduction:

Oxidant compounds cause damage in cell macromolecules, such as DNA, proteins, lipids and the degeneration of somatic cells which induce the pathogenesis of differ- ent diseases [1]. These diseases include aging, cancer [2] cardiovascular disease, cataracts and suppression of immune system [3] Antioxidants of food can neutralize these damages, by scavenging reactive oxygen species or by inducing endogenous defense systems. Polyphenol compounds are the most plentiful antioxidant in our food [1]. Antioxidant activities of polyphenols have been attributed to their reducing capacities or through their possible influences on intracellular redox status [4]. In other research it was reported that, the more amounts of total phenolic compounds in plant extract (*Zhumeria majdae* ethyl acetate fraction) might be account for more antioxidant activities [5].

Recently, it was reported that many dietary phenolic compounds derived from plants possess more antioxidant properties than vitamins E or C and thus might contribute significantly to the protective effects in vivo [1].

### Cancer

Cancer is the second most usual cause of death in Europe and USA after cardio –vascular disease. Therefore efforts are being started to isolate active components from the natural sources that could be consumed to treat this very serious illness [6]. For more than a million years, man has damaged from cancer [6]. Epidemiological researches have lately presented anti-proliferative activities of polyphenols on cancer cells. For example, resveratrol is a polyphenol and has been reported as a strong antiproliferative agent [7].

Anti cancer properties of natural compounds are presented by seven strategies which include genetic instability reduction, inhibition of genes abnormal expression, inhibition of abnormal signal transduction, encouragement of normal cell-to-cell communication, Inhibition of tumor angiogenesis, and increasing the immune response [8].

### Anticancer Natural compounds

Natural products have long been used as a rich source of heal for cancer, which is estimated to become the major cause of death in this century. However, there is a persistent necessary for development of new anticancer drugs, drug combinations and chemotherapy strategies. One thousand of 25000 plants species have been recognized to have significant anticancer properties [9] and usage of plants in treatment of cancer has been reported [3,10]. In many different kinds of plants, more than 8000 phenolic and polyphenolic compounds have been recognized and a lot of them find their way into human diet [9].

It is important that more than 60% of currently used anti-cancer compounds are derived from natural sources including plants, marine organisms and micro-organisms. While in the past, cancer has been considered mostly as a group of diseases afflicting the more developed countries, the incidence of different forms of cancer is now rapidly rising worldwide. In the 1950s the search for anti-cancer agents from sources of plants was started by the discovery and development of the vinca alkaloids, vinblastine and vincristine, and the isolation of the cytotoxic podophyllotoxins [9].

### Polyphenols in prevention of cancer

Prevention of cancer is one of the most documented biological properties of the polyphenols. The effects of polyphenols on human cancer cell lines are protection and reduction the number of tumors or their growth [11]. Polyphenols impact the metabolism of pro-carcinogens by modulating the expression of cytochrome P450 enzymes which prompt their activation to carcinogens. They may also enhance their excretion by intensify the expression of conjugating enzymes, phase II. Stimulation of these enzymes may cause toxicity in polyphenols.

Polyphenols can produce toxic quinones in the body that are, substrates of these enzymes. The absorption of polyphenols could then stimulate these enzymes for their own detox-ication effects and thus, stimulate our defenses against toxic xenobiotics [12]. Polyphenols can also stimulate apoptosis of tumor cells and can suppress the angiogenesis, therefore decrease the growth of tumors. Anticancer effects of polyphenols have been monitored at different tissues, including mouth, stomach, duodenum, colon, liver, lung, mammary, and skin. Many polyphenols, such as quercetin, catechins, isoflavones, lignans, flavanones, ellagic acid, red wine polyphenols, resveratrol, or curcumin, showed protective effects in some cancerous models by different mechanisms [9]. The effects of natural compounds on phase I and phase II of carcinogens activation are illustrated in Table 1 [9].

