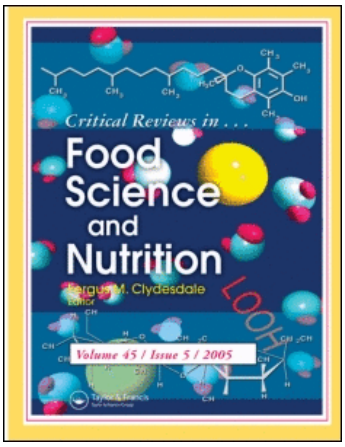

Critical Reviews in Food Science and Nutrition

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713606380

Dietary Polyphenols and the Prevention of Diseases

Augustin Scalbert [a]; Claudine Manach [a]; Christine Morand [a]; Christian Rémésy [a]; Liliana Jiménez [b]
[a] Laboratoire des Maladies Métaboliques et Micronutriments Centre de Recherche de Clermont-Ferrand/Theix, INRA, St-Genès-Champanelle, France [b] Danone Vitapole Recherche, Palaiseau Cedex, France

Online Publication Date: 01 June 2005

To cite this Article Scalbert, Augustin, Manach, Claudine, Morand, Christine, Rémésy, Christian and Jiménez, Liliana(2005)'Dietary Polyphenols and the Prevention of Diseases',Critical Reviews in Food Science and Nutrition,45:4,287 — 306

To link to this Article: DOI: 10.1080/1040869059096

URL: http://dx.doi.org/10.1080/1040869059096

Critical Reviews in Food Science and Nutrition, 45:287–306 (2005)

ISSN: 1040-8398
DOI: 10.1080/1040869059096

Taylor & Francis
Taylor & Francis Group

Dietary Polyphenols and the Prevention of Diseases

AUGUSTIN SCALBERT, CLAUDINE MANACH, CHRISTINE MORAND, and CHRISTIAN RÉMÉSY

Laboratoire des Maladies Métaboliques et Micronutriments, INRA, Centre de Recherche de Clermont-Ferrand/Theix, St-Genès-Champanelle, France

LILIANA JIMÉNEZ

Danone Vitapole Recherche, Palaiseau Cedex, France

Polyphenols are the most abundant antioxidants in the diet and are widespread constituents of fruits, vegetables, cereals, dry legumes, chocolate, and beverages, such as tea, coffee, or wine. Experimental studies on animals or cultured human cell lines support a role of polyphenols in the prevention of cardiovascular diseases, cancers, neurodegenerative diseases, diabetes, or osteoporosis. However, it is very difficult to predict from these results the effects of polyphenol intake on disease prevention in humans. One of the reasons is that these studies have often been conducted at doses or concentrations far beyond those documented in humans. The few clinical studies on biomarkers of oxidative stress, cardiovascular disease risk factors, and tumor or bone resorption biomarkers have often led to contradictory results. Epidemiological studies have repeatedly shown an inverse association between the risk of myocardial infarction and the consumption of tea and wine or the intake level of some particular flavonoids, but no clear associations have been found between cancer risk and polyphenol consumption. More human studies are needed to provide clear evidence of their health protective effects and to better evaluate the risks possibly resulting from too high a polyphenol consumption.

Keywords antioxidants, cancers, cardiovascular diseases, diabetes, flavonoids, neurodegenerative diseases, osteoporosis, polyphenols

INTRODUCTION

Polyphenols are common constituents of foods of plant origin and major antioxidants of our diet. The main dietary sources of polyphenols are fruits and beverages. Fruits like apple, grape, pear, cherry, and various berries contain up to 200–300 mg polyphenols per 100 g fresh weight. Typically, a glass of red wine or a cup of tea or coffee contains about 100 mg polyphenols. Cereals, chocolate, and dry legumes also contribute to the polyphenol intake. The total dietary intake is about 1 g/d. It is much higher than that of all other known dietary antioxidants, about 10 times higher than that of vitamin C and 100 times higher than those of vitamin E and carotenoids.[1]

Several hundreds of different polyphenols have been identified in foods.[1–3] The two main types of polyphenols are flavonoids and phenolic acids. Flavonoids are themselves distributed among several classes: flavones, flavonols, flavanols, flavanones, isoflavones, proanthocyanidins, and anthocyanins. Some of the most common flavonoids are quercetin, a flavonol abundant in onion, tea, and apple; catechin, a flavanol found in tea and several fruits; hesperetin, a flavanone present in citrus fruits; cyanidin, an anthocyanin giving its color to many red fruits (blackcurrant, raspberry, strawberry, etc.); daidzein, the main isoflavone in soybean; proanthocyanidins, common in many fruits, such as apple, grape, or cocoa and are responsible for their characteristic astringency or bitterness (Figure 1). One of the most common phenolic acids is caffeic acid, present in many fruits and vegetables, most often esterified with quinic acid as in chlorogenic acid, which is the major phenolic compound in coffee. Another common phenolic acid is ferulic acid, which is present in cereals and is esterified to hemicelluloses in the cell wall.

As antioxidants, polyphenols may protect cell constituents against oxidative damage and, therefore, limit the risk of various degenerative diseases associated to oxidative stress. As

Address correspondence to Augustin Scalbert, Laboratoire des Maladies Métaboliques et Micronutriments, INRA, Centre de Recherche de Clermont-Ferrand/Theix, 63122 St-Genès-Champanelle, France. E-mail: scalbert@clermont.inra.fr

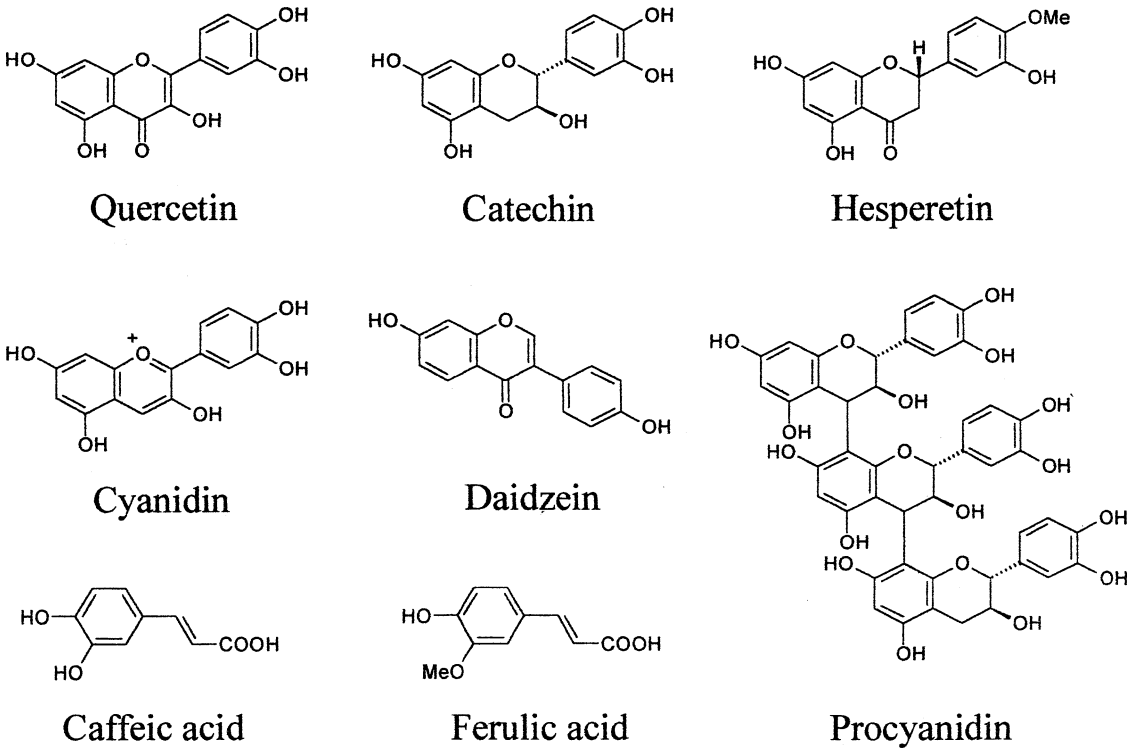

Figure 1 Chemical structures of a few common dietary polyphenols.

compared to other antioxidants, research on their health effects started more recently. This late interest for polyphenols is largely explained by the complexity of their chemical structures. Numerous studies on animal models have shown that, when added to the diet, they limit the development of cancers, cardiovascular diseases, neurodegenerative diseases, diabetes, and osteoporosis (see[4] for a review and references cited in the following sections). The purpose of this article is to critically review first the antioxidant effects of polyphenols and their relevance for health, and secondly the experimental evidence supporting a protective role of polyphenols against the main degenerative diseases effecting Westernized populations. Emphasis is placed on clinical and epidemiological studies. Evidence based on animal experiments is also presented and discussed with regards to the doses of polyphenols administered which may widely differ from those experienced by humans with their diet. The mechanisms of action as suggested by animal and *in vitro* studies are also briefly summarized. Lastly, the possible risks associated to high polyphenol consumption are discussed.

