

Cancer chemoprevention is defined as the application of natural or synthetic agents to suppress or reverse cancer development and progression. In this field especially diet derived compounds have recently attracted researchers' attention as potential therapeutics generally exerting low toxicity compared with regular drugs. This review presents a survey of recent findings concerning the most promising dietary chemopreventive agents such as green tea polyphenols (i.e. catechins), long-chain polyunsaturated fatty acids, carotenoids, glucosinolates/isothiocyanates, vitamins (i.e. vitamin D and folate) and minerals (i.e. calcium and selenium). Molecular targets involved in intrinsic pathways affected by these natural compounds are also shortly discussed.

**Key words:** cancer chemoprevention, green tea polyphenols, polyunsaturated fatty acids, glucosinolates, carotenoids.

# Dietary derived compounds in cancer chemoprevention

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## Introduction

As there is overall agreement that preventing disease is more desirable than curing, a multitude of potential chemopreventive compounds are under investigation. The term chemoprevention, first introduced by Sporn, means inhibiting, suppressing or reversing cancer development and progression with the use of natural or synthetic agents [1]. Chemopreventives should be characterized by low toxicity comparable with therapeutic drugs and a possibility to be taken orally [2, 3]. Nowadays, a new definition of chemoprevention can be stated and it can be described as the use of compounds suppressing or reversing the molecular pathways leading to cancer development and metastasis [4, 5].

Different dietary patterns in distinct countries are related to higher or lower incidences of cancer development in these ethnic groups, which confirms an inverse association between food borne preventive compounds and carcinogenesis. Lower incidence of breast, prostate and gastrointestinal tract cancer were always observed for Asian populations [6–8]. Migration of people and adopting nutritional habits leads to alterations in cancer types and rates [WHO]. Diet derived compounds broadly studied for their chemopreventive activity include a wide group of polyphenols (i.e. green tea polyphenols, soy flavonoid genistein, quercetin from onions, resveratrol from grapes or curcumin), polyunsaturated fatty acids (n-3 PUFAs), carotenoids (i.e.  $\beta$ -carotene, lycopene or lutein), vitamins (D, E, C or folic acid) and minerals (Se, Zn, Ca) as well a dietary fiber.

## Diet-derived chemopreventive agents

For many years it has been believed that diet can influence various diseases and the impact is often positive for the human organism. It was suggested already two and half thousand years ago by Hippocrates, who said "Let food be thy medicine and medicine be thy food". Diet can deliver both pro-healthy and harmful substances. Some can act as carcinogens and initiate or stimulate tumor growth. However, food includes an abundance of bioactive compounds which are beneficial to the human organism. There are data indicating a negative relationship between sufficient vegetable and fruit intake and cancer incidence. What is more, laboratory studies confirm this inverse association. It has been found that the risk of cancer incidence is half for people who eat at least five servings of fruits and vegetables per day [9]. A well-balanced diet should provide a rich source of macronutrients (omega-3 fatty acids, fiber) and micronutrients (i.e. selenium, calcium, vitamin D and E, folates) [10, 11], as well as phytochemicals (i.e. polyphenols, flavonoids, carotenoids) [4], which exert cancer preventive activities. Various ways of administration are proposed to deliver such food derived compounds in populations with normal risk of cancer. They include simple daily consumption of fruits and vegetables or functional food enriched with several phytochemicals. Food extracts can also be applied as food supplements [4, 12].

