

Dietary Polyphenols as Antioxidants and Anticancer Agents: More Questions than Answers

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High intake of fruit and vegetables is believed to be beneficial to human health. Fruit, vegetables and some beverages, such as tea and coffee, are particularly rich in dietary polyphenols. Various studies have suggested (but not proven) that dietary polyphenols may protect against cardiovascular diseases, neurodegenerative diseases and some forms of cancer. Dietary polyphenols may exert their anticancer effects through several possible mechanisms, such as removal of carcinogenic agents, modulation of cancer cell signaling and antioxidant enzymatic activities, and induction of apoptosis as well as cell cycle arrest. Some of these effects may be related, at least partly, to their antioxidant activities. In recent years, a new concept of the antioxidant effects of dietary polyphenols has emerged, i.e., direct scavenging activity toward reactive species and indirect antioxidant activity; the latter activity is thought to arise primarily via the activation of nuclear factor-erythroid-2-related factor 2 which stimulates the activities of antioxidant enzymes such as glutathione peroxidase (GPx), glutathione S-transferase, catalase, NAD(P)H: quinone oxidoreductase-1 (NQO1), and/or phase II enzymes. The direct antioxidant activity of dietary polyphenols in vivo is probably limited because of their low concentrations in vivo, except in the gastrointestinal tract where they are present in high concentrations. Paradoxically, the pro-oxidant effect of dietary polyphenols may contribute to the activation of antioxidant enzymes and protective proteins in cultured cells and animal models because of the adaptation of cells and tissues to mild/moderate oxidative stress. Despite a plethora of in vitro studies on dietary polyphenols, many questions remain to be answered, such as: (1) How relevant are the direct and indirect antioxidant activities of dietary polyphenols in vivo? (2) How important are these activities in the anticancer effects of dietary polyphenols? (3) Do the pro-oxidant effects of dietary polyphenols observed in vitro have any relevance in vivo, especially in the potential anticancer effect of dietary polyphenols? Apparently, more carefully-designed in vivo studies are needed to answer these questions. (*Chang Gung Med J* 2011;34:449-60)



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Epidemiological studies suggest that high dietary intake of polyphenols is associated with decreased risk of a range of diseases including cardiovascular disease and some forms of cancer.^(1,2) Fruit, vegetables and some drinks, such as tea and coffee, are particularly rich in polyphenols, and approximately 8000 different compounds have been identified.^(3,4) Numerous cell culture studies and animal studies have demonstrated the antioxidant and anticancer potentials of dietary polyphenols.⁽⁵⁻⁸⁾ The total polyphenol intake has been estimated to be as high as 1 g/d in subjects consuming diets rich in fruit and beverages (fruit juice, wine, tea, coffee, chocolate and beer) and, to a lesser extent vegetables, dry legumes and cereals.^(9,10) The major component of dietary polyphenols is flavonoids. Recently, the mean daily total flavonoid intake in the US was estimated to be 189.7 mg/d, with major food sources being tea (157 mg), citrus fruit juices (8 mg), wine (4 mg), and citrus fruits (3 mg).⁽¹¹⁾ Conceivably, the dietary intake of polyphenols could be much higher in countries where people consume large amounts of plant foods. Obviously, the human intake of dietary polyphenol far exceeds that of vitamins C (100-200 mg/d) and E (7-10 mg/d),^(12,13) although the bioavailability of most dietary polyphenols is very low.⁽¹⁴⁾

Antioxidant activities of dietary polyphenols

Definition of direct and indirect antioxidant activities

Many dietary polyphenols are known antioxidants.^(1,7,15) The term direct and indirect antioxidants were originally used by the Food and Drug Administration to distinguish nutrients that “trap and deactivate reactive oxygen molecules” (e. g., vitamin C, vitamin E, β -carotene) from those that are “precursors of coenzymes that are involved in oxidative stress but do not have direct antioxidant activities” (e. g., zinc, selenium, riboflavin).⁽¹⁶⁾ Later, these terms were redefined by Talalay and associates to describe two types of small-molecule antioxidants that protect against cellular oxidative damage.⁽¹⁶⁻¹⁸⁾ These authors designated direct antioxidants as low molecular-weight compounds (e.g., ascorbate, glutathione, tocopherols, lipoic acid, vitamin K, ubiquinol) that can undergo redox reactions and scavenge reactive species such as reactive oxygen species (ROS) and reactive nitrogen species. Because these direct antioxidants are either consumed or chemically modified in the process of their antioxi-

dant action, they have to be replenished or regenerated. The indirect antioxidants are small-molecule inducers of antioxidant enzymes or cytoprotective proteins that are either redox active or inactive and not consumed in their antioxidant action. It should be pointed out that many dietary polyphenols possess both direct and indirect antioxidant activities in vitro (Fig. 1).⁽¹⁶⁾