ANTIOXIDANT PROPERTIES OF POLYPHENOLS

Degenerative diseases, such as cancers, cardiovascular diseases, osteoporosis, and degenerative diseases, are associated with aging. Oxidative damage to cell components, DNA, proteins, and lipids accumulates with age and contributes to the degeneration of the somatic cells and to the pathogenesis of these diseases. Antioxidants present in food can help limit this damage by acting directly on reactive oxygen species or by stimulating endogenous defence systems. The phenolic groups in polyphenols can accept an electron to form relatively stable phenoxyl radicals, thereby disrupting chain oxidation reactions in cellular components.[5]

The antioxidant potency of polyphenols has been evaluated *in vitro* by measuring their ability to trap free radicals and reduce other chemicals. Their potency is compared to that of a reference substance, usually Trolox (a water-soluble derivative of vitamin E), gallic acid, or catechin. In all cases, the reaction studied is the reduction of an oxidant by polyphenols. The most commonly used oxidants are listed below:

1. $ABTS^{\circ+}$ formed from ABTS (2,24-azonobis(3-ethylbenzothiazoline-6-sulphonic acid) in the presence of metmyoglobin and hydrogen peroxide.[6] The reaction is monitored by colorimetric determination of the colored $ABTS^{\circ+}$ radical. This method is often referred to as the TEAC method (Trolox Equivalent Antioxidant Capacity).
2. Radicals formed by heating AAPH (2,2′-azobis (2-amidinopropane) dihydrochloride) or ABAP (2,2′-azobis (2-aminodopropane) hydrochloride). The radical concentration is usually monitored by following the degradation of phycoerythrin by fluorimetry. This technique is known as the ORAC (Oxygen Radical Absorbance Capacity)[7] or TRAP method (Total Radical-trapping Antioxidant Parameter).[8]
3. Ferric ions: This approach is known as the FRAP method (Ferric-Reducing Ability of Plasma).[9]
4. Radicals formed by autoxidation of linoleic acid.[10]

Polyphenols with catechol groups (aromatic rings with two hydroxyl groups in the ortho position) have greater antioxidant potency than those with simple phenol groups (aromatic rings with a single hydroxyl group). Quercetin and epigallocatechin, for example, have been shown to be excellent traps for $ABTS^{\circ+}$ and are almost five times more active than Trolox at equivalent molar concentrations.[11,12]

However, the value of such measurements for comparing the potential health benefits of isolated polyphenols or plant extracts is limited for a number of reasons:

1. Quite different results are observed when the antioxidant properties of different polyphenols are compared using different assays. There is, thus, no clear correlation between the ability of 13 different phenolic compounds to reduce $ABTS^{\circ+}$ on the one hand[11] or radicals derived from AAPH on the other hand[13] (Figure 2).
2. Polyphenols are extensively metabolized in the body, and the majority of catechol nuclei are methylated, dehydroxylated, or conjugated by *O*-glucuronidation and formation of sulphate esters.[1,3] These reactions modify their antioxidant capacity.[14] *O*-Conjugation of the catechol hydroxyl group prevent their oxidation and transformation into toxic quinones. The quinones formed from by oxidation of catechol substrates, such as plant polyphenols, oestrogens, and catecholamines, participate to redox cycles that generate superoxide radicals or react with nucleophilic cell components.[15–17] The catechol polyphenols with the greatest antioxidant capacity may, thus, also be the most toxic. Polyphenol metabolism could account for the absence of carcinogenicity of quercetin despite its well established mutagenic properties *in vitro*.[18]
3. Antioxidant properties of polyphenols largely depend on their chemical and physico-chemical environment, which varies according to tissues and physiological conditions and a fortiori from the conditions of the *in vitro* antioxidant assays.The major influence of the presence of plasma proteins, such as albumin,[19] and the presence of other antioxidants[20] has been described.
4. The impact of polyphenols on antioxidant protection of tissues has been previously determined by their bioavailability, which differs considerably from one polyphenol to the other.[1,3]

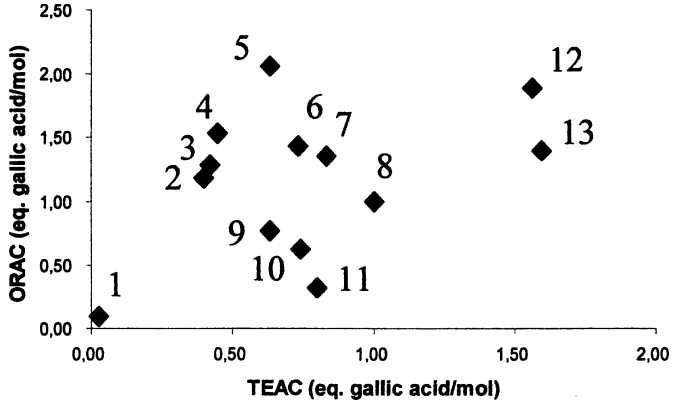

Figure 2 Comparison of the antioxidant potency of 13 different polyphenols using two different antioxidant assays. TEAC and ORAC data respectively reproduced from Rice-Evans et al., 1995[11] and Guo et al., 1997[13] 1, 4-Hydroxybenzoic acid; 2, 3,4-dihydroxybenzoic acid; 3, caffeic acid; 4, kaempferol; 5, dihydroquercetin; 6, catechin; 7, epicatechin; 8, gallic acid; 9, ferulic acid; 10, *p*-coumaric acid; 11, rutin; 12, quercetin; 13, epigallocatechin gallate.

It should, therefore, not be a surprise that no correlation between the antioxidant potency of various polyphenols measured *in vitro* and their biological activity determined *in vivo* or at the cellular level has ever been published.

In summary, health benefits of polyphenols cannot be merely reduced to their antioxidant potency as measured *in vitro*. Antioxidant assays applied to different polyphenols or to food extracts are of poor predictive value to compare their health benefits. A precise examination of the type and content of the different polyphenols in a given plant extract or food should clearly be prefered. However, this does not exclude redox properties of polyphenols from being key factors that may trigger various cell responses at the origin of their biological effects.[21]

When ingested, polyphenol-rich foods and beverages increase the antioxidative capacity of plasma. The antioxidative capacity is measured by the same methods as those used to compare different food extracts *in vitro*, chiefly ORAC and FRAP, or by a chemiluminescence assay, where the decomposition of free radicals formed by horseradish peroxidase from sodium perborate or hydrogen peroxide is followed by their reaction to luminol, which emits light on decomposition.[22,23] Increased antioxidative capacity is systematically observed over the hours following the intake of polyphenol-rich beverages, such as tea,[24–27] wine,[7,27–31] and beer,[32] as well as fruit and vegetables rich in polyphenols, such as strawberries and spinach.[7] This increase in the plasma antioxidative capacity of plasma following the consumption of polyphenol-rich food may be explained either by the presence of reducing polyphenols and their metabolites in plasma, by their effects upon concentrations of other reducing agents (sparing effects of polyphenols on other endogenous antioxidants), or by their effect on the absorption of pro-oxidative food components, such as iron (see section Risks Associated to Polyphenol Consumption).

