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Administration of herbal antioxidant to prevent and treatment of cancers

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Abstract

Cancer is known as the second leading cause of death in industrialized countries. Nowadays, the use of plants in prevention and treatment of diseases such as cancer to be increased. Plants contain different compounds such as herbal antioxidants that play a vital role with anti-proliferative and cytotoxic properties through biochemical and molecular mechanisms in different cancers like liver, breast, lung, prostate, leukemia, colon and ovarian cancers. Antioxidant compounds found in different herbal medicines and fruits that used in prevention or treatment of cancers. Considering the findings, it can be concluded that herbal antioxidants have a significant and useful effect on types of cancer cells via regulation expression of many genes involve in cancers.

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Introduction

Cancer is a main public health problem internationally and is the second principal cause of death in the United States (1). The reports indicate that about 13% of total deaths (7.6 million) are induced by cancers and its global burden is increased largely regarding both the aging and growth of the world population besides the growing of cancer inducing behaviors, especially smoking.

The current treatment for cancers usually includes a series of treatment methods to fight against the disease. The treatment options available for cancer patients are surgery, hormone therapy, radiation, biological therapy, chemotherapy, targeted therapy and immunotherapy. This treatment method and drugs used are highly toxic and often ineffective and have various side effects (2).

Recently, herbal antioxidants as phytochemicals convert to an attractive subject for scientists to prevent and treatment of diseases Epidemiological studies have shown that many of these antioxidant compounds possess anticarcinogenic, antimutagenic, antiviral, anti-inflammatory and antibacterial properties, or anti-atherosclerotic activities (3). Different studies have investigated that the natural antioxidant in herbal medicines such as green tea, red grape, *Allium hirtifolium*, *Artemisia annua*, *Viscum album*, *Silybum marianum* and *Ginkgo Biloba* can help to prevent the free radical damage associated with the development of cancer (4). Herbal antioxidants contain carotenoids, sulfur compounds, vitamin C, E, catechins, ellagic acid, anthocyanin, phenolic compounds, polyphenols, curcumin and conjugated fatty acids (5).

The purpose of this article is to review several herbal antioxidants that have anticancer properties in preventing, treating and reducing cancer growth.

Core tip

Plants contain different compounds such as herbal antioxidants that play a vital role with anti-proliferative and cytotoxic properties through biochemical and molecular mechanisms in different cancers like liver, breast, lung, prostate, leukemia, colon and ovarian cancers.

Materials and Methods

For this review, we used a variety of sources including PubMed, Embase, Scopus and directory of open access journals (DOAJ). The search was conducted by using combinations of the following key words

and/or their equivalents; cancer, herbal antioxidants, antioxidant activity and gene expression.

Flavonoids

Among the different natural products, much attention has been attracted to flavonoids due to their incredible spectrum of pharmacological activities like antimutagenic, antibacterial, antioxidant, anti-angiogenic, anti-inflammatory, anti-allergic, modulators of enzymatic activities and anticancer activity. Flavonoids are the water-soluble pigments in fruits, vegetables, grains, leaves, flowers and bark. These pigments are able to scavenge superoxide, hydroxyl, and proxy-radicals, breaking lipid peroxide chain reactions. They are able to protect cells from X-ray injury, to block development of cell cycle, to prevent mutations, to block prostaglandin synthesis, and to inhibit multistage carcinogenesis in experimental animals. These compounds (as protein kinase inhibitors) can inhibit several protein kinases like serine/threonine kinases, phosphatidylinositol-3 kinase, protein kinase C and cyclin-dependent kinases and additionally flavonoids contain topoisomerase antagonists to avoid creation of covalent enzyme-DNA complex, and in addition to prevent the subsequent steps of the catalytic cycle. Flavonoids can interfere with specific stages of the carcinogenic process, such as inhibiting cell proliferation and induce apoptosis in several types of tumor cells. Several other epidemiological studies confirmed the protective role of a high flavonoid intake against different cancers (6,7).