**Table 1: Effects of natural compounds on phase I and phase II enzymes (9)**

| Compound | Effects on P450 Enzymes | Efects on Phase II Enzymes |
|---|---|---|
| **Apigenin** | Inhibits | - |
| **Caffeic acid** | - | Induces |
| **Curcumin** | Inhibits/induces | inhibits/induces |
| **Genistein and daidzein** | - | Induces |
| **Luteolin** | Inhibits | Inhibits |
| **Quercetin** | Inhibits | Induces |
| **Resveratrol** | Inhibits | - |

**Table 2: Antimutagenic/anticarcinogenic properties of polyphenols (15)**

| Dietary polyphenols | Protective effects and mechanisms | Conditions | Levels |
|---|---|---|---|
| **Hydroxytyrosol** | Inhibiting cell proliferation<br>Inducing apoptosis by arresting the cells in the G0/G1 phase with a concomitant decrease in the cell percentage in the S and G2/M phases | In human promyelocytic | *In vitro* |
| **Resveratrol** | Inhibiting cell proliferation and down regulating telomerase activity | In human colon tumor cells | *In vitro* |
| | Inducing apoptosis mediated by p53-dependent pathway | In HepG2 cells | *In vitro* |
| | Inhibiting cell proliferation by interfering with an estrogen receptor- $\alpha$ (ER $\alpha$)-associated PI3K pathway | In estrogen-responsive MCF-7 human breast cancer cells | *In vitro* |
| | Suppressing COX-2 expression by blocking the activation of MAPKs and AP-1 | In dorsal skin of female ICR mice | *In vitro* |
| | Decreasing the expression of COX-1, COX-2, c-myc, c-fos, c-jun, transforming growth factor -beta1 (TGF- $\beta$ 1) and TNF- $\alpha$ | In mouse skin | *Ex vivo* |
| | Inhibiting oncogenic disease through the inhibition of protein kinase CKII activity | In HeLa cell lysates | *In vitro* |
| | Inhibiting the Ca(2+)-dependent activities of PKC $\alpha$ and PKC $\beta$ I | On the activities of PKC isozymes | *In vitro* |
| | Inhibiting nitrobenzene(NB)-DNA adducts and NB– Hb adducts | In male Kunming mice | *In vivo* |
| **Chlorogenic acid** | Inhibiting the formation of DNA single strand breaks | In supercoiled pBR322 DNA | *In vitro* |
| **Quercetin**<br>**Luteolin** | Blocking EGFR tyrosine kinase activity | In MiaPaCa-2 cancer cells | *In vitro* |
| **Myricetin**<br>**Apigenin**<br>**Quercetin**<br>**Kaempferol** | Inhibiting human CYP1A1 activities<br>Inhibiting the formation of diolepoxide 2(DE2) and B[a]P activation | On 7-ethoxyresorufin Odeethylation | *In vitro* |
| **Silymarin**<br>**Hesperetin**<br>**Quercetin**<br>**Daidzein** | Interacting with P-glycoprotein and modulating the activity of ATP-binding cassette transporter, breast cancer resistance protein (BCRP/ABCG2) | In two separate BCRPoverexpressing cell lines | *In vitro* |
| **EGCG** | Inhibiting telomerase | In human cancer cells<br>In nude mice models | *In vitro*<br>*In vivo* |

**Polyphenols**

Polyphenols contain different compounds that are present in fruits, wine, vegetables tea, extra virgin olive oil, chocolate. They are mostly derivatives of isoflavones, flavonols, catechins and phenolic acids. They possess different biological activities such as antio-xidant, antiapoptosis, anti-aging, anticarcinogen, anti- inflammation, anti-atherosclerosis and cardiovascular protection. Most of these biological properties have been attributed to their reducing power [11].

The structures of dietary polyphenols show a great diversity of simple molecules (monomers and oligomers) to polymers [1]. One of the largest groups of the plant metabolites is polyphenols which comprise a major part of human diet. Fundamentally, the polyphenols conjugated with one or more sugar subunits which linked to hydroxyl groups, also direct linkages of the sugar to an aromatic carbon can exist [12]. Flavonoids and phenolic acids are the most abundantly polyphenols in plants which comprise 60 % and 83% respectively of dietary polyphenols [9].

**Classification of phenolic compounds**

**Phenolic acids**

The most class within the phenolic compounds is the hydroxycinnamic acids, which are extensively distributed in plant kingdom. Caffeic acid is the main hydroxyl cinnamic acid, which exits in foods mostly as an ester with quinic acid called chlorogenic [13]. Caffeic, syringic and protocathecuic acids are phenolic acids obtained directly from food intake or produced following gut metabolism of polyphenols.