## Green tea polyphenols

Next to water, tea is the most widely consumed beverage in the world. It was estimated that mean consumption of tea per day is around 120 ml per person [15]. Green tea, always popular in China, Japan and India, now has gained popularity in many other countries. Black, oolong and green tea is derived from the same plant, *Camellia sinensis*, which is exposed to different processing methods before consumption. To obtain black tea the leaves of *Camellia sinensis* are fermented for a long period of time, which leads to formation of polymeric compounds, i.e. theaflavins and thearubigins. Oolong tea, often called half fermented, due to shorter fermentation time, contains polymeric as well as monomeric polyphenols. Non-fermented green tea is made from fresh tea leaves exposed to steaming and drying (to eliminate the oxidation process by inactivating the polyphenol oxidase) and contains an abundance of polyphenols naturally occurring in *Camellia sinensis* [14, 15]. Green tea contains proteins (including enzymes), amino acids, carbohydrates, lipids, vitamins (B, C, E) and minerals (i.e. Ca, Mg, Cr, Fe, Zn, F, K) [13]. Green tea has been found to exert a beneficial effect on the human organism and, although results are mixed, a number of studies have revealed a correlation with a reduction of chronic disease risk, including cancer (e.g. breast, esophageal, lung, colorectal, stomach, bladder, kidney, prostate, skin, pancreatic, ovarian) [13, 16–18], cardiovascular heart disease (coronary heart disease, hypertension, atherosclerosis) [19], Parkinson disease [20], and Alzheimer disease [21]. Green tea can also promote oral health [22, 23] and bone health [24]. Consumption of this beverage is also being linked with anti-ageing processes, mainly due to its antioxidant properties [14, 15].

The positive health effect of green tea is mostly associated with the abundance of polyphenols, particularly flavonoids. Catechins (flavan-3-ols) make up a major group of flavonoids present in green tea leaves, including epicatechin (EC), epicatechin-3-gallate (ECG), galliccatechin (GC), epigallocatechin (EGC) and predominant (-)-epigallocatechin-3-gallate (EGCG), which constitute approximately 60% of total catechins. Widely studied medical implications are mainly attributed to *epi*-catechins [14, 15]. It has been shown in animal studies that tea polyphenols, especially epigallocatechin gallate, influence several steps of carcinogenesis, including initiation, promotion and progression phases [25]. Three major mechanisms of action may benefit human health, including antioxidative, anticancer and antiangiogenic effects [14, 15, 26].

### Antioxidant activity

Green tea polyphenols are responsible for significant and widely studied antioxidant properties of this beverage. Together with reactive oxygen and nitrogen species' scavenging ability, they exert beneficial effects on the human organism, protecting against harmful cigarette smoke, pollution or stress as well as cancer development [26]. It has been revealed that catechins obtained from *Camellia sinensis* show higher antioxidant potential than generally known antioxidants, vitamin E and C [14, 27]. Epigallocatechin gallate (EGCG) after epicatechin gallate (ECG) is the most effective of tea catechins. Their phenolic hydroxy groups on B and D rings

are responsible for radical scavenging properties [14, 27]. Moreover, they have the ability to chelate metal ions such as iron and copper, thus leading to decreased hydroxylic radical creation through inhibition of Fenton and Haber-Weiss reactions [13]. Besides direct antiradical influence, they can also suppress redox-sensitive transcription factors or activate antioxidant enzymes, i.e. superoxide dismutases [15].

### Anticancer activity

Green tea polyphenols were shown to reduce the risk of a multitude of cancer types (see above). It is still not clear if the influence of green tea catechins on many molecular targets is attributed to their antioxidant activity or they directly and independently affect these cell signaling pathways [14]. Polyphenols from *Camellia sinensis* may act through stimulation of apoptosis in cancer cells, both by inactivating anti-apoptotic (Bcl-2, Bcl-Xl) and up-regulating pro-apoptotic (Bax, Bak, Bim, PUMA) proteins. Induced caspase-3 and -9 activities have also been shown [16, 29, 30]. The induction of cell cycle arrest in cancer cells by EGCG and other catechins has been broadly studied. It was reported that they stimulate the expression of p21 and p27 proteins, with simultaneous inhibition of cyclin D1, cyclin-dependent kinase 2 and cyclin-dependent kinase 4, thus leading to G1 growth arrest [14, 16, 31]. Multiple signaling cascades engaged in cell survival, proliferation, differentiation and metabolism were found to be influenced by green tea polyphenol activity. Mitogen-activated protein kinases (MAPK) and Akt kinase were established as molecular targets of EGCG activity. EGCG was also shown to inhibit cancer cells' growth-promoting activity of growth factors (i.e. epidermal or insulin growth factor) [16, 31].