There are different types from flavonoids, namely flavonols (e.g. quercetin and kaempferol, the most ubiquitous flavonoids in foods), flavones, flavanones, isoflavones, flavanols (catechins- monomers and proanthocyanidins-polymers, known as condensed tannins) and anthocyanidins (pigments responsible for the color of most fruits) (Figure 1) (2-6).

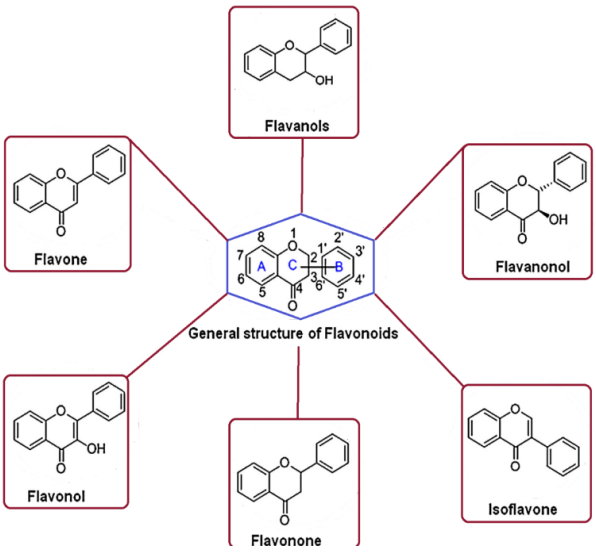

Figure 1. Structure of flavonoids.

Kaempferol

Kaempferol containing a diphenylpropane structure (C6-C3-C6) has been shown to have antioxidant, antineoplastic anti-proliferation, anti-metastatic and anti-angiogenesis activities in tumors (8). For example, anticancer activity this compound in cancer SW480 cells is through TRAIL induced apoptosis and preferentially inhibits the growth of HCT116 cells expressing wild-type p53 (9).

Kaempferol has been indicated that inhibits vascular endothelial growth factor (VEGF) gene expression by both HIF-dependent (Akt/HIF) and HIF-independent (ESRRA) pathways, tumorigenesis and angiogenesis in ovarian cancer cell lines and additionally it stimulates apoptosis in A2780/CP70 ovarian malignant cell lines via activating p53 (10). It has been suggested that kaempferol with quercetin reduce cell proliferation in HuTu-80 and Caco-2 gut cell lines and the PMC42 human breast cell line (11).

The results suggest kaempferol effect on A549 lung cancer cells via activation of apoptosis and the MEKMAPK signaling (12). It has been identified from various plants such as *Wedelia trilobata, Warburgia ugandensis, Vaccinium vitis-idaea, Tropaeolum majus, Trigonella foenum-graecum, Toona sinensis, Acacia nilotica, Tilia americana, Syzygium aromaticum, Symphytum officinale, Rosmarinus officinalis, Symphytum officinale, Sutherlandia frutescens, Solidago virgaaurea, Solenostemma argel, Solanum nigrum, Siraitia grosvenori, Siraitia grosvenori, Sanguisorba minor, Hypericum perforatum, Sambucus nigra, Rosmarinus officinalis, Ribes nigrum, Phyllanthus emblica, Malva parviflora, Lysimachia vulgaris, Cassia alata, Lycium chinense, Lycium barbarum, Lonicera japonica, Laurus nobilis, Lamium album, Bauhinia forficata, Impatiens balsamina, Houttuynia cordata, Adansonia digitata, Equisetum arvense, Bunium persicum, Albizia lebbeck, Angelica keiskei, Aloe vera, Coccinia grandis, Amburana cearensis, Ammi majus, Peumus boldus, Chromolaena odorata, Ardisia japonica, Bauhinia microstachya, Capparis spinosa, Centella asiatica, Cissus sicyoides, Crassocephalum, crepidioides Crocus, sativus, Cynanchum acutum, Cynanchum chinense, Dicliptera chinensis, Foeniculum vulgare, Euphorbia pekinensis, Ficaria verna, Hippophae rhamnoides, Galega officinalis, Ginkgo biloba, Glycine max, Grindelia robusta, Gymnema sylvestre* and *Helleborus niger* (8).