If it is well established that polyphenol ingestion results in an increase of the plasma antioxidant capacity, there is still some uncertainties about its efficiency to enhance the protection of cellular components, such as lipids or DNA, against oxidative stress in humans. In some studies, polyphenol intake reduced the plasma concentration of lipid oxidation products. The ingestion of tea catechins (250 mg) by healthy volunteers decreased the plasma concentrations of phospholipid peroxides.[33] Similarly, the consumption of polyphenol-rich blackcurrant and apple juice by healthy volunteers (1.5 l/d for 7 d) significantly reduced the plasma concentrations of malondialdehyde (MDA).[34] The consumption of chocolate (80 g) also resulted in decreased

concentrations of oxidised lipids, as measured by reaction with thiobarbituric acid.[35] In contrast, the consumption of red wine (200 mL per d for 10 d) had no significant effect on plasma MDA levels.[36] The consumption of 55 mg of isoflavones for 8 wk had no effect upon concentrations of F_2-isoprostane, a marker of lipid peroxidation.[37]

The effects of polyphenols on the stability of deoxyribonucleic acids (DNA) have also been examined. *In vitro*, polyphenols can have either harmful or protective effects. In the presence of transition metals, such as Cu(II) and Fe(III), phenolic compounds induce the breakage of DNA.[38,39] Such effects are caused by a reduction of these transition metals that, once reduced, catalyze the formation of hydroxyl radical (OH°) (Fenton reaction). These reactions have also been noted in cultured cells.[40] Such breakage of DNA has been considered both beneficial (cytotoxic and apoptotic effects on tumor cells) and toxic (mutagenic effects on normal cells).

Conversely, polyphenols may also protect DNA against degradation induced by cytotoxic agents. *In vitro*, they can inhibit the formation of adducts between activated polycyclic hydrocarbons and DNA.[41] In particular, the antimutagenic properties of ellagic acid have been clearly established, at least in *Salmonella typhimurium*,[42] and have been explained by the formation of inactive adducts between activated carcinogens and ellagic acid,[43] or by inhibition of aryl hydrocarbon hydroxylase responsible for the activation of polycyclic hydrocarbons.[44]

A number of *in vivo* studies have demonstrated the protective effect of polyphenol consumption against DNA damage. In the rat, wine polyphenols added to the diet protected hepatic DNA against oxidative damage induced by 2-nitropropane.[45] Similar effects were observed with ellagic acid, but not epigallocatechin gallate (EGCG).[46] Wine polyphenols added to the diet of rats also reduced basal DNA oxidative damage (without induction) to colonic mucosa.[47] Supplementation of rat diet with tea theaflavins and thearubigins protected DNA in the colonic mucosa against oxidative damage induced by 1,2-dimethylhydrazine[48] and oral administration of black tea to rats inhibited the formation of PhIP-DNA adducts in the colon.[49]

In humans, the consumption of antioxidants or of fruit and vegetables has been associated with reduced levels of oxidative damage to lymphocytic DNA.[50] Similar observations have been made with polyphenol-rich foods or beverages. The consumption of 240 mL wine per d for one mo resulted in pronounced reduction in levels of oxidized DNA bases (8-OHdG) in blood leukocytes, in particular, when the volunteers were fed a high-fat diet.[51] The consumption of onions (rich in quercetin) with meals helped increase resistance of lymphocytic DNA to *ex-vivo* induced oxidation and reduced urinary excretion of 8-OHdG.[52] The consumption of 400 g of onions and 6 cups of tea per d for 2 wk by diabetic patients also reduced the oxydizability of lymphocytic DNA, as assessed by the Comet assay.[53] However, other authors have observed no effects on lymphocytic DNA of a similar diet in healthy volunteers,[54] and no effects on urinary excretion of 8-OHdG following consumption of an extract of green tea for 3 wk.[55] These contradictory data make difficult the evaluation of the importance of DNA protection by polyphenols for disease prevention, particularly since the relationship between oxidative damage to DNA and disease risk (in particular, risk of cancer) has not been established.[56]

These difficulties in unravelling antioxidant effects of polyphenols *in vivo* may be due to some variations in the status of other antioxidants. It is likely that polyphenols act in synergy with other antioxidants.[57] It has been shown in several *in vitro* studies that the relatively polar polyphenols regenerate or spare lipophilic antioxidants, such as vitamin E.[58] Antioxidants effects of polyphenols may be more easily observed when the status in other antioxidants is low.

POLYPHENOLS AND CARDIOVASCULAR DISEASE

A number of animal studies have demonstrated that the consumption of polyphenols limits the development of atheromatous lesions. Supplementation of drinking water with dealcoholized wine, pomegranate juice, catechins, or quercetin reduced the size of these lesions in apoE-deficient mice.[59–61] These effects are associated with reduced low density lipoprotein (LDL) uptake by macrophages, lower oxidation of isolated LDL (TBARS method), and decreased susceptibility of LDL to aggregation. Similar results were obtained through supplementation of a cholesterol-enriched diet with an extract of grape seeds rich in proanthocyanidins and administered to rabbits.[62]

An abundant literature has shown that polyphenols can inhibit oxidation of LDL *in vitro*; this type of oxidation is considered to be a key mechanism in atherosclerosis. These antioxidant effects result in the decreased oxidation of LDL lipids and of α-tocopherol.[63] However, evidence in humans is contradictory. Certain studies have shown that the consumption of beverages and foods rich in polyphenols (red wine, cocoa, tea, or pomegranate juice) resulted in reduced susceptibility of LDL to oxidation induced *ex vivo* by Cu(II).[29,64–68] The lower levels of oxidation products of phosphatidylcholine (the main lipid found in LDL) observed after consumption of green tea catechins in man suggest that polyphenols effectively protect LDL against oxidation.[33] However, several other studies have shown no effects of polyphenol consumption on the *ex vivo* oxidation of LDL.[31,36,69–73] In the plasma, polyphenols are largely conjugated with glucuronide and sulfate groups.[3] They are, therefore, polar and, most probably, largely eliminated during the isolation of LDL preceding the *ex-vivo* oxidation test. This could explain the lack of protection observed in these last studies. This does not exclude the association of some polyphenol aglycones or of some esters with fatty acids to LDL, as has been suggested in an experiment where [^{3}H]-genistein was added to human plasma.[74]

These antioxidant effects are doubtlessly insufficient in themselves to account for the suggested protective effects of polyphenols against cardiovascular diseases. Tea catechins were shown to inhibit the invasion and proliferation of the smooth muscle cells in the arterial wall, a mechanism that may contribute to slow down the formation of the atheromatous lesion.[75,76] Polyphenols

may also modify lipid metabolism, but the data are, again, contradictory. Grape seed polyphenols have a hypocholesterolemic effect on rats fed a high-cholesterol diet.[77] The comsumption of flavanones by normolipemic or hyperlipemic rats during 2–6 wk reduced total plasma cholesterol, LDL-cholesterol, and triglycerides.[78–80] In contrast, in rabbits, dietary supplementation with cocoa polyphenols for 10 d had no effect upon the plasma lipid profile.[60,68] In apoE-deficient mice, catechins derived from tea did not affect plasma lipid concentrations, but induced a decrease in cholesterol and triglyceride levels in the aorta.[60] In man, acute consumption of one cup of black tea or consumption of 6 cups of green or black tea over a 4-wk period had no effect on plasma concentrations of cholesterol and triglycerides.[72,81] Several other clinical trials also failed to show any effects of isoflavones on plasma lipids.[82–84]