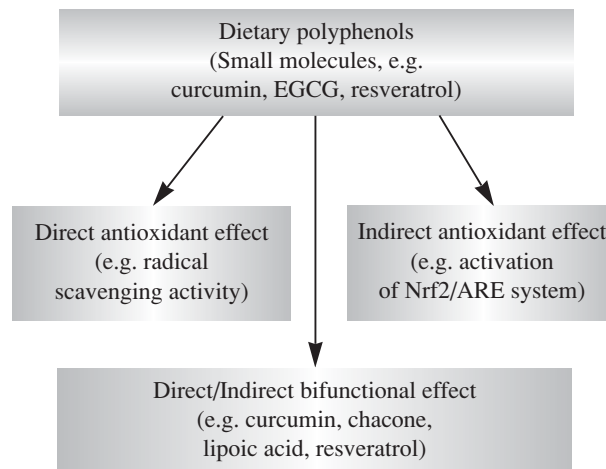


Fig. 1 Diagram illustrates the possible direct and indirect antioxidant activities of some dietary polyphenols.

Direct antioxidant activities of dietary polyphenols

Numerous cell culture studies and animal studies have shown that dietary phytochemicals possess antioxidant activities and can thus protect against oxidative insult to culture cells. However, despite the vast amount of research, the direct antioxidant effects have been questioned.^(8,19,20) For instance, many in vitro studies on the antioxidant activity of phytochemicals routinely employ relatively high concentrations in cell culture studies (often in the 10-100 μ M range) compared with the average concentration of most plant polyphenols in plasma, which rarely exceeds 1 μ M in subjects consuming large amounts of dietary polyphenols⁽²¹⁾ or 10-100 mg⁽¹⁰⁾ or 26 to 1549 μ mole⁽¹⁴⁾ in individuals taking supplements of a single phenolic compound. Indeed, most of the in vitro studies that have shown the biological effects of the green tea polyphenol (-)-epigallocatechin gallate (EGCG) employed EGCG concentrations that exceed those found in plasma and animal tissues by 10- to 100-fold, rendering the relevance of

these in vitro findings unclear for in vivo chemoprevention.^(20,22,23) In particular, such direct oxidant-scavenging activities in vivo would be relatively limited, if not completely absent, when one considers the competition from many antioxidants that are present in the serum at much higher levels. For instance, levels of plasma vitamin C range from 26.1 to 84.6 μM (average 50 μM)^(24,25) and those for vitamin E from 20-30 μM ,^(26,27) while albumin and urate are normally present at levels of several hundred μM .⁽²⁸⁾ Indeed, it is unclear whether the so-called antioxidant phytochemicals including plant polyphenols and flavonoids have any direct antioxidant effects in vivo,^(19,29) although they might be capable of exerting such effects within the gastrointestinal tract, where polyphenols may come into direct contact with cells without having undergone absorption and metabolism.⁽³⁰⁻³²⁾

Indirect antioxidant activities of dietary polyphenols

Evidence is cumulating which shows that many phytochemicals, such as EGCG, lycopene, curcumin and sulforaphane, are capable of exerting indirect antioxidant activities by enhancing the expression of antioxidant enzymes and cytoprotective proteins such as NAD(P)H: quinone oxidoreductase-1 (NQO1), superoxide dismutase, glutathione S-transferase (GST), glutathione peroxidase (GPx), heme oxygenase-1 (HO-1), glutamate cysteine ligase, catalase, and thioredoxin.^(7,16,20,33-36) Importantly, these indirect antioxidants may be more efficient antioxidants because they exert their antioxidant effects through upregulation of antioxidant enzymes or cytoprotective proteins that play important roles in cellular protection.^(17,18)