As migration and invasion play a crucial role in cancer metastasis to other tissues it is of high importance to stop these processes. It was reported that EGCG can affect the phase of tumor progression and it was attributed to direct or indirect inhibition of metalloproteinase (MMP) activity [16, 31, 32].

### Antiangiogenic activity

Creation of new blood vessels from pre-existing ones inside a tumor, called angiogenesis, promotes cancer development through its nourishment and oxygenation. Besides inhibiting activity of metalloproteinases which are involved in angiogenesis, EGCG was revealed to affect vascular endothelial growth factor (VEGF) binding ability to its receptor. VEGF is closely related to tumor-induced angiogenesis, acting as a mitogen factor for endothelial cells [16, 31, 33]. An independent study also revealed the ability of EGCG and green tea extract to inhibit the secretion of VEGF protein [34].

### Polyunsaturated fatty acids (PUFAs)

A multitude of epidemiological studies have indicated an association between polyunsaturated fatty acid consumption and cancer risk, especially breast, prostate and colon cancer [35–37]. A protective effect of the long-chain PUFAs is also revealed by *in vitro* and animal studies [38–41]. The ratio of consumed n-6 to n-3 polyunsaturated fatty acids seems to play the major role in cancer development [42]. They are not synthesized in humans (essential fatty acids), so they must

be supplemented with diet. The metabolic precursors of n-3 PUFAs [i.e. eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and n-6 PUFAs (i.e. arachidonic acid (AA),  $\gamma$ -linolenic acid (GLA)], are respectively  $\alpha$ -linolenic acid (ALA, n-3) and linoleic acid (LA, n-6) [43]. Linoleic acid is found in large amounts in sunflower, soy and corn oils, while ALA is present in linseed and rapeseed oils. Long-chain fatty acids n-3 can be found in cold-water fish, including herring, halibut, salmon, mackerel and tuna, or warm-water fish like cod [7, 43, 44]. Since the same enzymes are engaged in LA and ALA conversion to subsequent polyunsaturated PUFAs, diet may have an important influence on types of fatty acids present in the body. However, reactions of interconversion to some n-3 fatty acids (i.e. DHA) are very inefficient; thus supplementation of the diet with these fatty acids seems to be the most efficient way to elevate their concentrations in plasma and tissue [45].

Although diet rich in dietary fat is often linked with increased risk of cancer, especially hormone-dependent cancer incidence, the types of consumed fatty acids have a significant impact. A preventive effect of n-3 PUFAs and cancer stimulating effect of n-6 PUFAs is suggested [45]. Nowadays, Western diets are rich in n-6 PUFAs due to high plant oil intake and industrial meat production from animals fed with grains containing n-6 fatty acids. The ratio of n-6 to n-3 fatty acids has increased and is in the range 15–20 : 1, while it should be 4–5 : 1 [46, WHO]. Changing dietary patterns in populations originally consuming large amounts of n-3 PUFAs, e.g. Japanese, may be responsible for elevated breast cancer incidence [7].