Polyphenols may exert antithrombotic effects. They inhibit platelet aggregation *in vitro*.[85,86] They were also shown to inhibit platelet aggregation in several animal models: the consumption of red wine (rich in polyphenols), rather than white wine or alcohol, in the rat prevented the platelet rebound effect (measured by *ex-vivo* thrombin-induced platelet aggregation), otherwise observed in the hours following alcohol withdrawal.[87] The consumption of red wine or non-alcoholic red wine reduces bleeding time and platelet aggregation induced by collagen in the rat.[88] Thrombosis induced by stenosis of the coronary artery in the dog is inhibited when red wine or grape juice, but not white wine, is administered by gastric intubation.[89] Platelet aggregation induced *ex vivo* by collagen is inhibited in the monkey by consumption for 7 d of grape juice, but not by orange juice or grapefruit juice.[90] Evidence in humans is more limited. The consumption of a procyanidin-rich cocoa beverage by human subjects inhibited the activation of platelets when stimulated *ex-vivo* by epinephrine or ADP in the 2–6 h following ingestion.[91] However, no effects were observed with other flavonoid-rich foods, such as onion, parsley, soy, citrus juices, or tea.[81,92–95]

Polyphenols can improve endothelial dysfunction, an early event in atherogenesis. Endothelial dysfunction is associated with different risk factors for atherosclerosis before the plaque is formed; its use as a prognostic tool for coronary heart disease has been proposed.[96,97] The endothelial-dependent vasorelaxing activity of isolated polyphenols, such as wine anthocyanins,[98] soy isoflavones,[99] resveratrol, quercetin,[100] and cocoa proanthocyanidins,[101] has been observed on isolated rat or rabbit aorta and in female macaques. These effects could be mediated by the protection of the vasorelaxant factor nitric oxide against oxidation. In human subjects, endothelial dysfunction can be assessed by measuring the brachial artery flow-mediated dilation. The consumption of black tea (450 mL) increased artery dilation 2 h after intake by coronary patients.[102] A similar improvement of endothelial function was observed when the same patients consumed 900 mL of tea/d during 4 wk. The consumption of 240 mL red wine during 30 d also counteracted the endothelial disfunction induced by a high-fat diet.[103]

Associations between polyphenol intake or the consumption of polyphenol-rich foods were examined in several epidemiological studies. Both the consumption of tea and a moderate consumption of wine have been regularly associated to a lower risk of myocardial infarction in both case-control and cohort studies.[104,105] However, an increased risk was observed in two studies carried out in the UK, where the consumption of tea is particularly high.[106,107] This could be explained by an insufficient adjustment for lifestyle factors. An inverse association between flavonol and flavone intake and the risk of coronary death or non-fatal myocardial infarction has been observed in several cohort studies.[108–111] Catechin intake has also been associated to a lower risk of coronary death but not to stroke.[112,113] These results of molecular epidemiology are still fragmentory, as flavonols, flavone, and catechins do not account for more than one tenth of the total polyphenol intake.[1] Reliable food composition data are needed to estimate the consumption of other polyphenols and to study its association with disease risk.

POLYPHENOLS AND CANCER

Anticarcinogenic effects of polyphenols are well documented in animals. Polyphenols, when given to rats or mice before and/or after the administration of a carcinogenic agent or the implantation of a human cancer cell line, are most often protective and induce a reduction of the number of tumors or of their growth.[114] These effects have been observed at various sites, including mouth, stomach, duodenum, colon, liver, lung, mammary, or skin. Many polyphenols, such as quercetin, catechins, isoflavones, lignans, flavanones, ellagic acid, red wine polyphenols, resveratrol, or curcumin, were tested; all of them showed protective effects in some models. Different mechanisms have been suggested to explain their anticarcinogenic effects.[115] First, polyphenols may act as blocking agents at the initiation stage. They influence the metabolism of procarcinogens by modulating the expression of cytochrome P450 enzymes involved in their activation to carcinogens. They may also facilitate their excretion by increasing the expression of phase II conjugating enzymes.[116] This induction of phase II enzymes may have its origin in the toxicity of polyphenols. Polyphenols can form potentially toxic quinones in the body that are, themselves, substrates of these enzymes.[17] The intake of polyphenols could then activate these enzymes for their own detoxication and, thus, induce a general boosting of our defenses against toxic xenobiotics.[117] Polyphenols may also limit the formation of initiated cells by stimulating DNA repair.[118,119]

Secondly, polyphenols can act as suppressing agents, and inhibit the formation and growth of tumors from initiated cells; they inhibit cell proliferation *in vitro*.[120,121] It was also shown that some polyphenols can affect growth-related signal transduction pathways through inhibition of protein kinase C and AP-1-dependent transcriptional activity.[122,123] They inhibit oncogene expression[124] and the activity of ornithine decarboxylase, a key enzyme in the synthesis of polyamines associated to cell proliferation.[125,126] They may also inhibit cell proliferation through their effect on the metabolism of arachidonic acid.

Both green tea polyphenols and curcumin were found to inhibit cyclooxygenase-2 activity and arachidonic metabolism in the colonic mucosa of rats.[127] Phenolic phytoestrogens could influence the growth of hormone responsive tumors through their estrogenic properties or their capacity to affect the response to endogenous estrogens.[128,129] This may explain the protective effects of isoflavones against mammary and prostate cancers observed in different animal models.[130]

Polyphenols can induce apoptosis of tumor cells and, therefore, reduce the growth of tumors. Evidence has been given both *in vitro*[121] and *in vivo*.[131,132] However, the significance of this mechanism in cancer prevention is not clear, as polyphenols may also have opposite effects. They were shown to inhibit apoptosis of some non-tumorigenic cells when induced by hydrogen peroxide.[133,134] Lastly, polyphenols, such as those of green tea, can also inhibit angiogenesis and, therefore, limit the growth of the tumors,[135,136] or prevent tumor invasion through inhibition of the matrix metalloproteinases.[137,138] However, in an experiment with nude-mice inoculated sub-cutaneously with a human colon carcinoma cell line, the growth of the tumors was inhibited by EGCG added in the drinking water from d 45, after inoculation and thereafter.[139] The authors concluded that an effect on angiogenesis starting earlier in the development of the tumor was unlikely; they showed that an inhibition of telomerase was involved.

The anticarcinogenic properties of polyphenols could, thus, be explained by many different mechanisms. To explain their protective effect by their antioxidant properties and inhibition of DNA oxidative damage is certainly an oversimplification. However, various antioxidants, including polyphenols, inhibit NF-kB activation, probably through triggering a redox-sensitive signal in the cells.[140,141] The inhibition of such transcription factors by polyphenols may play an essential role in the prevention of cancers.[142,143] Beyond these, many hypotheses on mechanisms of action, the most difficult task, remain to demonstrate their anticarcinogenic effects in humans.

Often, the doses used in animal or cell experiments largely exceed those that can be expected in humans on a regular diet. All the corresponding literature should clearly be re-examined to take into account the doses applied, as well as the mode of administration. More credit should be given to the effects observed at low doses. Intravenous administration of very high doses of quercetin (up to 2000 mg/m^2) at a 3-wk interval to 51 patients having a cancer resistant to standard therapies induced a decrease of some tumor markers.[144] These doses are clearly far beyond what could be expected from dietary exposure, and such results are of low value to elucidate the role of dietary polyphenols in cancer prevention. A clear distinction between cancer treatment at pharmacological doses and cancer prevention at dietary levels of exposure should be made when discussing experimental results obtained on animal models or on cell lines grown *in vitro*. The confusion is often maintained on purpose, to communicate on the beneficial health effects of polyphenol-containing food products. For example, resveratrol has interesting anticarcinogenic properties that may lead to the development of new drugs.[145] Its presence in wine and absence in any food sources has stimulated the interest of the industry to promote the health properties of wine. However, its very low concentration in wine (0.3–2 mg/L in red wines)[146] makes the attribution of the wine health benefits to this molecule unlikely.