The Nrf2/Keap1-ARE system

The enhanced expression of antioxidant enzymes such as GPx, catalase, NQO1, GST and cytoprotective proteins by many phytochemicals are often controlled by nuclear factor-erythroid-2-related factor 2 (Nrf2), a member of the NF-E2 family of the basic leucine zipper transcription factors. Under normal physiological conditions, Nrf2 is inactive due to binding by the skeletal actin-binding protein, Kelch-like ECH-associated protein 1 (Keap1), which targets Nrf2 for proteasome degradation.^(1,37-39) Phosphorylation of Nrf2 protein allows its translocation to the nuclei and binding to the antioxidant responsive ele-

ment (ARE) of antioxidant genes, leading to the activated expression of antioxidant enzymes. Nuclear translocation and transcriptional activation of Nrf2 are regulated by several upstream kinases, such as mitogen-activated protein kinases (MAPK), phosphatidylinositol 3-kinase (PI3K)/Akt, protein kinase C (PKC) and casein kinase-2.^(1,6,37,39)

The cysteine residues present in Keap1 appear to function as redox sensors, and certain dietary chemopreventive agents can oxidize or chemically modify the specific cysteine thiols.^(16,37,39) Such oxidation or chemical modification of some of the highly reactive thiol groups facilitates the dissociation of Nrf2 from Keap1 and subsequent nuclear translocation. As a result, the Nrf2/Keap1-ARE signaling pathway has been considered a unique "redox switch" that can be turned on in response to oxidative stress.^(1,37,39) It is noteworthy that many dietary polyphenols can modify or oxidize Keap1 cysteine thiols, possibly through spontaneous or enzymatic oxidation to form ROS.^(37,39) In this respect, epigallocatechin gallate (EGCG) is known to produce a substantial amount of hydrogen peroxide (H_2O_2) under cell culture conditions. In addition, some polyphenols that contain Michael acceptors, such as curcumin and sulforaphane, can react with Keap1 thiol groups directly to result in conformational changes of Keap1 protein that leads to its separation from Nrf2.^(1,37,39)

NF- κ B signaling

Nuclear factor kappa B (NF- κ B) regulates expression of genes that are involved in cellular differentiation, proliferation, apoptosis, oxidative response, inflammation, and immune response,⁽⁴⁰⁾ and as such it has been identified as a promising therapeutic target in chronic diseases.⁽⁴¹⁾ NF- κ B has been described as a redox-regulated transcription factor because it can be activated by oxidative stress and inhibited by various antioxidants.⁽⁴²⁾ Normally, the NF- κ B dimers (predominantly a heterodimer of p50 and p65 proteins) are mainly located in the cytosol bound to the inhibitors of NF- κ B, the I κ Bs. Numerous agents can activate NF- κ B through phosphorylation of I κ B by the I κ B-kinase complex. Upon phosphorylation, I κ B is degraded, and the NF- κ B dimer translocates into the nucleus, binds to specific target sequences in DNA and promotes transcription.⁽⁴³⁾ Persistent and aberrant upregulation of NF-

κ B activity is associated with the etiology of many human diseases including cancers.^(44,45) Notably, the anticancer activities of many phytochemicals appear to be associated with the inhibition of NF- κ B.^(6,46,47) However, mild and moderate repetitive activation of NF- κ B can be protective against certain diseases.⁽²⁸⁾ In this respect, it has been shown that pre-conditioned activation of NF- κ B is protective against sepsis,⁽⁴⁸⁾ coronary heart disease,^(49,50) hepatic ischemia injury⁽⁵¹⁾ and cerebral diseases such as ischemia or epilepsy.⁽⁵²⁾ Thus, it is evident that the activation of NF- κ B can be either cytoprotective or cytotoxic, depending on the extent of the activation by a stimulus.

It should be pointed out that, although NF- κ B is redox-sensitive and that most dietary phytochemicals possess antioxidant activities, the effects of dietary polyphenols on NF- κ B are not necessarily dependent on their antioxidant properties. In this respect, an earlier study has shown that the inhibitory effects of the antioxidant compounds N-acetyl-L-cysteine and pyrrolidine dithiocarbamate, on NF- κ B activation are not dependent on their antioxidant activities but are likely due to non-antioxidant properties.⁽⁵³⁾ In addition, after screening 34 dietary plants for their ability to induce basal NF- κ B activity or to inhibit lipopolysaccharide (LPS)-induced NF- κ B activity, Paur et al. found no correlation between the ability to inhibit LPS-induced NF- κ B activity and antioxidant activity.⁽⁵⁴⁾ Instead, as proposed by these authors,⁽⁵⁴⁾ the ability of several plant extracts and spices to slightly induce basal (i.e., not LPS-induced) NF- κ B activity may be one mechanism underlying the preventive effect of a diet rich in plant-based foods on the development of chronic diseases. They further suggest that small and repetitive activation of NF- κ B by such diets may be beneficial in preconditioning cells and tissues against later, stronger insults.