#### *Chemopreventive activity of n-3 PUFAs*

Dietary PUFAs exert a suppressing (n-3) or promoting (n-6) effect on cancer mainly through their derivatives, eicosanoids, hormone-like lipids. Prostaglandins (PG), thromboxanes (TX) and leukotrienes (LT) are synthesized in enzymatic reactions with use of cyclooxygenases (COX) and lipoxygenases (LOX). The n-3 and n-6 long chain fatty acids compete for the enzymes and eicosanoids derived from them reveal opposing effects on cell proliferation, differentiation, angiogenesis, metastasis and inflammatory responses [32, 45]. The first step of eicosanoid production is the hydrolytic release of PUFA from the cell membrane. Since arachidonic acid (AA, n-6) is the most abundant PUFA among phospholipids in cell membranes, pro-inflammatory and cancer promoting eicosanoids are mainly produced. Diet enrichment with n-3 PUFAs may silence the effect of AA-derived eicosanoids through replacement of AA in membranes, thus increasing the amount of precursors for biosynthesis of cancer suppressing prostaglandins and leukotrienes [47]. Moreover, high consumption of n-3 long chain fatty acids leads to decreased production of AA from LA, due to stronger affinity of n-3 than n-6 PUFAs to enzymes involved in this process [42, 43].

It was revealed that PUFAs and their derivatives may influence several molecular signaling pathways involved in basic processes including cell growth, differentiation, apoptosis or metastasis. The n-3 PUFAs were found to down regulate protein kinase C and ras [48, 49], ERK1/2 [50], NF $\kappa$ B [51] and COX-2 [52]. Activation of PPAR- $\gamma$  receptor by DHA was

shown to stimulate cell apoptosis [53]. Animal and human studies demonstrated the protective effect of EPA and DHA against free radicals and reactive oxygen species formation [42, 54, 55].

#### *Glucosinolates/isothiocyanates*

Crucifers (the plant family *Cruciferae*, also known as *Brassicaceae*) include several widely consumed vegetables, e.g. cabbage, broccoli, cauliflower, parsnip, Brussels sprouts, radish, horseradish, turnip and kale [56]. Epidemiological data suggest an inverse association between cruciferous vegetables intake and risk of many cancers, e.g. lung, breast, stomach, pancreas, prostate, bladder, thyroid, skin and colon cancer. Significantly, this correlation was found to be more prominent than the general effect linked to vegetable and fruit consumption [56, 57]. Despite the variety of bioactive compounds present in crucifers, i.e. polyphenols, minerals and vitamins, a superior role in cancer prevention is ascribed to glucosinolates and their decomposition products, isothiocyanates [58]. Glucosinolates (GS) characterized to date are a well-defined group of chemical compounds consisting of three basic structures including a  $\beta$ -D-thioglucose group, sulfonated oxime group and side chain derived from one of the protein amino acids [59]. Due to the acidic nature of sulfate groups, in plants glucosinolates are accumulated as potassium salts sequestered to vacuoles and probably protect against herbivores and microbes [60]. Glucosinolates are highly stable and when consumed cannot act as bioactive compounds until subjected to enzymatic hydrolysis due to myrosinase action. This  $\beta$ -thioglucosidase is released from myrosin cells when crucifers are subjected to cutting or mastication and catalyze hydrolysis of the glycoside bond [61]. Glucosinolates commonly found in cruciferous vegetables include gluconasturtiin, sinigrin, glucoraphanin and glucobrassicin, which are hydrolyzed, resulting in creation of phenyl isothiocyanate, allyl isothiocyanate, sulforaphane and indole-3-carbinol, respectively [58]. The overall content and form of GS within plants are strongly affected by environmental conditions such as location, soil conditions and time of harvest. Importantly, the total amount of glucosinolates varies due to conditions of processing and domestic cooking, considering thermal degradation and washout occurrence [56, 59].

Several mechanisms of cancer protection by glucosinolates/isothiocyanates have been proposed. The most studied is the influence of the compounds on detoxification pathways leading to increased activity of phase I and phase II enzymes and resulting in lowered amounts of carcinogens within the body due to their decreased formation as well as increased excretion. Moreover, altered activity of the enzymes was reported *in vitro* and *in vivo* [62]. Glucosinolates/isothiocyanates were also shown to decrease cancerous cell proliferation and regulate numerous proteins engaged in apoptosis control, i.e. caspases, p53, cyclin-dependent kinases, and pro-apoptotic members of the Bcl-2 protein family, or affect tubulin polymerization, thus leading to cell apoptosis [58]. Furthermore, some of the GS derivatives were reported to decrease expression of mandatory cyclins and cell cycle inhibitors, thus dysregulating the cell cycle leading to G<sub>1</sub>S or G<sub>2</sub>M arrest depending on cell type [63]. What