Quercetin

Quercetin (3, 3', 4, 5, 7-pentahydroxyflavone, R= OH) belongs to an extensive class of polyphenolic flavonoid compounds almost ubiquitous in herbal and food sources. The average daily dietary intake of quercetin by an individual is 25 mg in the United States (13).

Quercetin has a wide range of biological effects such as anti-oxidative effects, cardiovascular diseases, and ameliorating diabetic as shown in animal models and, to some extent, in humans. Recent studies indicate that quercetin to decrease expression of mutant p53 protein

and inhibition of lymphocyte tyrosine kinase and additionally to suppress the expression of the p21-ras oncogene in human colon cancer cell lines. Results of researches have confirmed that quercetin is an inhibitor NF-κB (with reduces IKK), PI3K and other kinases involved in intracellular pathway. The transcription factor NF-κB shows an outstanding role in tumorigenesis and tumor growth (14,15). Studies have shown that quercetin isolate of green tea, red wine and onions, as having antioxidant activity in prevention of cancers (16).

Epigallocatechin gallate

Epigallocatechin gallate (EGCG) is the most abundant and powerful antioxidant in green tea for cancer chemoprevention and a major constituent of catechins are reported as having many beneficial biological activities on HT-29 colon cancer through induction of apoptosis, inhibition of cell growth, inactivation of COX-2 expression, ROS generation and AMPK activation (17). Studies have observed that EGCG is the most potent antiproliferative in HCT116 and SW480 colorectal cancer cell lines (18) and additionally it can inhibit cervical cancer cell growth by cell cycle arrest, induction of apoptosis and adjustment of gene expression (19).

It had been reported that EGCG to be effective on osinophilic leukemia EoL-1 cell line through inducing the differentiation and suppressing the proliferation of the leukemia cells (20). Several studies demonstrated a link between EGCG and various breast and prostate cancer cell lines for example EGCG inhibits the expression of XIAP, Bcl-2 and epithelial-mesenchymal transition marker (EMT), cell viability, TCF-1/LEF activity and induces caspase-3 activation in prostate cancer stem cells (CSCs) (21). The studies indicated that EGCG prevented the phosphorylation of extracellular signal-regulated protein kinase 1/2 (ERK1/2), and p38 MAPK activity in human fibrosarcoma HT1080 cells (22).

Tannin

Tannins or tannic acid are natural polyphenols with a molecular weight ranging from 500 to 3000–4000, usually classified into condensed tannins (proanthocyanidins) and hydrolyzable tannins (gallo-ellagitannins). The role of tannins in human health is due to antimicrobial, anti-carcinogenic, anti-mutagenic and anti-nutritional effects. The green tea plant as a potential source of tannin is effective on various types of tumors, including forestomach, small intestine, duodenum, lung, esophageal, liver, mammary gland, pancreas, colon and skin of different animal model (3,23). Tannin extracted from black bean inhibits Caco-2 colon, MCF-7 and Hs578T breast, and DU 145 prostate cancer cells proliferation (24).

The inhibitory effects of tannin on breast cancer are through changes in morphology of MCF7 estrogen receptor-positive (ER^+), stimulate apoptosis (activation of the caspases 3/7 and 9), inhibition of fatty acid synthase. Other study demonstrated tannic acid inhibits EGFR/STAT1/3TA by binding to EGF-R and enhances p38/STAT1 signaling axis in breast cancer cells. Numerous plants are considered as potential sources of tannin e.g., grains, fruits, nuts and legumes and additionally in drinks such as wine, green tea and coffee (25,26).

Genistein

Genistein [4', 5, 7-trihydroxyisoflavone or 5, 7-dihydroxy-3-(4-hydroxyphenyl) chromen-4-one] is a typical sample of a phytoestrogenic compound. Studies have demonstrated genistein in soybean products decreases the incidence several types of cancers, like breast, prostate, leukemia, colon, liver, lung, ovarian, bladder, neuroblastoma and brain tumors. Additionally consumption of soybean was related to a reduced risk for gastric tumors (27).