The question of doses is essential, as opposite effects have been observed at different exposure levels. Caffeic acid induces hyperplasia and tumors in the forestomach and kidney when administered in the diet of rats or mice at a dose of 0.5–2% of the diet, whereas it shows anticarcinogenic effects at doses of 0.05–0.15 %.[147] On the contrary, genistein at high doses (50–100 μM) inhibits the growth of human breast cancer cells *in vitro*, whereas it induces proliferation at lower doses (0.01–10 μM), effects that were explained by their estrogenic properties at low doses and cytotoxicity at higher doses.[148] A similar influence of the dose of genistein was observed on the expression of prostate-specific antigen by prostate cancer cells.[149] Neurodegeneration induced in mice by N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine was prevented by low doses of green tea (0.5–1 mg/kg i.p.), whereas higher doses (5 mg/kg) increased the toxicity of the drug.[150] In the future, more attention should be paid to those studies showing effects at doses compatible with exposure experienced by humans with their diet, or to *in vitro* studies using polyphenol concentrations close to documented plasmatic or tissular concentrations. When calculating the dose to be administered to animals, extrapolation from human dietary intake should be made, preferentially at a constant content in the diet rather than at a constant intake per body weight unit, as has been recently discussed.[151] For example, an intake of 40 mg/d isoflavone, an average value for Japanese populations,[152] would correspond to a dose of about 0.01% in the diet, well below most of the doses tested in animal experiments.

More credit should also be given to the studies where polyphenols were administered *per os*, or to *in vitro* studies using polyphenol metabolites (largely conjugated metabolites), and not polyphenols in their ingested form. Indeed, as stressed above, polyphenols are essentially present in blood and tissues as conjugated metabolites, and there is still limited evidence that they can be deconjugated *in vivo*.[3,153] Thus, studies where dietary polyphenols are administered by injection are of limited value to understand their health effects, and *in vitro* studies with non-conjugated polyphenols should be re-evaluated using their conjugated metabolites.[14,133,154–156]

The final evidence on the prevention of cancers by polyphenols will come from clinical and epidemiological studies. Tumor biomarkers are useful tools for prognosis, for the monitoring of therapy in various cancers, and for the evaluation of the influence of diet on the disease.[157] Some polyphenols have been shown to reduce the levels of tumor biomarkers in different cancer cell lines. Genistein decreased the expression of protein-specific antigen (PSA) in prostate cancer cells[149] and EGCG, epicatechin gallate, or genistein significantly reduced in a human lung cancer cell line, the levels of heterogeneous nuclear ribonucleoprotein B1, a new biomarker for early clinical diagnosis of lung cancer.[158] However, clinical evidence of an effect of polyphenols

on tumor biomarkers is still very limited. The comparison of a 6-wk consumption of an isoflavone-rich and isoflavone-poor soy beverages providing 69 and 3 mg/d isoflavones, respectively, failed to show any impact of isoflavones on two tumor biomarkers in 34 elderly men with elevated PSA.[159] On the other hand, the consumption of a soy-containing diet providing an average of 154 mg/d isoflavones by 10 women during 1 mo resulted in a significative decrease of estradiol and progesterone plasmatic levels, two biomarkers for breast cancer risk.[160] More studies are needed to establish dietary recommendations for cancer patients.

Polyphenol supplements might be useful as adjuvants in chemotherapy or radiotherapy treatments. Some polyphenols were shown to reinforce the antiproliferative activities of anticancer drugs. EGCG showed synergistic effects with sulindac or tamoxifen on apoptosis of the lung cancer cell line PC-9,[161] and quercetin potentiated the growth inhibition of ovarian cancer cells and leukemia cells by cisplatin.[162,163] The oral administration of green tea to Ehrlich ascites carcinoma tumor-bearing mice enhanced the anti-tumor activity of doxorubicin.[164] However, such adjuvant effects vary widely between polyphenols. Galangin, when tested on leukemia cells, showed opposite effects to quercetin and inhibited the anti-apoptotic effects of cisplatin.[163] Tangeretin, a citrus polymethoxylated flavonoid, when added to the diet of nude mice, inhibited the cytotoxic effects of tamoxifen on MCF-7 breast cancer cell inoculated subcutaneously.[165] Clinical trials will be needed to establish adjuvant effects of the most promising polyphenols in cancer patients.

The associations between the consumption of coffee, tea, and wine and the risk of cancer have been studied in different epidemiological studies. The consumption of coffee has been associated to a reduced risk of colorectal cancer but not with cancers at other sites.[166] Experimental evidence on tea strongly suggests a protective role of tea consumption against cancers, but the epidemiological evidence is inconclusive. Although some inverse associations between stomach or colon cancer risk and tea consumption were observed in some case-control and prospective cohort studies,[167,168] the majority of ecologic, cohort, or case-control studies suggest that tea drinking has no clear effect on cancer, possibly due to the much lower intake compared to the animal experiments.[169–172] The possible existence of confounding factors in epidemiological studies has also been proposed to explain such discrepencies.

A prospective study has suggested that wine polyphenols may protect against the deleterious effects of alcohol on cancers of the upper digestive tract. The consumption of alcoholic beverages, such as beer or spirits, increased the risk of upper digestive tract cancer in a Danish cohort, whereas a moderate consumption of wine did not increase this risk.[173] Another study on the same cohort also suggested the protective effects of wine consumption against lung cancer.[174] However, the existence of some confounding factors cannot be excluded, as a positive correlation between esophagal cancer risk and wine consumption was observed in a case-control study carried out in Italy, where wine is the most common alcoholic beverage.[175] An increase of esophageal cancer risk was observed in people consuming 3 glasses of wine or more per d, as compared to those consuming less than 3 glasses. If wine may appear less toxic with regard to cancer risk than other alcoholic beverages, it should be, in the present state of our knowledge, regarded as a risk factor rather than a protective factor, as it was found to increase the risk of gastric, breast, and lung cancer in several epidemiological studies.[176–179] Furthermore, encouraging a moderate wine consumption may also result in an increase of alcoholism.[180]

Different attempts have been made to directly relate the intake of some polyphenols to the risk of cancer. Flavonol intake (quercetin and kaempferol) was inversely associated to the risk of lung cancer in 5 case-control and cohort studies,[181–185] but no association was found in 3 other studies.[109,186,187] For cancers at sites other than the lung, no association was found with flavonol intake in 3 large prospective studies,[109,182,185] but 2 case-control studies showed a lower risk of cancer of the stomach and of the upper-aerodigestive tract at high flavonol intake.[188,189]

Catechin intake was not significantly associated to cancer in a cohort of Dutch men,[190] but an inverse association was found with rectal cancer in a large American cohort of postmenopausal women.[191] The intake of catechin originating from fruits, but not from tea, was also associated to a lower risk of cancer of the upper-digestive tract in the same American cohort,[191] whereas the urinary excretion of epigallocatechin was inversely associated to gastric and esophageal cancer in a nested case-control study carried out in Shangai.[167]

The consumption of dietary sources of phytoestrogens has been repeatedly associated to a lower cancer risk. Epidemiological studies have suggested a protective role of the consumption of soy products, rich in isoflavones, against various cancers and, more particularly, hormone-related cancers.[192] The consumption of whole-grain cereals, a major source of lignans, has also been associated to a reduced risk of various cancers.[193] Several attempts were made to relate the exposure to dietary phytoestrogens to cancer risk. Three case-control studies showed a lower urinary excretion of isoflavones or lignans in breast cancer patients compared to controls,[194–196] but no significative association with genistein and enterolactone excretion was found in another study.[197] Other authors found more a complex relationship with a higher risk of breast cancer associated to both the lowest and the highest plasma levels of enterolactone.[198] Similar studies on prostate cancer suggested either a protective effect[199,200] or no association[201] with isoflavone or lignan exposure.