is more, some of the isothiocyanates were revealed to affect estrogen metabolism, resulting in decreased incidence of hormone-dependent cancers. The effect is attributed both to increased estrogen metabolism resulting in its lowered concentration in the blood [64] and altered estrogen receptor (ER) activity due to inhibited transcription of ER-coding genes or its degradation [65].

### Carotenoids

Among other phytochemicals present in food, carotenoids constitute a wide group of approximately 600 compounds found in almost all colored vegetables, while around 40 of them are present in daily diet. However, only 21 carotenoids are found in human serum/plasma due to differences in their bioavailability and absorption in the gut. The most commonly studied are lycopene (watermelon, tomatoes – well absorbed from tomato juice and sauce, red grapefruit, briar),  $\beta$ -carotene (carrots, leafy greens), lutein (dihydroxy form of  $\alpha$ -carotene, present in kale, spinach, mango, and oranges) and zeaxanthin (dihydroxy form of  $\beta$ -carotene, present in corn). Since high consumption of fruits and vegetables is associated with decreased cancer risk, carotenoids are being extensively investigated for anticarcinogenic activity [66–68].

At first, the cancer preventing effects were linked mainly to the precursors of vitamin A, then non-provitamin A carotenoids were also found to act as anticarcinogens [69]. They exert growth inhibitory activity in a wide group of cancer cells, including colon, prostate, breast and lung tumor cells [70]. Carotenoids were found to be modulators of many signaling pathways, engaged in cell proliferation and apoptosis. Akt and MAPK kinase activity was revealed to be impaired in the presence of carotenoids. They can also play a role as stimulators of apoptosis by activation of caspase cascades and by altering the status of Bcl-2 proteins [69, 71]. Carotenoids may influence the cell cycle of cancer cells, thus leading to their growth inhibition. Lycopene was found to stop cell cycle progression in  $G_0/G_1$  [72] or  $G_1/S$  [73] dependently on cancer cell type. Additionally, the levels of p53 protein are altered in cells treated with carotenoids [69]. Lycopene has also been found to suppress IGF-I stimulated growth of cancer cells by preventing the binding of this growth factor to its receptor [2, 74]. COX-2 activity was revealed to be decreased in colon cancer cells exposed to  $\beta$ -carotene [75]. Moreover, lycopene was found to enhance gap junction communication through up-regulation of connexin-43 in breast cancer cells, which can lead to the improvement of cell differentiation [76].

### Vitamins and minerals

Intake of minerals and vitamins in daily diet is essential for health maintenance. Although they are present in trace amounts within tissues, they play a significant role in a variety of biological processes. Some of them also have a positive impact on the process of carcinogenesis. Anticancer activity of vitamins E and C was observed, mostly due to their antioxidant effects. The protective influence of vitamin C is revealed in relation to e.g. gastric cancer through inhibiting formation of N-nitroso compounds. Besides the reactive oxygen species moderating effect, vitamin E may also induce can-

cer cell differentiation and apoptosis. Vitamin D and folic acid were also observed to have an impact on carcinogenesis [3].