In a major advance study, genistein was able to induce the apoptosis of primary gastric cancer cells through increase Bax expression and reduce Bcl-2 expression. Genistein has been investigated leading to apoptosis in malignant cells through inhibition of VEGF and FGF-2 expression, inhibition of phosphorylation of the receptor tyrosine kinase, and activation of Akt. It also prevents the proto-oncogene HER-2 protein tyrosine phosphorylation in breast malignance cells. Generally, molecular targets of genistein in inducing apoptosis containing expression reducting of Bcl-2, Bcl-XL, Survivin, IAP, XIAP and expression enhancing of Bax, PARP, BAD and active caspases (28,29). Other studies have suggested that pure genistein has a strong dose-dependent inhibiting effect on the proliferation of the endothelial cells. It inhibits proliferation of other vessels' endothelial cells like cells derived from the bovine adrenal cortex and the aorta (4).

Anthocyanin

Anthocyanins, (a class of flavonoids) exist widely in plants that containing antioxidant, antibacterial, anti-inflammatory, anticancer properties (30). The common forms of anthocyanidins are peonidin, petunidin, delphinidin, cyanidin, pelargonidin and malvidin (Figure 2).

Anthocyanin has been shown to induce apoptosis in different types of cancer cells. It inhibited NF-κB in HCT-116 cells and reduced B16-F10 melanoma murine cell proliferation. In animal model studies, anthocyanin affects colon cancer cells by regulation of mTOR signaling. An anti- progression mechanism of cancer chemoprevention, anthocyanin is inhibited metastasis by the activity of tumor matrix metalloproteinases (MMPs) and induction of apoptosis by c-Jun N-terminal kinases (JNKs) phosphorylation, activated caspase-3 and c-Jun gene expression. The anthocyanin-rich sources were observed in bilberry (*Vaccinium myrtillus* L.), elderberry (*Sambucus nigra* L.), purple carrot (*Daucus carota* L.), grape (*Vitis vinifera* L.), purple corn (*Zea mays* L.), red radish (*Raphanus sativus* L) and chokeberry (*Aronia melanocarpa* E.). Presence of anthocyanin and anthocyanin-pyruvic acid in blueberry (*Vaccinium myrtillus*) plant

Anthocyanins	R_1	R_2
Cyanidin	OH	H
Delphinidin	OH	OH
Peonidin	OCH3	H
Pelargonidin	H	H
Petunidin	OCH3	OH
Malvidin	OCH3	OCH3

Figure 2. Structure of anthocyanin.

extracts has an inhibition effect on breast cancer cell line proliferation and cell invasion by anti-invasive factors and inhibition the growth of HL60 human promyelocytic leukemia cells and HCT116 human colon carcinoma cells through the induction of apoptosis (30,31). Anthocyanins isolated from *Vitis coignetiae* Pulliat were able to reduce NF-κB regulated proteins such as MMP-2 and MMP-9 expression through the inhibition of NF-κB activation in PANC-1 and AsPC-1 pancreatic cancer and HT-29 human colon cancer cells respectively (32).

Alkaloid

Alkaloids are nitrogenated compounds (a nitrogen atom with an unshared pair of electrons), pharmacologically actives, which represent one of most vast secondary metabolites (i.e. chemical substances) with specialized activities in nature, showing a great diversity of chemical structures, biosynthetic paths and biological activities. They are isolated from reptiles, birds, insects, amphibians and mammals (33). Recently, it has been founded many plant-derived alkaloids with alteration of the MAPK pathway, suppression of the NF-κB pathway, cell-cycle arrest, induction apoptotic and caspase activators properties on different cancer cells (34).

Therefore, the different alkaloids isolated from *Daphniphyllum* have cytotoxic activities of various cancer cells, such as human epidermoid carcinoma KB cells, P-388 cells, SGC-7901 cells, HL-60 cells, MCF-7 cells, A549 cells, HL-60, p-388, A-549, Bel-7420 cells and murine lymphoma L1210 (35).

