

Polyphenols in plants as anticancer agents

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Abstract:

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Lack of success with standard treatments for cancer has led to continuous search for anticancer agents in botanic sources. Various polyphenolic constituents of some plants has shown potent chemopreventive effect in carcinogenesis models and induce cell growth inhibition and apoptosis in human tumor cells. Epidemiologic studies has suggested that consuming food and beverages rich in polyphenols is associated with a lower incidence of cancer. This paper will summerize current knowledge about preventive and therapeutic potential of polyphenols.

Key words: anticancer agents, polyphenols, flavonoids, green tea, wine, medicinal plants

Introduction

Plant-based formulations have been used since ancient times as remedial measures against various human and animal ailments. Nowadays, cancer is major life threatening disease. The latest data for European population reveals that almost 6 million people are currently living with cancer. During this year more then 3 million new cases will be diagnosed and 2 million people will die because of inappropriate traditional treatment (surgery, chemotherapy or radiation therapy) (Sancho-Garnier et al. 2004). This has led to increasing interest in plant research as source of new weapons in cancer arena. The aim of this paper to reveal some data about potentials of polyphenols from plants as chemopreventional and anticancer agents.

What are polyphenols?

Polyphenols are a group of chemical compounds widely distributed in the plant kingdom. At least 8,000 polyphenolic compounds

have already been identified. These phytochemicals have similar basic structural chemistry including »aromatic« or »phenolic« ring structure. Polyphenols are responsible for the brightly colored pigments of many plants and they protect plants from diseases and ultraviolet light preventing damage to the seeds until they germinate.

Flavonoids

Flavonoids are considered the most important class of polyphenols from a nutritional perspective. They are widely distributed in plant foods and include: lignins (nuts, whole grain cereals), proanthocyanins (grapes, pine bark), anthocyanins/anthocyanidins (brightly colored fruits and vegetables, berries), isoflavones – genistein/diadzein (soybeans), catechins (tea, grapes, wine), tannins (tea, nuts), quercetin (grapes, wine, onions), naringenin/hesperidin (citrus fruits).

The flavonoids are among the most potent plant antioxidants. They have shown anti-inflammatory, anti-thrombotic and anti-neoplastic

activities. We will refer only to the last one which is the scope of this paper. Flavonoids possess pharmacological properties for preventing tumor progression by inhibiting cell proliferation and tumor promotion (Kandaswami et al. 1991, Singhal et al. 1995, Kang et al. 1997, Shen et al. 1997, Shao et al. 1998, Huang et al. 1999, Murakami et al. 2000).

The core structure of the flavonoids, 2-phenyl-4H-1-benzopyran-4-one or flavone, induces apoptosis, differentiation and growth inhibition in human colon carcinoma cells in vitro (Wenzel et al. 2000). Moreover, compared to the clinically established anticancer agent camptothecin, flavone displayed higher selectivity and potency for the induction of apoptosis and growth inhibition only in transformed colonocytes.

The anti-invasive activity of flavonoids apigenin and quercetin was tested on melanoma cells in vitro (Caltagirone et al. 2000). It was demonstrated that apigenin and quercetin inhibit melanoma growth and invasive and metastatic potential more effectively than the anti-estrogen tamoxifen.

A polymethoxy flavonoid, nobiletin, from *Citrus depressa*, showed both antiproliferative and anti-invasive effects in vitro and in vivo (Kandaswami et al. 1991, Minagawa et al. 2001, Sato et al. 2002). Study of Sato et al. (2002) revealed that nobiletin inhibits tumor cell invasive activity not only by suppressing the expression of matrix metalloproteinases -1 and -9 (MMP-1 and -9), but also augmenting tissue inhibitor of metalloproteinases -1 (TIMP-1) production in tumor cells.

Recent comparative analysis of different flavonoids in fruits and vegetables demonstrated: quercetin and strawberry and plum extracts as potent inducers of apoptosis, apple, grape and onion extracts as potent inhibitor of proteasome-activity, elagitannins from strawberries, red raspberries and walnuts as anticancerogenic and chemopreventive agents (Chen et al. 2004, Cerda et al. 2005, Ramos et al. 2005).

Tea polyphenols

Next to water, tea is the most ancient and widely consumed beverage in the world.

