Dietary Components That Protect from Cancer: Polyphenols

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Polyphenols are potential candidates for the discovery of anticancer drugs. Polyphenols are defined as compounds having at least one aromatic ring with one or more hydroxyl functional groups attached. Natural polyphenols refer to a large group of plant secondary metabolites ranging from small molecules to highly polymerized compounds

Based on chemical structures, natural polyphenols can be divided into five classes, including flavonoids, phenolic acids, lignans, stilbenes and other polyphenols. Flavonoids and phenolic acids are the most common classes, and account for about 60% and 30% of all natural polyphenols, respectively

The anticancer efficacy of natural polyphenols has largely been attributed to their potent antioxidant and anti-inflammatory activities as well as their abilities to modulate molecular targets and signaling pathways, which were associated with cell survival, proliferation, differentiation, migration, angiogenesis, hormone activities, detoxification enzymes, immune responses..

A high dietary intake of total flavonoids on lung cancer risks. For women, the intake of total flavonoids, as well as flavones and anthocyanidins, was inversely associated with the risk of gastric cancer.

For colorectal cancer, the protective roles of high dietary isoflavone intake. The dietary intake of total flavonoids and lignans might decrease colorectal cancer risks

The risk of breast cancer was reduced in women with a high intake of flavonols and flavones. Studies also suggested that soy isoflavone intake reduced breast cancer risk for Asian women..

For hepatocellular carcinoma (HCC), the European Prospective Investigation into Cancer and Nutrition suggested that a high intake of dietary flavanols, but not total flavonoids, might modestly decrease HCC risks

Flavonoids in the Diet

Among chemopreventers, one of the most studied group of antioxidant compounds are flavonoids. Flavonoids are a large heterogeneous group of benzo-γ-pyrone derivatives that share a common carbon skeleton of dyphenylpropanes and can be divided into six different classes, namely flavonols, flavones, flavanones, flavanols, isoflavones and anthocyanidins, according to their molecular structure

Flavonoids in the Diet

Flavonoids are largely present in fruits, vegetables, aromatic plants, medical herbs, tea and red wine. The average daily intake of the most abundant flavonoids, catechins, is ~100 mg. Similar to daily intake, it is also quite complex to assess and quantify the bioavailability of flavonoids. Nevertheless, metabolized forms of flavonoids present in blood significantly differ from the native compounds, and plasma concentration of total metabolites can have a range 0–4 μmol L^{-1} with an intake of 50 mg of aglycone, which is the non-sugar compound left after partial metabolization of the original flavonoid.

Cancer Chemoprevention by Flavonoids: Molecular Mechanisms

- ✓ Flavonoids exert positive preventive effects in carcinogenesis and neurodegenerative disorders essentially because of their antioxidant activity, their capacity to affect the expression of several detoxifying enzymes, and their ability to modulate protein signaling cascades.
- ✓ Flavonoids can interfere with specific stages of the carcinogenic process, and can inhibit cell proliferation and induce apoptosis in several types of cancer cells.

EGCG is one of the most intensively studied flavonoids as it is the major polyphenolic component of green tea. EGCG inhibits cell proliferation and induces apoptosis in several human tumor cell lines, including;

- ✓ cervical cells,
- ✓ laryngeal squamous carcinoma cells,
- ✓ bladder urothelial cells,
- ✓ melanoma cells,
- ✓ adrenal cancer cells and
- ✓ A549 lung cancer cells

The mechanisms by which apoptosis is triggered differ depending on the cell line and include via death receptor, or via mitochondrial and endoplasmic reticulum-dependent pathways

- ✓ The cancer-preventive properties of flavonoids can be attributed to their capacity of quenching ROS, reactive nitrogen species (RNS) and other radicals.
- ✓ Tea catechins, especially EGCG, react with superoxide radical, hydroxyl radical, peroxyl radical and peroxynitrite.
- ✓ **Resveratrol**, present in red wine, grapes and peanuts, is a scavenger of superoxide and peroxynitrite radicals, and **genistein**, mainly derived from soy, can scavenge exogenous or endogenous hydrogen peroxide in cell models.
- ✓ Moreover, flavonoids exert their protective antioxidant effect not only by quenching ROS, but also by modulating the activity of several detoxifying enzymes, including lipoxygenase, cycloxygenase, inducible nitric oxide synthase, monoxygenase, xanthine oxidase and NADH oxidase.
- ✓ Among enzymes that are inhibited by flavonoids, thioredoxin reductases have to be quoted, as they are involved in cellular redox control, and are overexpressed in different aggressive tumors