Altogether, the epidemiological data on polyphenols and cancer do not appear conclusive. It is possible that protective effects are limited to sub-groups of the population with particular genotypes or at a higher risk of developing disease.[202] The causative role of dietary polyphenols, when a protective role is suggested, in observational studies must also be questionned. An association of myricetin or kaempferol intake with a lower prostate or gastric cancer risk has been reported,[181,188] but such an association could be explained by some unknown confunding factors, as average daily intakes of myricetin and kaempferol do not

exceed 4 and 1.4 mg, respectively, in the Western diet.[203] As, previously stressed, for cardiovascular diseases, flavonols, catechins, and phytoestrogens considered in epidemiological studies so far published, only account for a minor fraction of the total polyphenols. Here, again, more complete polyphenol food composition tables or validated exposure biomarkers for other types of polyphenols, such as proanthocyanidins, flavanones, phenolic acids, and anthocyanins, are needed.

POLYPHENOLS AND NEURODEGENERATIVE DISEASES

Neurodegenerative diseases represent an increasing burden to our aging societies. About 15% of the population over 65 are afflicted by Alzheimer's disease and 1% by Parkinson's disease, not including other type of dementia resulting from ischemic injury.[204] Such diseases are dependent of oxidative stress, which particularly affects brain tissues,[205] and antioxidants may, therefore, contribute to their prevention.[204] Feeding aging rats a diet supplemented with aqueous extracts of spinach, strawberry, or blueberry rich in polyphenols improved their cognitive functions and neuronal signal transduction.[206,207] Blueberries rich in anthocyanins were particularly effective. These effects were not explained by a sparing of vitamins E and C in the brain;[208] a direct implication of polyphenols as antioxidants is, therefore, suspected.

Intravenous injection of epicatechin or catechin to mice improved the memory impairment induced by cerebral ischemia.[209] Polyphenols also protect experimental animals against some neurotoxic drugs whose toxicity is linked to a stimulation of oxidative stress. Dietary supplementation with grape polyphenols reduced the neurodegenerative changes induced by chronic ethanol consumption, and improved the synaptic function measured on isolated synaptosomes.[210] The oral administration of EGCG restored the dopaminergic neurotransmission in rats injected with *N*-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a drug used to reproduce a parkinsonian syndrome, and prevented the increase of SOD and catalase induced by this drug.[150] The chronic consumption of ferulic acid with the drinking water protected mice from the deleterious effects of an intracerebral injection of β-amyloid peptide, a component of senile plaques postulated to be involved in the pathogenesis of Alzheimer's disease.[211] It prevented the drop of learning and memory performance and the increase in the level of inflammation markers in the brain induced by the β-amyloid peptide, possibly via a transitory activation of hippocampal astrocytes. Similar protective effects were observed with curcumin in an Alzheimer transgenic mouse model.[212]

In vitro experiments showed that catechins improve the survival of cultured neuronal cells when challenged by a β-amyloid peptide, 6-hydroxydopamine, or oxidized LDL.[213–215] These effects appear to be mediated by restoration of protein kinase C activity or the inhibition of NF-κB translocation, both mechanisms involved in the regulation of cell proliferation and apoptosis. These effects are dose dependent. At low doses (0.1–10 μM), epigallocatechin gallate protects neuronal cells against oxydative damage and improves cell survival, whereas at higher doses (50 μM), it appears pro-oxidant and toxic.[213] Therefore, low polyphenol concentrations would be more effective to prevent neurodegenerative diseases. Little is known about the polyphenol concentrations in the brain. The concentrations reached in the brain after feeding rats with genistein are much lower (0.04 nmol/g tissue) than those reached in the plasma (2 μmol/L) and other tissues.[216] The poor permeability of the blood-brain barrier to polyphenols was confirmed in other studies with naringin or quercetin.[217,218] The glucuronide conjugate of epicatechin was unable to protect cortical neurons against oxidative stress induced by H_2O_2.[154] However, the low amounts of polyphenols present in the brain may be only aglycone, as has been shown for genistein, and due to the poor permeability of the blood-brain barrier, to anionic conjugates.[216,219]

The relationship between polyphenol or wine consumption and neurodegenerative risk has been studied in a few epidemiological studies. A moderate wine consumption was negatively associated to the risk of dementia in 3 prospective studies carried out in France, Denmark, and Canada.[220–222] Such an association was not observed for beer or spirits in the Danish cohort. This indicates a possible contribution of polyphenols to the prevention of dementia. Cognitive impairment was also found to be lower in moderate alcohol drinkers compared to non-drinkers in an Italian cohort, but the probability of cognitive impairment was increased in heavy alcohol drinkers.[223] An inverse association between the intake of flavonols and flavones and the risk of dementia has also been observed in a French cohort.[224]

POLYPHENOLS AND DIABETES

Many plants have been traditionally used in the treatment of diabetes. Polyphenols contained in these plants may explain some of their therapeutic activity.[225,226] The acute or chronic administration of polyphenols to experimental animals influences glycemia. Caffeic acid and isoferulic acid, when administered intravenously to rats, reduce the fasting glycemia and attenuate the increase of plasma glucose in an intravenous glucose tolerance test.[227–229] These effects were observed in a genetic model of insulin-dependent diabetes of rats or in streptozotocin-treated rats, but are less pronounced in normal rats.

More interestingly, some hypoglycemic effects were also observed with polyphenols administered orally, shortly before consumption of the glucose source. A diacylated anthocyanin reduced the peak of glycemia induced by maltose consumption in normal rats.[230] An ill-defined leucodelphinidin (probably a mixture of prodelphinidins) reduced fasting glycemia in rats and lowered the plasma glucose peak in a glucose tolerance test.[231] Similar effects were observed with 4-hydroxybenzoic acid.[232] Catechin improved the tolerance to glucose induced by starch or sucrose ingestion in rats.[233] A fermented tea extract showed hypoglycemic effects in mice.[234] These effects were also

observed in rats or mice rendered diabetic by stroptozotocin or alloxane.[231,234,235]

Polyphenols may affect glycemia through different mechanisms, including the inhibition of glucose absorption in the gut or of its uptake by peripheral tissues. The hypoglycemic effects of diacetylated anthocyanins at a 10 mg/kg diet dosage were observed with maltose as a glucose source, but not with sucrose or glucose.[230] This suggests that these effects are due to an inhibition of α-glucosidase in the gut mucosa. Inhibition of α-amylase and sucrase in rats by catechin at a dose of about 50 mg/kg diet or higher was also observed.[233] The inhibition of intestinal glycosidases and glucose transporter by polyphenols has been studied *in vitro*. An IC_{50} of 60–200 μM was reported for a rat intestinal α-glucosidase.[236] Quercetin (10–20 μM) inhibited glucose transport by GLUT2 in a transfected oocyte model and also inhibited glucose absorption in Zucker fa/fa rats.[237] At much higher concentrations (1 mM), quercetin 3-*O*-glucoside, tannic acid, and chlorogenic acid inhibited the Na^+-dependent hexose uptake in a rat everted gut sac model, or isolated rat brush border vesicules; catechin, ferulic acid, and caffeic acid were inactive.[238,239] Polyphenols could not only inhibit the glucose absorption in the small intestine, but they could also limit their reabsorption in the kidney, as has been shown for phlorizin.[240]

Several *in vitro* studies on cultured cells have shown that polyphenols may increase glucose uptake by peripheral tissues. Caffeic acid increases glucose uptake by rat adipocytes and mice myoblasts.[227,241] Black and green tea extracts and EGCG also increased glucose uptake by rat epididymal adipocytes, both in the presence or absence of insulin.[242] Isoferulic acid increased glucose uptake by soleus muscle isolated from streptozotocin-diabetic rats.[228] However, opposite results were also reported for quercetin and genistein, which both inhibited glucose uptake when induced by insulin on rat adipocytes or hydrogen peroxide on leukemic cell lines.[243,244] Genistein, but not daidzein, also inhibited glucose uptake by HL-60 cells and erythrocytes.[245] Active polyphenol concentrations differed widely (1 to 115 μM) according to the studies. It is still difficult to explain these contradictory results. They could be explained by the different nature of the polyphenols tested or by the concentrations used in the assays.