**Flavonoids**

Other groups of polyphenols are flavonoids. Laboratory studies data, epidemiological researches, and human clinical trials demonstrated that flavonoids have significant effects on cancer chemoprevention and chemotherapy [14]. Flavonoids are a class with more than 4000 polyphenolic components which present naturally in foods of plant origin. These compounds have a common phenylbenzopyrone structure (C6-C3-C6), and they are divided according to the saturation level and opening of the central pyran ring, mostly into flavones, flavanols, isoflavones, flavonols, flavanones, and flavanonols. Flavonoids may be existed in the plant kingdom for more than one billion years. They are existed in all dietary plants, like fruits and vegetables [14]. Flavonoids are the most plentiful polyphenols in human diets, and are principally divided into: (a) anthocyanins, glycosylated derivative of anthocyanidin which present in colorful flowers and fruits.

(b) Anthoxanthins, a class of colorless compounds further divided into various groups, including flavones, flavans, flavonols, flavanols, isoflavones, and their glycosides deriviates [14]. Many researchers have been reported in vitro studies on the potential anticancer activity of flavonoids in diverse cell systems.

**Stilbenes**

Other group of polyphenols is stilbenes. Recent studies show that like other polyphenols, stilbenes also possesses direct antioxidant property, in comparison to dynamic valuable effects, stilbenes gets superiority over the other polyphenols. Resveratrol (3, 4, 5-trihydroxystilbene) is one of the best studied of polyphenol stilbene naturally occurres. Resveratrol is famous for its anti- carcinogenic, anti-inflammatory properties.

Lately, document suggests that stilbenes modulate the expression of genes and proteins in the tissues and cells as a signaling molecule [15].

**Lignans**

Other groups of polyphenols are lignans which are diphenolic components that include a 2, 3-dibenzylbutane structure that is constructd by the dimerization of two cinnamic acid residues. Lignans are naturally occurring compounds that are common in the plants. Some lignans, such as secoisolariciresinol, are believed to be phytoestrogens. Lignans are converted to enterodiol and enterolactone by the intestinal microflora [14].

Prevention of cancer is believed as one of the possible functions of lignans, especially against breast cancer [8]. Antitumour activities of different classes of lignans are also reported. For example, burseran, a mono epoxylignan which is extracted from *Bursera microphylla* (Burseraceae) posssesses cytotoxic activity [8].

A species, *Penstemon deustus*, which is a member of Scrophulariaceae Family composes of a furofuranoid lignan liriodendrin and can be consumed as a cytotoxic factor [8]. Styraxin, another furofuran lignan, obtained from *Styrax officinalis* (Styraxaceae), also has antitumour potential [8]. The Antimutagenic/anticarcinogenic properties of polyphenols are illustrated in Table 2, [11]. Phenolics may retard carcinogenesis by affecting the molecular

processes in the initiation, promotion, and progression phases. They controlled the secretion of protein kinases in tumor cell proliferation, and induced the expression of anticarcinogenic enzymes or suppressed the cancer-promoting enzymes [16]. Phenolic antioxidants in the medicinal plants and their properties play a role in inhibiting and treating cancer [17]. Another property of polyphenols for prevention of cancer is anti-proliferative activity [18]. Another anticancer mechanism of polyphenols is mobilization of endogenous copper, perhaps chromatin bound copper and the consequent prooxidant action [19].

Polyphenols may stimulate changes in the signaling pathway and subsequent gene expression. Natural polyphenols inhibit the activity of one or several protein kinases. For example, myricetin inhibits MAPK kinase 4 (MKK4) directly by competing with ATP [11].

**Antitumor potentials of curcumin**

Antitumor potentials of curcumin presented by inhibition of cellular proliferation and angiogenesis, prevention of tumor cell cycle, antikinase activity and inducing programmed cell death in vitro and in vivo [20]. Also it was reported that curcumin could control NF-KB activation AP-1 DNA binding, signal transducer and activator of transcription-3 (STAT 3) phosphorylation in vitro [11].