Additionally, the phenanthroindolizidine and phenanthroquinolizine (as a family of alkaloids) derived from *Tylophora indica* affect various cancer cell lines for example KB, NCI panel, HepG2 and PANC-1 (36). Kava (*Piper methysticum Forst. f., Piperaceae*) plant extract is a source of alkaloids (flavokawains A and B) that have demonstrated effective effects on HepG2 human hepatocyte cells line through activating both the antioxidant and heat shock responses and protection from H_2O_2-mediated cell (37). It had been reported that the isolated protoberberine alkaloids from *Alangium salviifolium* inhibits superoxide anion radical formation,

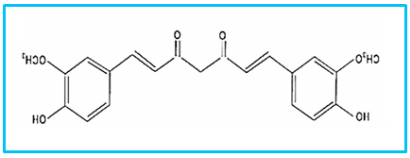

Figure 3. Structure of curcumin.

the growth and aromatase (38).

Curcumin

Curcumin or diferuloylmethane with chemical formula of (1, 7-bis (4-hydroxy-3-methoxyphenyl)-1, 6-heptadiene-3, 5- dione) derived from the herbal *Curcuma longa*, namely turmeric that it has been reported the broad-spectrum antimicrobial activity of curcumin including antifungal, antimalarial, antibacterial and antiviral activities (39). The main chemical compounds of curcumin are (Figure 3): curcumin, demethoxy curcumin, and bisdemethoxycurcumin. Effects of curcumin on cancer cell types is through different pathways such as inhibition of the activation of transcription factor NF-κB, inhibition of transcription factor, inhibition of serine protein kinase pathway, inhibition of growth factor pathway and inhibition of the AP-1 signaling pathway. Curcumin from ginger species (like *Curcuma longa*) represents a chemo-preventive agent that possesses anti-apoptotic, anti-proliferative and anti-angiogenic properties and it has shown that it affects diverse cancers such as colorectal, pancreatic, breast, prostate, lung, head and neck, ovarian and cancer lesions (40,41). Recently, a study has been indicated that curcumin can inhibit sarco/endoplasmic reticulum Ca^{2+} ATPase activity, causing apoptosis in ovarian cancer cells (42).

Organosulfur compounds

Organosulfur compounds such as diallyl disulfide (DADS and DATS), N-acetylcysteine and S-allyl cysteine are organic compounds to prevent carcinogenesis (Figure 4). There is evidence that diallyl disulfide (DADS) can protect against tumor in humans with molecular mechanisms such as inhibition of carcinogen-induced activity, induction of apoptosis, induction of cell-cycle arrest, inducing cell differentiation, increases in histone acetylation, prevention of cell invasion (43).

Diallyl trisulfide (DATS) induce apoptosis pathway pancreatic cancer cells (Capan-2) via increased expression of cyclin B1, p21, Fas, p53 and Bax and decreased expression of MDM2, cyclin D1 and Bcl-2 (44). The *Allium* genus like leeks (*Allium porrum*), garlic (*Allium sativum*) and shallots (*Allium ascalonicum*) are some vegetable rich organosulfur compounds and several epidemiologic studies have shown the organosulfur compounds of *Allium* vegetables contribute to reducing stomach, colorectal, esophageal and prostate cancers (45).

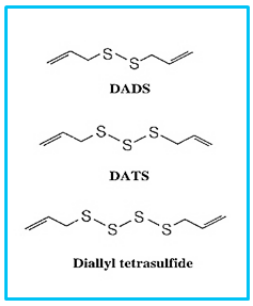

Figure 4. Structure of organosulfur compounds.

Conclusion

Numerous study results indicated that different herbal phytochemicals with the capability to affect diseases like carcinoma, metabolic syndrome or stroke. Herbal antioxidants as one of phytochemicals have been used in various diseases as cancers. It can be concluded that herbal antioxidants have a significant and useful effect on types of cancer cells.

Authors' contribution

BY is the single author of the paper.

Conflicts of interest

The author declared no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

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