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PLANT PHENOLICS IN CANCER CHEMOPREVENTION

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ABSTRACT

Phenolics are generally widely distributed in the plant kingdom and are the most plentiful secondary metabolites of plants. Plant polyphenols have pinched increasing attention due to their effective antioxidant properties and their marked effects in the prevention of a variety of oxidative stress related diseases such as cancer. The antioxidant content of fruits and vegetables may contribute to the protection they put forward from disease. Because plant foods include many different classes and types of antioxidants, information of their total antioxidant capacity (TAC), which is the cumulative capacity of food components to hunt free radicals, would be valuable for epidemiologic purposes. Evidence reviewed here demonstrates exogenous antioxidants alone produce beneficial effects in various cancers. Among fruits, the highest antioxidant activities found in berries (i.e., blackberry, red currant and raspberry) has shown a significant effect on the deterrence of cancer development. This review provides a rationalized and ample overview on phenolic antioxidants from natural sources with their *in-vitro* and *in-vivo* anticancer activity. The anticancer effects of phenolics *in-vitro* and *in-vivo* animal models are viewed, together with recent human intervention studies.

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INTRODUCTION

Epidemiological data on a good number of cancer sites suggest that consumption of plant foods, which contain elevated levels of antioxidants, might slow or prevent the appearance of cancer. The utilization of fruits and vegetables has been inversely associated with morbidity and mortality from degenerative diseases (Rimm *et al*., 1996; Gillman *et al*., 1995; La Vecchia *et al*., 2001; Terry *et al*., 2001; Cohen, 2002). It is not known which dietary constituents are responsible for this association, but antioxidants appear to play a major role in the protective effect of plant foods (Gey, 1990). The scientific community is continually studying the role of diet in the development of cancer. Many results are preliminary and more is being learned every day. Research is discovering that intake of fruits, vegetables, and cereal grains may interfere with the process of reducing the risk of developing cancer, the risk of developing heart disease, hypertension, obesity, diabetes, and that other chronic diseases might also be prevented by eating more fruits and vegetables.

Although research studies are inconclusive at this time, preliminary evidence suggests that some components of food may play a role in decreasing the risk of developing cancer, together with phytochemicals, antioxidants, and omega-3 fatty acids. Phytochemicals are chemicals found in plants that protect plants against bacteria, viruses, and fungi. Eating large amounts of brightly colored fruits and vegetables (yellow, orange, red, green, white, blue, purple), whole grains/cereals, and beans containing phytochemicals may decrease the risk of developing certain cancers as well as diabetes, hypertension, and heart disease (Gey *et al*., 1991). Antioxidants are substances that inhibit the oxidation process and act as protective agents. They protect the body from the damaging effects of free radicals (by-products of the body's normal chemical processes). Free radicals attack healthy cells, which changes their DNA, allowing tumors to grow. Research is underway to investigate the role of antioxidants in decreasing the risk of developing cancer. Plant antioxidants are believed to inhibit lipid peroxidation and offer protection against oxidative damage to membrane functions.

Antioxidants have been isolated from conventional food sources, such as tea (green and black), sesame and wild rice, and also from other plant sources, such as rice hulls, and crude plant drugs (Willett, 1991). They are plentiful in fruits and vegetables, as well as in other foods including nuts and grains. Phenolics are compounds possessing one or more aromatic rings with one or more hydroxyl groups. They are broadly distributed in the plant kingdom and are the most abundant secondary metabolites of plants, with more than 8,000 phenolic structures currently known, ranging from simple molecules such as phenolic acids to highly polymerized substances such as tannins. Plant phenolics are usually involved in defense against ultraviolet radiation or aggression by pathogens, parasites and predators, as well as contributing to plants' colors. They are ubiquitous in all plant organs and are therefore an essential part of the human diet. Phenolics are widespread constituents of plant foods (fruits, vegetables, cereals, olive, legumes, chocolate, *etc.*) and beverages (tea, coffee, beer, wine, *etc.*). Phenolic acids can be divided into two classes: derivatives of benzoic acid such as gallic acid, and derivatives of cinnamic acid such as coumaric, caffeic and ferulic acids (Gescher *et al*., 1998).