- ✓ Growing evidences suggest that flavonoids (in particular, resveratrol and quercetin) may contribute to chromatin remodeling and thus interfere with epigenetic alterations that are important in cancer progression. Chromatin is remodeled by chemical modifications of DNA and histones, such as DNA methylation and multiple histone modifications, such as methylation, phosphorylation, acetylation, sumoylation and ubiquitination; for example, resveratrol activates sirtuin (SIRT)-1, a member of histone deacetylase (HDAC) family, which plays key roles in cell survival and apoptosis
- ✓ The network of SIRT1-modulated signals is wide and complex, and involves SIRT1 direct interactions with several proteins involved in cell survival (p53), DNA repair and cell cycle/apoptosis (β-catenin, NFκB). The activation of SIRT1 by resveratrol induces the formation of SIRT1-p300 complexes, causing the inactivation of p300 acetyltransferase and a reduction in the acetylation of both β-catenin and NFκB-p65.
- ✓ The main consequence of this phenomenon is the downregulation of the multidrug resistance (MDR)-1 and Bcl-xL genes with the subsequent stimulation of cell death, as well as the reduction of chemoresistance in breast tumor cells

Among anthocyanins, delphinidin possesses strong anticancer activities. Studies have shown that delphinidin treatment induced apoptosis and cell cycle arrest in several types of cancer. This effect might be due to suppression of the NF-κB pathway. A study found that two anthocyanins extracted from black rice, peonidin-3-glucoside and cyaniding-3-glucoside, could induce apoptosis and selectively decrease cell proliferation and tumor growth of human epidermal growth factor receptor 2 (HER2) positive breast cancer.

Peonidin-3-glucoside treatment significantly suppressed invasion and metastasis of lung cancer cells by down-regulating the matrix metalloproteinase (MMP). In similar ways, cyanidin-3-O-sambubioside from *Acanthopanax sessiliflorus* fruit inhibited angiogenesis and invasion of breast cancer cells

Though anthocyanins are usually considered as antioxidants, a study showed that certain anthocyanins (cyanidin and delphinidin) exhibited oxidative stress-based cytotoxicity to colorectal cancer cells. It is the impact of chemical structures on chemopreventive activities of anthocyanins in colon cancer cells.

The apoptosis induced by treatment of xanthohumol to HepG2 liver cancer cells was due to modulation of the NF-κB/p53 signaling pathway.

Another study reported that xanthohumol treatment mediated anticancer activity in human liver cancer cells through suppression of the Notch1 signaling pathway. In addition, xanthohumol could block the estrogen signaling pathway. By doing so, it selectively suppressed the growth of breast cancer both in vitro and in vivo.

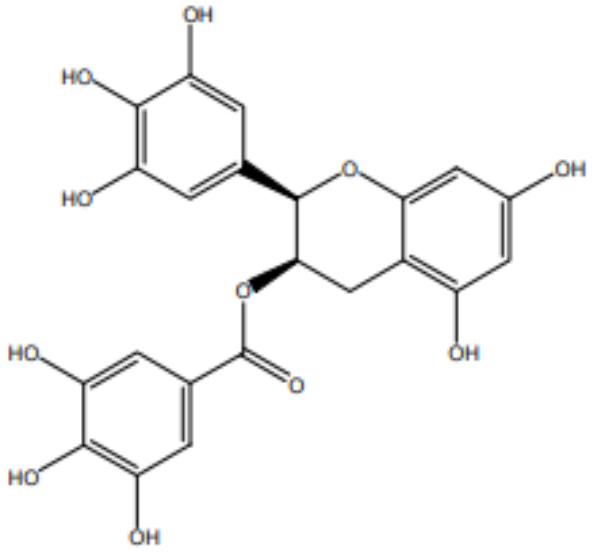
In another study, by promoting production of reactive oxygen species (ROS), xanthohumol treatment inhibited the progression of advanced tumor and the growth of poorly differentiated prostate cancer.