Polyphenols may exert different actions on peripheral tissues that would diminish glycemia. They include the inhibition of gluconeogenesis,[228,246,247] adrenergic stimulation of glucose uptake,[241] or the stimulation of insulin release by pancreatic β-cells.[248] The involvement of such mechanisms is still hypothetical. *p*-Hydroxybenzoic acid, which shows hypoglycemic effects in diabetic rats when submitted to a glucose tolerance test, had no effect on insulinemia and hepatic glycogen.[235] On the contrary, some polyphenols might have opposite effects and decrease glucose uptake in peripheral tissues by inhibiting the GLUT1 glucose transporter, as shown on transfected Chinese hamster ovary cells overexpressing this transporter,[245] or by inhibiting the response to insulin.[243]

In humans, evidence of the effects of polyphenols on glycemia or diabetes risk is still very limited. The consumption of 400 mL decaffeinated coffee did not affect glycemia or insulinemia when ingested with glucose, but it decreased the secretion of glucose-dependent insulinotropic polypeptide and increased that of glucagon-like peptide 1 in a manner consistent with a delayed intestinal glucose absorption.[249] The effects of the consumption of polyphenol supplements were also evaluated in diabetic patients. No effect on glycemia was observed in type II diabetic patients after consumption for 2 mo of 50 mg/d of a red orange supplement containing anthocyanins, flavanones, and phenolic acids.[250] In another clinical trial, type I diabetic patients ingested larger doses of diosmin (1800 mg/day) and hesperidin (200 mg/day) as tablets for 3 mo. Although the doses administered per body weight unit were similar to many of the animal studies previously described, such a supplementation had no effect on glycemia, but it significantly reduced the level of glycated hemoglobin (HbA_{1c}).[251] Polyphenols could, thus, limit the risk of diabetic complications, as advanced glycation end (AGE) products are known to generate oxidative stress. This effect on AGE products could explain the reduction of renal damage by curcumin observed in streptozotocin-treated rats.[252]

Epidemiological evidence is also very limited. The consumption of coffee (rich in chlorogenic acid) has recently been associated with a decreased risk of type II diabetes.[253] The consumption of decaffeinated coffee (20 g/d solids for 14 d, i.e., the equivalent of about 10 cups of coffee per d) lowered fasting glycemia in healthy volunteers.[254] The consumption of 400 mL decaffeinated coffee containing 25 g glucose by healthy volunteers reduced the postprandial level of glucose-dependent insulinotropic-polypeptide (GIP) and enhanced that of glucagon-like peptide-1 (GLP-1), suggesting that chlorogenic acid decreases the rate of intestinal absorption of glucose.[249] Chlorogenic acid could, therefore, counter the known hyperglycemic effects of caffeine.

POLYPHENOLS AND OSTEOPOROSIS

Estrogen deficiency in postmenopausal women is an important cause of osteoporosis, and hormone replacement therapy is often recommended to prevent bone loss. However, many women have been reluctant to follow such a treatment because of the fear of possible side effects and long-term risks. Isoflavones with weak estrogen-like activity have attracted much attention as a possible alternative treatment to prevent osteoporosis.[255] Their osteoprotective effects have been evaluated in mice or rats in which an estrogen deficiency has been induced by ovariectomy. The supplementation of the diet with genistein, daidzein, or their glycosides during several weeks prevents the loss of bone mineral density and trabecular volume caused by the ovariectomy.[256–259] These effects were observed at daily doses of 10–50 mg/kg body weight. The highest doses also induced uterine hypertrophy, but the lowest protective doses did not affect the uterine weight.[257,259] Feeding soy proteins with either normal or reduced isoflavone content to ovariectomized rats also suggested that the osteoprotective effects of soy proteins were due

to their isoflavones.[260] The restoration of the bone mineral density was not observed when the isoflavones were administered 80 d after the ovariectomy of the rats, suggesting that they may prevent bone loss, but not reverse an established osteopenia.[261]

The mechanisms responsible for these protective effects are still poorly understood. *In vitro*, daidzein was shown to inhibit the differentiation of osteoclasts developping on dentine slices and to diminish the dentine resorption.[262] On the other hand, the daily subcutanous injection of genistein to ovariectomized rats increased the number of osteoblasts associated to bone formation, but had no effects on bone resorption.[263] Structurally related isoflavones may protect bones through different mechanisms of action,[258] and with different magnitude.[259]

Evidence of protective effects in humans is based on observational and intervention studies. The consumption of soybeans, a major source of calcium in Japan, was associated to a higher bone mineral density in Japanese women.[264] A soy-rich diet followed by postmenopausal women stimulated their bone osteoblastic activity.[265,266] Such effects of soy food consumption could also be explained by the intake of isoflavones, as soy foods are their main dietary sources. However, no correlation between isoflavonoid urinary excretion and rate of bone loss was observed in postmenopausal women in the Netherlands.[267] Higher intake levels may be required to prevent bone loss. The consumption of soy proteins providing 80 mg/d isoflavones during 24 wk was more effective than isoflavone free soy protein to improve bone mineral density and content in perimenopausal women.[268] Furthermore, in 3 other studies, isoflavone supplementation at a dose of 37–62 mg/d during 4 wk-1 yr significantly improved the urinary excretion level of several biomarkers of bone resorption.[269–271] Femur and lumber spine mineral density was also improved in the longer study.

Much less is known on the possible impact of other polyphenols on osteoporosis. Rutin, a glycoside of quercetin, added to the diet of ovariectomized rats restaured the loss of bone mineral density induced by the ovariectomy and was even more efficient than isoflavones.[272,273] It also reduced the urinary excretion of deoxypyridinoline, a marker of bone resorption, and increased osteocalcinemy, a marker of osteoblastic activity. Such an effect of rutin likely explains the inhibition of bone resorption observed in rats fed a diet rich in onions (the main source of quercetin in Western diets), whereas several other vegetables were without effects.[274]

The consumption of tea has been associated with a higher bone mineral density in a cohort of English older women.[275] Catechins abundant in tea could possibly counteract the effects of tea caffeine, known for its adverse effects on bone metabolism. No effect of the consumption of coffee was observed in the same study. A rat experiment also showed no effect of coffee on bone metabolism. Feeding rats during 140 d with a diet supplemented with instant coffee containing both chlorogenic acid and caffeine had no influence on bone histomorphometry, deoxypyridinoline urinary excretion, and osteocalcinemy.[276] The effects of catechins or chlorogenic acid on bone resorption in animal models so far have not been examined.

RISKS ASSOCIATED TO POLYPHENOL CONSUMPTION

The scientific data summarized above on the effects of polyphenols on diseases have led to the marketing of new polyphenol dietary supplements and polyphenol-rich food products. Although no precise claims are attached to these products, different polyphenols have been proposed to limit oxidative stress and aging, and isoflavones have been recommended to limit hot flushes and to improve bone health in post-menopausal women. The consumption of such products leads to increase the intake of particular polyphenols beyond common levels of exposure associated to the diet.

Cases of acute toxicity have been reported in animals consuming plants rich in tannins.[277] In humans, no such acute toxicity has ever been reported after the consumption of dietary polyphenols. However, a high consumption of polyphenols could increase the risk of some diseases. The large majority of published studies were focussed on health benefits, rather than on disease risks. Our knowledge on risks is, therefore, very limited.

It is often said that polyphenols consumed in high amounts could have pro-oxidant effects. They can reduce iron (III) to iron (II) and, thus generate hydroxyl radicals through the Fenton reaction. Such pro-oxidant effects have never been demonstrated *in vivo*. Most dietary polyphenols have catechol groups that can be oxidized to quinone *in vivo* and generate free radicals through redox cycling. However, quinone reductase, catechol-O-methyltransferase, and other conjugating enzymes limit the formation of such quinones in endogenous tissues. Similarly, a number of polyphenols, including quercetin, were shown to be mutagenic in cultured cells. A pro-carcinogenic effect of quercetin in rat models of nitrosomethylurea-induced pancreatic cancer or azoxymethane-induced colon cancer have been reported.[278,279] But the majority of the studies carried out with quercetin in rodents showed anticarcinogenic effects. Conjugating enzymes likely plays an essential role to detoxify polyphenols and limit their mutagenicity *in vivo*.