Potential cross talk between Nrf2 and NF- κ B

Although dietary polyphenols can modulate various signal transduction cascades,⁽⁶⁾ very little is known whether there is cross talk between Nrf2 and NF- κ B for any specific compound in the same cell or tissue. Theoretically, cross talk between these two transcription factors seems likely because their upstream signaling pathways, such as MAPK, PI3K and PKC, are closely interconnected.⁽³⁸⁾ For example, using gene expression profiling to identify genes

modulated by genistein in LNCaP cells, an androgen-dependent prostate cancer cell line, Bhamre et al. found that genistein (at 2 and 15 μ M) significantly and dose-dependently alters expression of transcripts involved in cell growth, carcinogen defenses and steroid signaling pathways.⁽⁵⁵⁾ The effective activation of NQO1 enzymatic activity by genistein is indicative of activation of Nrf2, and additional pathways, such as PI3K signaling, appear to be modulated by physiologically relevant levels of genistein. Some phytochemicals, such as curcumin and sulforaphane, can inhibit overexpression of NF- κ B and/or activate Nrf2, and these actions may involve the modification of the cysteine moiety in p50 (one of the heterodimers in NF- κ B) and Keap1.⁽²⁰⁾ Interestingly, a recent study by Tusi et al. on the neuroprotective effects of triazine derivatives, which possess various biological properties including anticancer activity, showed that these compounds exert their protective effect by up-regulation of HO-1, glutamylcysteine synthetase, GPx and Nrf2, while they inhibit NF- κ B and decrease lipid peroxidation.⁽⁴⁰⁾ These results suggest that there is potential cross talk between NF- κ B and Nrf2.

Dietary polyphenols as anticancer agents

The term “anticancer activity” of any substance including phytochemicals in the literature is often loosely defined, as it refers to both in vitro and in vivo chemopreventive effects and the treatment of cancer cells that may include antiproliferation, killing cancer cells, causing cell cycle arrest and/or inhibition of cancer angiogenesis and metastasis. In other words, the term “anticancer activity” encompasses, but is not equivalent to “chemotherapeutic activity.” The chemotherapeutic activity in cultured cells and animal models is sometimes referred to as inhibition of tumor angiogenesis and inhibition of metastasis,⁽⁶⁾ in addition to direct killing of cancer cells.

It is widely accepted that a diet rich in plant-based foods is beneficial for cancer prevention and that the polyphenols from fruits or vegetables are responsible, at least in part, for the chemopreventive effects.^(6,7,35) Notable examples of anticancer polyphenols include green tea catechins, curcumin, resveratrol and genistein. The process of carcinogenesis includes initiation, promotion and progression.^(56,57) It has been shown that dietary phytochemicals can

interfere with each stage of carcinogenesis to halt cancer development.^(1,5) As in the case of direct antioxidant effects, dietary polyphenols are most likely to exert their chemopreventive effects in the gastrointestinal tract where they are present in the highest concentrations.^(29,58-60) Indeed, studies have shown that various polyphenol-rich fruits and vegetables are particularly effective in protecting against colon cancer development.^(59,60)

Possible anticancer mechanisms of dietary polyphenols

Dietary polyphenols may exert their anticancer effects via a variety of mechanisms such as removal of carcinogenic agents, modulation of cancer cell signaling and antioxidant enzymatic activities, and induction of apoptosis and cell cycle arrest.^(6-8,37) Some of these effects may be related, at least partly, to their indirect antioxidant activities. For example, the enhancement of GPx, catalase, NQO1, GST and/or phase II enzyme activities by polyphenols could help the detoxification of carcinogenic agents, as we discussed earlier. Paradoxically, the pro-oxidant activity of dietary polyphenols may also contribute to their anticancer effects, as discussed below.