3. Flavanols

Flavanols, also known as flavan-3-ols, have the most complex structures among subclasses of flavonoid. Flavanols include simple monomers (catechins) as well as oligomers and polymers, the latter two are known as proanthocyanidins or condensed tannins. Flavanols can be commonly found in foodstuffs

3.1. Epigallocatechin gallate (EGCG)

EGCG (Figure 3) treatment suppressed nicotine-induced migration and invasion of A549 lung cancer cells in vitro as well as in mice through inhibiting angiogenesis and epithelial-mesenchymal transition (EMT)



The chemical structure of EGCG.

The effects of EGCG varied with dose. In lung cancer cells, at concentration of 5–20 μM, EGCG effectively suppressed the invasion and migration through suppressing MMP-2 expression. While at higher concentration (>20 μM), it exhibited anti-proliferation activities through induction of G2/M cell cycle arrest but not apoptosis…

Many signaling pathways might be affected by EGCG treatment. A study showed that EGCG (20 μM) exerted anti-proliferative effects in gastric cancer cell by preventing the β-catenin oncogenic signaling pathway.

Another study on colon cancer suggested that extracellular signal-related kinase (ERK) 1/2 and alternative p38MAPK signaling pathways were involved in the chemopreventive effects of EGCG.

The combination of EGCG and sodium butyrate inhibited DNA methytransferases and histone deacetylase in colorectal cancer cells, thus modulating global DNA methylation and histone modifications..

The cancer stem cell plays a key role in chemoresistance and recurrence. Both in vitro and in vivo studies showed that EGCG could suppress cancer stem cell growth of colorectal cancer as well as breast cancer

The anticancer activities of EGCG might involve modulation of hormone activities. It is known that exposure to estrogen is an important risk factor of breast cancer.

4.1. NARINGENIN

Naringin is a flavanone glycoside found in grapes and citrus fruits. It possesses the distinct bitter taste of grapefruit juice. Two rhamnose units are attached to its aglycon portion, naringenin, at the 7-carbon position. Naringin contents in various citrus species are summarized in Table 1. Both naringin and naringenin are strong antioxidants, however, naringin is less potent compared with naringenin because the sugar moiety in the former causes steric hindrance of the scavenging group. Naringin is moderately soluble in water. The gut microflora breaks down naringin to its aglycon naringenin in the intestine; it is then absorbed from the gut..

In A549 lung cancer cells, naringenin treatment enhances apoptosis by up-regulating the expression of death receptor.

In gastric cancer cells, naringenin treatment inhibites cancer cell proliferation, invasion, and migration and induced apoptosis.

Naringenin treatment to HepG2 liver cancer cells induces mitochondrial-mediated apoptosis and cell cycle arrest through up-regulation of p53.

In breast cancer cells, naringenin demonstrates anti-estrogenic activity in estrogen-rich status and estrogenic activity in estrogen-deficient status.

In addition, oral administration of naringenin suppressed breast cancer metastases after surgery by modulating the host immunity..

In gastric cancer cells, hesperetin treatment decreased cell proliferation andinduced mitochondria-mediated apoptosis via promoting intracellular ROS accumulation. Meanwhile, the compound significantly suppressed the growth of gastric cancer in mice…

In breast cancer cells, hesperetin induced growth inhibition also involved mitochondria-mediated apoptosis,increased ROS and activationof JNK pathway..

Cancer cells usually have high levels of glucose uptake and metabolism, which plays an important role in tumor growth. A study suggested that the anti-proliferative effects of hesperetin on breast cancer were possibly due to the suppression of glucose uptake.

Another study found that hesperetin treatment decreased proliferation and induced apoptosis in prostate cancer cells, which was likely mediated by inhibition of the NF-κB pathway.

In addition, hesperetin exhibited potential anticancer effects on cervical cancer cells through the induction of apoptosis..

Treatment of apigenin induces apoptosis and DNA damage in H460 lung cancer cells by increasing ROS production.

Apigenin induces apoptosis in gastric cancer cells..