### Vitamin D

Vitamin D is a fat-soluble prohormone naturally occurring in very small amounts in food. Two forms of this vitamin can be distinguished: calciferol ( $D_2$ ) and cholecalciferol ( $D_3$ ), which is produced in skin after exposure to UV-B light. Active forms of vitamin D are obtained in the body after their conversion in the liver to calcidiol (25-hydroxyvitamin D) and in kidneys to calcitriol (1, 25-dihydroxyvitamin D) [77]. It has been revealed that human cells, both normal and cancer cells, demonstrate specific receptors (VDR) for vitamin D metabolites, thus being susceptible to their activity [78]. Vitamin D action has been attributed to the regulation of multiple genes (more than 60) engaged in cell proliferation, differentiation, apoptosis and angiogenesis [79–84]. Biological activity of calcitriol is exerted when it binds to VDR receptors, which leads to formation of a heterodimer with retinoid X receptor and expression of specific genes containing vitamin D response element [85]. The inhibition of cell proliferation and metastasis as well as stimulation of cell differentiation is observed as an effect of vitamin D action [77, 86]. This activity of calcitriol is linked to decreased risk of prostate and colon cancer risk. Moreover, it was noted that sunlight exposure was inversely associated with cancer incidence [87].

### Folate

Folic acid (also known as vitamin  $B_9$ ) is a constituent found in large amounts in green leafy vegetables and fresh fruits. It plays a crucial role in proper cell division and growth and takes part in nucleotide biosynthesis [10]. Its cancer preventive effects are mainly attributed to the delivery of methyl groups for DNA synthesis and gene expression, thus protecting against DNA damage. It was suggested that insufficient folic acid consumption may trigger loss of DNA integrity through misincorporation of uracil to the chain of DNA and induces breaks in chromosomes. Reversion of these defects was shown after folate supplementation [88, 89]. A reverse association was observed between folic acid intake and colon and breast cancer incidence. Animals fed with a diet poor in folate were more likely to suffer from colorectal cancer. A number of epidemiological studies revealed 25–35% reduction in colon cancer incidence when comparing the groups with the highest and lowest folate intake [3, 10]. Decreased risk of colorectal cancer by approximately 75% was noted in women taking high-folate multivitamins for more than 15 years [10, 90].

### Selenium

A variety of *in vitro*, animal and epidemiological studies suggest a preventive role of selenium against human cancer development, especially tumors of the gastrointestinal tract. Low levels of selenium in serum were associated with increased risk of prostate cancer. It is suggested that selenium may inhibit initiation and promotion phases of carcinogenesis [10]. Besides its antioxidant effect on lipid peroxidation, it can alter the process of DNA adduct formation.

It blocks formation of carcinogens and their binding to DNA. Selenium may also reduce cancer progression through improving the immune response in the organism, e.g. by stimulation of cytotoxic activity of natural killer cells [91]. Several studies have revealed selenium-induced apoptosis in tumor cells [92] as well as inhibition of cell proliferation involving alternations in MAPK kinases and Akt kinase signaling pathways [93]. It was also proposed that it could act as a chemopreventive agent by decreasing angiogenesis within the tumor [94–96]. What is interesting, small amounts of Se added to a diet deficient in this micronutrient results in improved activity of selenoproteins and detoxification enzymes of phase I and II as well as ameliorated function of the immune system, whereas supranutritional intake of selenium leads to cancer prevention through the above-described influence on the cell cycle, apoptosis and angiogenesis [58, 97].

### Calcium

Calcium constitutes an essential macroelement for human health. Dairy products (milk, yogurts, and cheese), dark green vegetables, legumes and nuts constitute a good source of this micronutrient. Although some results are inconsistent, a number of epidemiological studies have attributed calcium intake with decreased colon adenoma and cancer [90, 98]. The mechanism underlying this protective effect is mainly due to binding and inactivating the pro-carcinogenic activity of bile acids on colon epithelial cells. In addition, calcium was found to inhibit epithelial cell proliferation or induce their differentiation through altering cell signaling pathways [86, 87, 99, 100].

### Conclusion

Based on various studies outlined in this review reporting a broad spectrum of naturally occurring compounds with chemopreventive activity, intense consideration of them as potential therapeutics is quite intelligible. Some of these may be already found as extracts or pure substances available for daily supplementation and are becoming a common dietary habit. However, providing a well-balanced diet containing an abundance of biologically active compounds should become a daily habit.

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