Dietary and endogenous antioxidants prevent cellular destruction by reacting with and eliminating oxidizing free radicals. Due to the chemical diversity of antioxidant compounds present in foods, complete databases on food antioxidant content are not yet available. The importance of this concern is underlined by a study which estimates 23 percent of cancer patients take antioxidants (VandeCreek, 1999). The study of antioxidant use in cancer treatment is a rapidly evolving area. Antioxidants have been comprehensively studied for their ability to prevent cancer in humans (Singh, 1998). Cinnamic acid derivatives, caffeic acid and ferulic acid are known to down modulate survival and proliferation signaling cascades such as PI3K-Akt and MAPK pathways, respectively (Anantharaju1 *et al*., 2016). However, it is not fully known how these cinnamic acid derivatives are retarding these signaling cascades. Regarding natural compounds, namely phenolic compounds, and considering that only 20% of the world's plants have been investigated (Pan *et al*., 2010) it is legitimate to think that many more compounds will be discovered, and in those compounds, many anticancer molecules could be found (Márcio Carocho and Isabel Ferreira, 2013). There has been significant investigation of this area, with promising findings which indicate that continuing investigation in this direction is warranted (Prasad *et al*., 1999).

Mechanisms of chemoprevention

Carcinogenesis is generally recognized as a multistep process in which distinct molecular and cellular alterations occur. From the study of experimentally induced carcinogenesis in rodents, tumour development is considered to consist of several separate, but closely linked, stages — tumor initiation, promotion and progression. Although these divisions are an oversimplification of carcinogenesis, it is useful to think in terms of these stages when considering possible opportunities for chemoprevention. Initiation is a rapid and irreversible process that involves a chain of extracellular and intracellular events. These include the initial uptake of or exposure to a carcinogenic agent, its distribution and transport to organs and tissues where metabolic activation and detoxification can occur, and the covalent interaction of reactive species with target-cell DNA, leading to genotoxic damage. In contrast to initiation, tumour promotion is considered to be a relatively lengthy and reversible process in which actively proliferating preneoplastic cells accumulate. Progression, the final stage of neoplastic transformation, involves the growth of a tumor with invasive and metastatic potential. According to the conventional classification originally proposed by Lee Wattenberg, chemopreventive agents are subdivided into two main categories — blocking agents and suppressing agents (Wattenberg, 1985). Blocking agents prevent carcinogens from reaching the target sites, from undergoing metabolic activation or from subsequently interacting with crucial cellular macromolecules (for example, DNA, RNA and proteins). Suppressing agents, on the other hand, inhibit the malignant transformation of initiated cells, in
either the promotion or the progression stage. Chemopreventive phytochemicals can block or reverse the premalignant stage (initiation and promotion) of multistep carcinogenesis. They can also halt or at least retard the development and progression of precancerous cells into malignant ones. Recent advances in our understanding of the carcinogenic process at the cellular and molecular level have shown this blocking and suppressing categorization to be an oversimplification, and numerous cellular molecules and events that could be potential targets of chemopreventive agents have been more specifically identified (Wattenberg, 1985; Manson, 2003; Milner *et al*., 2001). Therefore, the ability of any single chemopreventive phytochemical to prevent tumour development should be recognized as the outcome of the combination of several distinct sets of intracellular effects, rather than a single biological response.

It has been suggested that antioxidants might interfere with the oxidative mechanisms of alkylating agents (Gescher *et al*., 1998). These drugs generate substantial DNA damage, resulting in cell necrosis. However, evidence indicates a sizeable amount of chemotherapy damage is by other mechanisms, which trigger apoptosis (Labriola, 1999). Antioxidants have been shown to increase cell death by this mechanism (Chinery *et al*., 1997). Many research reports on the anticancer properties of vitamin A and the related retinoids have been published over the last 30 years. Most of these studies examined all-trans retinoic acid (RA). RA is formed in human tissues from beta-carotene and retinol, does not accumulate in the liver, thus it is not associated with significant hepatotoxicity (Mediavilla *et al*., 1999). Evidence exists to support the use of retinoids concomitantly with radiotherapy. *In vitro* studies have shown retinoic acid (RA) causes radiosensitization in human tumor cell lines at concentrations which do not cause cellular toxicity. This effect was reversible with removal of RA (Smith *et al*., 1992).The use of vitamin C in the treatment of cancer has been the source of many claims and controversies over the last 25 years. Initial reports from Drs. Pauling and Cameron were promising, and gained much notoriety. They reported 100 cases of terminal cancer, independently assessed and refractory to conventional treatment, which lived on average four times longer than 1000 age- and disease matched controls (Duchesne *et al*., 1995). Phenolic extracts or isolated polyphenols from different plant food have been studied in a numeral of cancer cell lines representing different evolutionary stages of cancer. For example, berry extracts prepared from blackberry, raspberry, blueberry, cranberry, strawberry and the isolated polyphenols from strawberry including anthocyanins, kaempferol, quercetin, esters of coumaric acid and ellagic acid, were shown to inhibit the growth of human oral (KB, CAL-27), breast