Dietary polyphenols and signaling pathways

As discussed earlier, dietary polyphenols are known to modulate Nrf2 and NF- κ B. Indeed, dietary polyphenols may exert their biological effects through modulation of various cellular signaling pathways.^(6,61,62) A plethora of in vitro evidence shows that dietary polyphenols are specifically capable of affecting MAPK and PI3K, which are involved in cancer cell proliferation.⁽⁶³⁻⁶⁵⁾ Importantly, the MAPK signaling pathway has been considered an attractive pathway for anticancer chemotherapy because of its pivotal role in regulating the growth and survival of various cancer cells.⁽⁶⁶⁾ In this respect, apple procyanidins were found to inhibit cell growth, activate caspase-3 and increase MAPK levels and PKC activity in SW620 cells (a colon cancer-derived metastatic cell line).⁽⁶⁷⁾ Similarly, olive oil polyphenols have been shown to strongly inhibit the growth of colon adenocarcinoma cells through the inhibition of p38/CREB signaling.⁽⁶⁸⁾ However, a dietary polyphenol may exhibit opposite effects on MAPK depending on the concentrations. For example, it has been shown that low concentrations of dietary polyphenols,

such as quercetin, green tea polyphenols and EGCG, can activate MAPK pathways [extracellular signal-regulated kinase (ERK), C-Jun N-terminal Kinase (JNK)] leading to expression of survival genes (c-fos, c-jun),⁽⁶⁹⁾ whereas higher concentrations of quercetin and EGCG can activate the caspase pathway that leads to apoptosis.⁽⁷⁰⁻⁷²⁾

Differential apoptosis-inducing effects of dietary polyphenols in cancer cells

Apoptosis is a complex process that leads to programmed cell death involving either the mitochondria (the intrinsic pathway) or the activation of death receptors (extrinsic pathway). The intrinsic and extrinsic pathways induce the activation of caspases, which are classified as initiator caspases (caspase-2, -8, -9 and -10) and effector caspases (caspase-3, -6 and -7). The two pathways then converge to induce the activation of caspase-3, leading to apoptosis.⁽⁷³⁾ DNA damage and oxidative stress are the common signals that activate the mitochondrial apoptotic pathway, leading to mitochondrial membrane rupture and cytochrome C release.^(73,74)

Numerous studies have suggested that the anticancer ability of some dietary polyphenols such as quercetin, luteolin, genistein, apigenin, and resveratrol, is attributable to the induction of apoptosis in various cancer cells and animal models.^(1,4,6-8,37,38,75) Along the same line, the apoptosis-inducing effect of EGCG in numerous cell lines has been shown to result from increased Fas expression and caspases-3, -9 and -8,⁽⁷⁶⁻⁷⁹⁾ as well as from the inhibition of apoptosis-suppressing proteins, B-cell lymphoma (Bcl)-2, Bcl-extra large (Bcl-xL) and BH3 interacting domain death agonist.^(78,80) Along the same line, ellagic acid was found to induce apoptosis in colon cancer Caco-2 cells via the intrinsic pathway (FAS-independent, caspase 8-independent) by down-regulation of Bcl-xL and release of cytochrome C.⁽⁸¹⁾ Interestingly, ellagic acid and quercetin synergistically induce apoptosis in diverse cancer cell lines.⁽⁸²⁾

Importantly, many dietary polyphenols have been shown to be more cytotoxic in various cancer cells than in normal cells.⁽⁸³⁻⁸⁹⁾ Some studies have even found that polyphenols such as EGCG and genistein cause apoptotic cell death in cancer cell lines but not in normal cells.^(90,91) However, it is unclear how this differential effect may occur. Recently, it has been proposed that dietary phyto-

chemicals may differentially modulate signal transduction cascades in normal cells and cancer cells.⁽³⁸⁾ This hypothesis states that dietary phytochemicals can protect cells by activation of Nrf2 in normal cells but cause cytotoxicity by overexpression of transcription factors NF- κ B and activator protein (AP-1) in abnormal cancer cells. However, it should be noted that some dietary polyphenols can also activate Nrf2 signaling in cancer cells, as exemplified by the effective activation of NQO-1 enzymatic activity by genistein in LNCaP cells,⁽⁵⁵⁾ which is indicative of activation of Nrf2. Additional examples are the induction of the Nrf2 signaling pathway by EGCG in colon cancer Caco-2 cells and in mice⁽⁹²⁾ as well as by sulforaphane (an organosulfur compound found in high amounts in cruciferous vegetables) in Caco-2 cells.⁽⁹³⁾ Therefore, the activation of Nrf2 by dietary polyphenols can occur in both normal cells and cancer cells. More studies are needed to test the hypothesis of differential cytotoxic effects of dietary polyphenols.⁽³⁸⁾