There are 3 main types of tea: green, black and oolong tea and they are prepared from the tea plant *Camellia sinesis* in different manufacturing processes (Mukhtar, Ahmad, 2000). Chemical analysis of the constituents of green, black and oolong teas elucidates over sixty polyphenols (Hashimoto et al. 2003). The chemical

composition of green tea is similar to that of unprocessed leaf of *Camellia sinesis*. Green tea's polyphenols include flavanols, flavandiol, flavonoids and phenolic acids and account for 30% of the dry weight of green tea leaves (Mukhtar, Ahmad, 2000). Most of the polyphenols in green tea are flavanols, commonly known as catechins and the major catechin is (-)-epigallocatechin-3-gallate (EGCG).

Numerous studies provided strong evidence of both anti-oxidative, anti-mutagenic, anti-proliferative and anti-neoplastic activities of tea extracts (Hashimoto et al. 2003). Positive correlation between human consumption of green tea and lower incidence of gastric, esophageal, ovarian, pancreatic and colorectal cancers is observed (Naasani et al. 2003). The major polyphenol in green tea, EGCG, was found to be potent chemopreventive and anticancer agent and enters phase II clinical trial (Azam et al. 2004, Moyers, Kumar, 2004). Various mechanisms for these effects were suggested – antioxidant activities, interaction with certain enzymes or proteins implicated in cancer (e.g. urokinase, ornithine decarboxylase, NADPH-cytochrome P450 reductase, protein kinase C, steroid 5 α reductase, tumor necrosis factor and epidermal growth factor expression, nitric oxide synthase, cyclooxygenase 2, Bcl-x(L), Bcl-2, MMP-2 and telomerase) (Annabi et al. 2002, Leone et al. 2003, Naasani et al. 2003). Recently, metastasis-associated 67-kDa laminin receptor that mediates the anticancer activity of EGCG has been identified (Tachibana et al. 2004).

Other polyphenols

Trans-resveratrol is a polyphenolic compound accounting to the stilbene class. It is detected in trees, in a few flowering plants, in peanuts and in grapevines. Its major impacts studied both in vitro and in vivo are antioxidative, anti-inflammatory, estrogenic, chemoprotective and anticancer effect (Soleas et al. 2002, Fuggetta et al. 2004, Wenzel, Somoza, 2005). Resveratrol is a promising candidate for treatment of malignant melanoma which is considered as a chemotherapy-refractory tumour. It inhibits cell growth and induce apoptosis in melanoma cell lines (Fuggetta et al. 2004). It is usually consumed as beverage, since it is constituent of red wine.

The beneficial effects of medicinal plants prepared as herbal teas on human health is associated with antioxidative effects of their polyphenols as shown for *Pulmonaria officinalis* L., *Hypericum perforatum* L., *Agrimonia eupatoria* L.,

Origanum vulgare L., *Melissa officinalis* L., *Rubus sp. diversus*, *Cotinus coggygria* Scop. (Ivanova et al. 2005). The same pharmacological activity is confirmed for plants used in traditional Indonesian medicine (Steffan et al. 2005).

Conclusions

Plant kingdom is unlimited source of potential agents for cancer prevention and inhibition of tumor promotion and progression. Polyphenols are promising chemopreventive and anticancer agents. Animal and epidemiological studies reveal that consuming plant food and beverages (tea, wine) rich in polyphenols is associated with a lower incidence of cancer. EGCG and resveratrol may be used as valuable tools in the combinational therapy of metastatic tumours.

Some medicinal plants used in ethnomedicine display their anticancer activities thanks to their polyphenol compounds. Many of them are waiting out there in the wilderness to be discovered and pharmaceutically used.

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Summary

Polifenoli u biljkama kao antikancerogeni agensi

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Neuspeh standardnih terapija kancera doveo je od potrage za antikancerogenim agensima u biljnim izvorima. Različite polifenolne komponente nekih biljaka pokazale su značajni hemopreventivni efekat na modelima kancerogeneze i indukovali inhibiciju rasta i apoptozu humanih tumorskih ćelija. Epidemiološke studije su povezale upotrebu određene vrste hrane i pića sa smanjenom incidencom kancera. U ovom radu je dat pregled polifenola i njihovog preventivnog i terapijskog dejstva na kancer.