**Anticancer mechanism of genestin**

Targeting specific of protein kinases to attack cancer shows a major focus of oncolo-gy research within the so named targeted therapy approach. The anti-kinase activity of some polyphenols, including mostly curcumin and the green tea polyphenol **(**15**)**-epigallocatechin 3-gallate (EGCG) was reported. Inhibition of protein kinases are a well-established class of clinically beneficial drugs, especially for the treatment of cancer [13]. DNA topoisomerase II is an enzyme that catalyzes the breakage of double-strand and rejoining of DNA; it is essential for several cell functions [21]. Several flavonoids, containing genestin which suppress DNA topoisomerase II activity by stabilizing the cleavage complex there by promoting apoptosis [22-23].

**Anticancer mechanism of resveratol**

Resveratrol arrests cell cycle and causes apoptosis in many human cancer cells, such as prostate cancer cells, colon adenocarcinoma cells and esophageal carcinoma cells. The induction of apoptosis by resveratrol has been showed to be related with intensified caspase activity, cell cycle dysregulation, decreased Bcl-2 and Bcl-XL levels, and increas-ed Bax levels [24]. The other anticancer mechanism of resveratrol is that resveratrol–Cu (II) is indeed capable of inducing DNA degradation in cancerous cells. Resveratrol could protect in vitro through activation PI3-kinase/Akt pathway, MAPK proteins, ERK (extracellular signal-regulated protein kinase), JNK (c-jun N-terminal kinase), P38 and the transportation into the nucleus of Nrf2. Resveratrol could activate MnSOD (superoxide dismutase), and HO-1 expressions against oxidative stress by MAPK-ARENrf2 pathway in PCcells [13].

**Anticancer mechanisms of EGCG**

Gallocatechins are components of green tea, which the usage of it is considered to reduce the risk of various cancers such as those of bladder, prostrate, esophagus and stomach [7]. It is believed that anticancer and apoptosis properties of green tea are caused by its polyphenolic constituents specially catechins. Also it is reported that green tea contains polyphenol epigallocatechin-3-gallate EGCG [25]. The anticancer mechanisms include, the retardation of specific protein kinase activities, blocking receptor-mediated functions and inhibition of proteases.

**Anticancer mechanisms of flavonoids**

Flavonoids of *Astragalus mongholicus* possess anti-injury and anti-mutation properties. Also, these components possess an important suppression effect on human hepatocellular carcinoma BEL-7402 cells and induce the cell cycle retardation in the G0/G1 phase, particularly in G1 phase.

Cyclin D1 starts to express between the G0 and G1 phases and participates in the regulation of the G1 phase by linking to cyclin-dependent kinases 4 (CDK4) and 6 (CDK6), conducting to the progression of the cells into the S phase (replication of DNA). Uncontrollable expression of cyclin D1 deregulation of the cell cycle will be caused by CDK4/CDK6. Flavonoids can notably decrease the expression of cyclin D1, which is likely related to the effects of these compounds in inhibiting the propagation of K562 and maintaining more cells in G0/G1 phase [26]. Suppression of angiogenicprocess and modulation of multidrug resistance [26].

**Inhibition of signal transduction**

Signal transduction is the entrance of a signal from outside of the cell toward the cell's nucleus, where it can induce proliferation or other activities [27]. There are different protein kinases like protein tyrosine kinase (PTK), protein kinase C and ras protein which cause proliferation of cells especially in cancer cells. Protein tyrosine kinase inhibitorsprone to decrease the proliferation of cancer cells more than that of normal cells [27]. Like protein tyrosine kinase, protein kinase C (PKC) aids transfer of chemical signals through the cell, and a wide range of procancer events depend on high abnormally of PKC activity occurred [9]. Ras proteins play a role in signal transduction and are usually overproduced in cancer cells [27]. Activation of ras, in turn, induces the phosphorylation of the kinases series raf, MEK and MAPK. MAPK activation plays a central role in initiating cell proliferation [27].

## Conclusion:

Polyphenols are effective in cancer treatment especially when consumed in synergistic mixtures. Even flavonoids like anthocyanidins and proanthocyanidins, which are doubtfully to retard progression of cancer through direct cytotoxicity, may be more effective when consumed in mixture. Their consumption in mixture could intensify the overall anticancer effects by intensify the number of procancer events targeted [27].

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