Helicobacter pylori

infection is known to cause ulcers and is possibly linked to gastric cancer. Gastritis was suggested to be a critical step in Helicobacter pylori induced carcinogenesis. A study found that apigenin administration could prevent Helicobacter pylori-induced atrophic gastrit is as well as gastric cancer development

- ✓ Luteolin potently inhibits human cytochrome P450 (CYP) 1 family enzymes thereby suppressing the mutagenic activation of carcinogens

- ✓ Luteolin is able to inhibit the proliferation of cancer cells derived from nearly all types of cancers, mainly through regulating the cell cycle

- ✓ Luteolin kills cancer cells by inducing apoptotic cell death in many types of cancer cells, including epidermoid carcinoma, leukemia, pancreatic tumor, and hepatoma

- ✓ Luteolin also activates the apoptosis pathway through inducing DNA damage and activating p53

LUTEOLIN AS AN ANTICANCER OR CHEMOPREVENTION AGENT

Luteolin induces apoptotic cell death in a variety of cancers, inhibits cancer cell proliferation, and suppresses tumor angiogenesis. Thus, luteolin is expected to be a putative anticancer therapeutic.

Combination therapy with distinct anticancer drugs can improve the therapeutic value of the combined agents by allowing the use of lower, subtoxic doses to achieve more effective cancer cell killing.

Cancer cells often have constitutively activated cell survival pathways Cancer therapeutics also activate these pathways, dampening their cancer cell-killing activities [142,143]. Thus, luteolin's suppression of the constitutive or drug-induced cell survival pathways contributes to the sensitized anticancer activity. Additionally, luteolin is also capable of promoting apoptotic pathways.

Based on the observations that luteolin is able to interfere with almost all the aspects of carcinogenesis, and it is relatively safe for animals and humans, it is assumed to be a potential chemopreventive agent against cancer through blocking cell transformation, suppressing tumor growth, and killing tumor cells. Using luteolin to suppress chronic inflammation can potentially prevent inflammation-associated carcinogenesis.

6.1 QUERCETIN

Quercetin (Qu) is considered an excellent free-radical scavenging antioxidant, even if such an activity strongly depends on the intracellular availability of reduced glutathione. Apart from antioxidant activity, Qu also exerts a direct, pro-apoptotic effect in tumor cells, and can indeed block the growth of several human cancer cell lines at different phases of the cell cycle. Both these effects have been documented in a wide variety of cellular models as well as in animal models. The high toxicity exerted by Qu on cancer cells perfectly matches with the almost total absence of any damages for normal, non-transformed cells.

Qu and Its Molecular Role in Cancer Chemoprevention

Qu (3,3′,4′,5,7-pentahydroxyflavone) is an important dietary flavonoid, present in different vegetables, fruits, seeds, nuts, tea and red wine. The average daily intake of Qu can reach 30 mg, and its bioavailability depends on the metabolic form present in the food. Qu obtained from plant source is in the form of Qu-glucose conjugates (Qu glucosides), which are absorbed in the apical membrane of the enterocytes.

Once absorbed, Qu glucosides are hydrolyzed to generate Qu aglycone which is further metabolized to the methylated, sulfonylated and glucuronidated forms by the enterocytic transferases. Qu metabolites are then transported first to the intestinal lumen, and then to the liver, where other conjugation reactions take place to form Qu-3-glucuronide and Qu-3′-sulfate, which are the major Qu-derived circulating compounds in human plasma. Qu bioavailability, when Qu is absorbed in the form of Qu glucosides, the peak plasma concentration ranges from 3.5 to 5.0 μmol L^{-1}. In the unconjugated form, Qu absorption is less efficient.

- ✓ Qu is considered an excellent free-radical scavenging antioxidant owing to the high number of hydroxyl groups by which Qu can donate electrons or hydrogen, and scavenge H_2O_2 and superoxide anion ($\bullet O_2^-$)

- ✓ Qu also reacts with H_2O_2 in the presence of peroxidases, and thus it decreases H_2O_2 levels and protects cells against H_2O_2 damage; nevertheless, during the same process potentially harmful reactive oxidation products are also formed. The first oxidation product of Qu is a semiquinone radical. This radical is unstable and rapidly undergoes a second oxidation reaction that produces another quinone (Qu-quinone, QQ). Since QQ can react with proteins, lipids and DNA, it is responsible for protein and DNA damage as well as lipid peroxidation. As far as DNA is concerned, QQ can mediate DNA strand breaks and can induce the oxidation of 2′-deoxyguanosine to form 8-hydroxy-2′-deoxyguanosine.