Pro-oxidant effects of dietary polyphenols

Many polyphenols are known to have pro-oxidant activities both in vitro and in vivo, and these pro-oxidant activities may contribute to some of their biological properties such as antioxidant and anti-cancer effects.^(29,37) This pro-oxidant activity is most prominent under in vitro conditions such as at a high pH in the presence of high concentrations of transition metal ions and oxygen molecules.⁽⁹⁴⁾ Notably, small phenolics that are easily oxidized such as quercetin and gallic acid possess pro-oxidant activity, whereas high molecular weight phenolics, such as condensed and hydrolysable tannins, have little or no prooxidant activity.⁽⁹⁵⁾ The pro-oxidant property of dietary polyphenols may result from several possible mechanisms such as chemical instability, deletion of cellular glutathione (GSH) and mobilization of cellular copper ions.

Instability of polyphenols under cell culture conditions

Many polyphenols are structurally unstable and can undergo enzymatic or spontaneous oxidation in the presence of metal ions, especially in cell cultures, to form ROS.^(1,39,96) For instance, EGCG was found to produce substantial amounts of H₂O₂ under cell culture conditions.^(97,98) Similarly, the cytotoxicity of

green tea and red wines on PC12 cells in Dulbecco's modified Eagle's medium (DMEM), can be attributed, at least partially, to H₂O₂ produced by these beverages.⁽⁹⁹⁾ Exactly how phytochemicals such as polyphenols become pro-oxidant is not clearly understood. However, cell culture media are known to be contaminated with transition metal ions; an example is DMEM, which contains added inorganic iron, usually as Fe (NO₃)₃, giving it even greater pro-oxidant properties.^(28,96) In addition, most cells in culture are grown under high oxygen conditions (i.e., 95% air/5% CO₂ or about 150 mm Hg) and low concentrations of ascorbate, vitamin E and selenium, leading to artifact results. Amusingly, such artificial conditions have been referred to as *Culture shock*.⁽⁹⁶⁾

Depletion of cellular GSH

Several dietary polyphenols have been shown to cause depletion of cellular GSH, which may contribute to tumor cell apoptosis. For instance, Kachadourian and Day showed that the flavones chrysin and apigenin effectively deplete GSH in lung tumor (A549) and myeloid tumor (HL-60) cells, while hydroxychalcone (2'-HC) and the dihydroxy-chalcones (2',2-, 2',3-, 2',4-, and 2',5'-DHC) are more effective in prostate PC-3 tumor cells.⁽¹⁰⁰⁾ When chrysin and 2',5'-DHC were tested for their abilities to potentiate the toxicities of pro-oxidants (etoposide, rotenone, 2-methoxyestradiol, and curcumin), these authors found that the potentiating effects of these two flavones involve mitochondrial dysfunction by depletion of mitochondrial GSH levels, decreased mitochondrial membrane potential and increased cytochrome C release.⁽¹⁰⁰⁾ Similarly, Galati et al. have shown that luteolin and quercetin exert their pro-oxidant activity in isolated rat hepatocytes by depleting GSH without causing glutathione disulfide formation.⁽¹⁰¹⁾ Using mass spectrometry, these polyphenols were found to form GSH conjugates.⁽¹⁰¹⁻¹⁰³⁾ Later, Galati et al. showed that green tea catechins and phenolic acids cause mitochondrial toxicity and formation of ROS in isolated rat hepatocytes.⁽¹⁰⁴⁾ However, they also identified the GSH conjugates of gallic acid and EGCG, and they proposed a possible mechanism for metabolism of gallic acid which involves the reaction of GSH with the metabolite ortho-quinone.⁽¹⁰⁴⁾ The identification and quantification of phenolic metabolites in vivo represent an important area that requires vigorous study.