(MCF-7), colon (HT-29, HCT-116), and prostate (LNCaP, DU-145) tumor cell lines in a dose-dependent manner with different sensitivity between cell lines (Cameron, 1976). Katsube *et al*. compared the antiproliferative activity of the ethanol extracts of 10 edible berries on HL-60 human leukemia cells and HCT-116 cells and showed that bilberry extract was the most effective (D'Archivio *et al*., 2007). Ross *et al*. (2007) showed that the antiproliferative activity of raspberry extract in human cervical cancer (Hela) cells was predominantly associated with ellagitannins (Seeram *et al*., 2006). By comparing the phytochemical diversity of the berry extracts with their antiproliferative effectiveness, McDougall *et al*. (2008) suggested that the key constituent that related to the inhibition of cancer cell development could be ellagitannins from the *Rubus* family (raspberry, arctic bramble, and cloudberry) and strawberry, whereas the antiproliferative activity of lingon berry was caused predominantly by procyanidins (Katsube *et al*., 2003). In addition to *in vitro* studies on cancer cell lines, numerous *in vivo* experiments have also been performed to verify the antitumor efficacy of plant food-derived phenolic extracts or compounds with tumor incidence and multiplicity (e.g., number of tumors per animal) as endpoints (Ross *et al*., 2007). Lala *et al*. investigated the chemoprotective activity of anthocyanin-rich extracts (AREs) from bilberry, chokeberry, and grape. In the study 344 male rats were treated with a colon carcinogen, azoxymethane (AOM) (McDougall *et al*., 2008). After 14 weeks, rats on ARE diets had significantly fewer colonic aberrant crypt foci (ACF) when compared with the control group. Moreover, rats fed bilberry ARE had 70% fewer large ACF compared with rats fed the control diet, indicating significant chemoprevention. Human intervention studies on potential health promoting or cancer preventive activity of polyphenol rich food or food preparations have been conducted in healthy volunteers or individuals at high risk of developing cancer. Most studies have employed biomarkers reflecting antioxidant status or oxidative stress as endpoints, for example, plasma or serum antioxidant capacity, plasma malondialdehyde concentration, glutathione status, oxidative DNA damage in mononuclear blood cells (MNBCs), urinary 8-*epi*-prostaglandin F2α (8-Iso-PGF2) and 8-hydroxy-2′-deoxyguanosine (8-OHdG) concentration, *etc.* Improvement of antioxidant status and/or protection against oxidative stress was observed in short term intervention studies (1 dose) with various polyphenol-rich food including fruit juices (Yang *et al*., 2002), red wines (Lambert, 2003), chocolates (Gerhauser, 2008) and fruits such as strawberries as well as food preparations such as lyophilized blueberry powder (Thomasset *et al*., 2009) black currant anthocyanin concentrate (Lala *et al*., 2006) and grape seed concentrate (Jensen *et al*., 2008). In a 6-month chemopreventive pilot study conducted by researchers from the Ohio State University, patients with Barrett's esophagus (BE) were treated with 32 or 45 g (female and male, respectively) of freeze-dried black raspberries (FBRs)(Cao *et al*., 1998; Kresty *et al*., 2006; Spechler, 2002). BE is a premalignant esophageal condition in which the normal stratified squamous epithelium changes to a metaplastic columnar-lined epithelium and is underscored by the fact that it increases the risk for the development of esophageal adenocarcinoma, a rapidly increasing and extremely deadly malignancy by 30- to 40-fold. Their results suggested that daily consumption of FBRs reduced the urinary excretion of 8-Iso-PGF2 and 8-OHdG, among patients with BE indicating reduced oxidative stress.

Conclusion

Although plant derived phenolic compounds have been studied extensively for inhibiting tumor cell growth in vitro and in vivo, many gaps still persist that require additional studies. For example, it is not fully known how cinnamic acid derivatives like caffeic acid and ferulic acid are retarding the signaling cascades in down modulating the survival and proliferation of PI3K-Akt and MAPK pathways, respectively. It is not known whether they are they binding to Akt or Raf proteins or they are inhibiting the upstream kinases/binding proteins. Therefore, additional studies are required to address these concerns. Also more experimental data is required to bring down the variations in treatment response among individuals on phenolic acid rich diet. Additional studies are also required to improve the therapeutic efficacy and tumor cell selectivity of phenolic compounds. More studies related to strategies to reduce the dose and toxicity are required. Hence, future studies could focus on developing targeted nanoformulations loaded with anti-tumor phenolic compounds.

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