Mobilization of cellular copper ions

Several dietary polyphenols such as resveratrol and caffeic acid have been shown to cause cellular DNA damage through mobilization of endogenous copper ions, possibly chromatin-bound copper, leading to the production of ROS.⁽¹⁰⁵⁻¹⁰⁹⁾ The preferential cytotoxicity toward cancer cells is likely due to the elevated levels of copper, but not iron ions, in cancer tissues and cells.^(110,111) The mechanism behind the increased copper concentration in tumors is not yet clear, but it has been shown that copper transporter 1, a high-affinity copper transporter in humans, is over-expressed in malignant cells, leading to increased uptake and accumulation of copper.⁽¹¹²⁾ In addition, it has been suggested that copper may be required for the expression of ceruloplasmin, which is a major copper-binding protein that is also elevated in cancer cells⁽¹¹³⁾ and has been proposed to be an endogenous angiogenic stimulator.⁽¹¹⁴⁾ Thus far, very little *in vivo* evidence is available for this notion. One study has shown that curcumin increases lipid peroxidation, presumably by interaction with copper ions, in the Long-Evans cinnamon rat, which has defective gene for coding Cu²⁺-transporting ATPase, leading to accumulation of copper in the liver.⁽¹¹⁵⁾ More *in vivo* studies are needed to substantiate such a mechanism.

Conclusion

Various studies have suggested (but not proven) that dietary polyphenols are more than just antioxidants; they have multiple biological functions including anticancer effects. The anticancer effects of dietary polyphenols may involve several possible mechanisms in addition to antioxidant activity, which can be classified as direct and indirect antioxidant activities. While the *in vivo* relevance of the direct antioxidant activity of dietary polyphenols has been questioned in recent years, the *in vivo* importance of their indirect antioxidant activities is gaining increasing recognition. Paradoxically, the activation of antioxidant enzymes and protective proteins by some phytochemicals in cultured cells or in animal models is likely due to the pro-oxidant effect of these phytochemicals, because cells can adapt to mild to moderate oxidative stress by enhancing the synthesis of antioxidant enzymes and cytoprotective proteins. However, many questions remain to be answered. First, do dietary polyphenols and other phytochemicals have any significant direct and indirect antioxi-

dant activities *in vivo*? Second, even if dietary polyphenols do have antioxidant activities *in vivo*, how important are these activities in the anticancer effects of dietary polyphenols? Third, are the pro-oxidant effects of dietary polyphenols of any physiological relevance? Are these effects related to the anticancer effects of dietary polyphenols? Apparently, more studies are required to answer these questions. Thus far, it seems that the comment made by Halliwell that “a protective effect of diet is not equivalent to a protective effect of antioxidants in diet,”^(28,55) is a prudent conclusion to some of these questions.

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膳食多酚類的抗氧化以及抗癌活性：問題多於答案

胡淼琳

多攝取蔬果對於人體健康具有益處。許多研究指出蔬果及茶類飲料中的多酚化合物具有預防心血管疾病、神經退化性疾病以及某些癌症的發生。這些膳食多酚類可藉由移除致癌物、調控癌細胞訊號傳遞、調節抗氧化酵素活性以及誘導癌細胞凋亡與遏止細胞週期，而達到抗癌作用。膳食多酚類的抗癌作用至少部分與其抗氧化活性有關。近幾年來對於膳食多酚類的抗氧化作用出現一些新的概念，亦即區分為直接清除活性分子的『直接抗氧化作用』以及經由誘發細胞抗氧化酵素的『間接抗氧化作用』；後者主要藉由活化轉錄因子 Nrf2，進而刺激下游抗氧化酵素活性如穀胱甘肽過氧化酶、穀胱甘肽轉移酶、觸酶等。在活體內，膳食多酚類要達到直接抗氧化的能力相當困難，原因是它們在活體內的濃度很低，只有在腸胃道才會有較高濃度。吊詭的是，細胞及動物研究顯示，膳食多酚類可在細胞與組織內產生溫和的氧化壓力，而此種溫和促氧化作用可能是使細胞抗氧化酵素及保護性蛋白表現增加的原因。雖然有關膳食多酚類的活體外研究已經很多，但許多問題仍待解決，如：(1) 膳食多酚類及其他植物化合物在活體內是否具有直接及間接抗氧化活性？(2) 即使膳食多酚類在活體內具有抗氧化活性，此種抗氧化活性與膳食多酚類的抗癌作用是否有關？(3) 膳食多酚類在活體外的促氧化作用在活體內是否會發生？是否與它們的抗癌作用有關？顯然，這些問題都需要更多活體內研究才可能會有答案。(長庚醫誌 2011;34:449-60)

關鍵詞：膳食多酚類，抗氧化，促氧化，抗癌，訊息傳遞

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