Phytoestrogens, acting as estrogen agonists, may stimulate the proliferation of estrogen responding cells and increase the risks of some cancers.[280,281] Genistein was shown to stimulate the growth of breast cancer cells implanted in ovariectomized mice.[282] The consumption of soy proteins by premenopausal women increased the level of plasma estradiol and stimulated the appearance of hyperplastic epithelial cells in nipple aspirate fluid.[283] On the contrary, in other models or conditions, phytoestrogens were shown to act as antiestrogens and antiproliferative agents and could, therefore, affect reproductive functions. Problems of infertility in sheep grazing on pastures or fodders rich in phytoestrogens were at the origin of their discovery.[284] Supplementation of the diet of rat dams during the first 21 postnatal d with coumestrol (0.1 g/kg diet) produced a persistant estrus state in female offspring and a deficit in the sexual behavior of male offspring.[285]

Flavonoids may also influence the thyroid function and have goitrogenic effects. A reduction of thyroid peroxidase activity

was observed in rats fed a diet supplemented with genistein.[286,287] These effects of genistein on the thyroid function are more pronounced when iodine is deficient. Other flavonoids, such as daidzein, quercetin, kaempferol, or naringenin, were also shown to irreversibly inhibit thyroid peroxidase.[288] These data are of particular concern for soy-fed babies exposed to particularly high doses of isoflavones.[289] Vitexin, a *C*-glycosylflavones abundant in millet, is another inhibitor of thyroid peroxidase. When administered to rats, it increased thyroid weight and decreased the plasma levels of thyroid hormones.[290] It is thought to contribute to the genesis of endemic goiter in West Africa, where millet is a staple food.

Most dietary polyphenols have catechol group in their structures and, thus form very stable chelates with ferric ions. This fundamental property explains the inhibition of non-heme iron absorption by polyphenols and polyphenol-containing beverages, such as coffee, wine, or tea, as shown in several clinical trials.[291–293] As these effects involve direct chelation of iron by polyphenols in the gut, they are only observed when the source of polyphenols is ingested together with the source of iron.[294] This is why it is often recommended for people at risk of developing iron deficiencies to drink tea and other polyphenol-rich beverages between the meals rather than during the meals. The effects of polyphenols on iron absorption have been well demonstrated in clinical studies; however, the impact of dietary polyphenols on iron status is not as firmly established in free-living populations.[295] In contrast, for other people with a high iron status, the inhibition of iron absorption by polyphenols may be rather beneficial, as high levels of plasma ferritin have been associated to a higher risk of cardiovascular diseases and colon cancer.[296]

Adverse effects of polyphenol consumption on cardiovascular diseases have recently been suggested. High polyphenol intake could increase the risk of cardiovascular diseases through an effect on homocysteinemia, an independent risk factor of cardiovascular diseases. The consumption of 2 g chlorogenic acid/d during 1 wk by volunteers significantly increased homocysteinemia.[297] Such a dose corresponds to the consumption of about 2.5 l coffee/d.[1] A similar increase of homocysteinemia was also observed in L-DOPA-treated Parkinsonian patients.[298] Just like chlorogenic acid, L-DOPA contains a catechol group and is largely methylated to 3-*O*-methyldopa with as a consequence, the conversion of the methyl donor *S*-adenosylmethionine to *S*-adenosylhomocysteine and homocysteine. A common L-DOPA dose used in the treatment of Parkinsonians is 500 mg/d (2.5 mmol/d), a dose close to that used for chlorogenic acid above (5.6 mmol/d). It is not known whether lower polyphenol intakes also affect homocysteinemia.

In the future, more attention should be paid to possible adverse effects of polyphenol consumption. This is particularly important when considering the growing development of new polyphenol-containing dietary supplements. The consumption of such supplements may lead to particularly high exposure of some specific polyphenols, well above those commonly associated to the diet. The addition of specific polyphenols to different foods should also be strictly controlled to limit their consumption to persons for whom an expected health benefit has been well established. More clinical trials and epidemiological studies are needed to better assess the balance between benefits and risks.

CONCLUSIONS

A protective role of polyphenols against degenerative diseases is supported tod by many studies carried out on animals, and different mechanisms of action have been proposed to explain such protective effects. Much progress has also been made on the evaluation of their bioavailability. The significance for human health of all *in vitro* data obtained on cultured cells or isolated enzymes and receptors will have to be properly re-evaluated in the light of this new knowledge on bioavailability.

More human studies are needed to provide definitive proofs of the protective role of polyphenols. Conclusive evidence will largely come from clinical and epidemiological studies. The number of clinical studies so far published is still limited, and the results are often contradictory. If it is clear that the consumption of polyphenols improves some oxidative stress related parameters, but the associations between these parameters and disease risk are still not well clarified, we need to identify proper markers of disease risk and demonstrate that they are influenced by the consumption of polyphenols.

First, epidemiological data on polyphenols were published approximately 10 yr ago and since then progress has been relatively slow because of the lack of food composition tables and lack of validated biomarkers of polyphenol intake. Such tables or biomarkers are needed to evaluate the consumption of polyphenols in populations, but their obtention/identification is rendered difficult because of the large number of phenolic compounds present in food. A table for flavonoids based on the surveys of 97 literature sources is now available.[299] More research is still needed to cover missing polyphenols and food sources.

It is impossible to conclude today that some particular polyphenols offer more health benefits than others and research efforts continue at an increasing pace for all polyphenol classes. All polyphenols share common properties as reducing agents. Most of the dietary polyphenols can chelate iron and other metal ions. As such, they may all trigger common cell responses through mechanisms that have been partly unravelled.[21] On the other hand, some polyphenols, like phytoestrogens, show specific properties and may be more indicated for the prevention of specific diseases. More intervention studies are needed to clarify the impact of the most active polyphenols on specific diseases or disease biomarkers.

When developping new polyphenol-containing products for specific effects on a given pathology, we will also have to make sure that they do not increase risks for other pathologies. For exemple, resveratrol shows promising anticarcinogenic properties, but it also increases the risk of cardiovascular diseases in mice.[300] Quercetin may be effective to prevent different diseases,

but it also reduces the life-span of mice, when added to the diet on a long term basis.[301]

It can be anticipated that the most protective polyphenols and the most appropriate levels of intake will be determined in the near future, for both the general population and populations at risk of developing particular diseases. Before this goal is reached, caution is necessary before recommending to increase their consumption. This is particularly important for dietary supplements, as their promotion may result in increases of polyphenol intake, sometimes far-exceeding the common intake levels associated to the diet. Once the most protective levels of polyphenol intake are been established, it will be possible to improve the quality of food through plant breeding or food processing, and to make sound dietary recommendations for an effective health benefit.

REFERENCES

[1] Scalbert, A. and Williamson, G. 2000. Dietary intake and bioavailability of polyphenols. *J. Nutr.*, **130**:2073S–2085S.

[2] Shahidi, F. and Naczk, M. 1995. *Food phenolics, sources, chemistry, effects, applications*. Lancaster, PA, Technomic Publishing Co. Inc.

[3] Manach, C., Scalbert, A., Morand, C., Rémésy, C., and Jimenez, L. 2004. Polyphenols—Food sources and bioavailability. *Am. J. Clin. Nutr.*, in press.

[4] Yang, C.S., Lee, M.J., Chen, L.S., and Yang, G.Y. 1997. Polyphenols as inhibitors of carcinogenesis. *Environmental Health Perspectives*, **105**:971–976.

[5] Kehrer, J.P. and Smith, C.V. 1994. Free radicals in biology: Sources, reactivities, and roles in the etiology of human diseases. In: *Natural antioxidants*. 25–62. Frei, B., ed. San Diego, Academic Press.

[6] Rice-Evans, C. and Miller, N.J. 1994. Total antioxidant status in plasma and body fluids. *Methods Enzymol*, **234**:279–293.

[7] Cao, G., Russell, R.M., Lischner, N., and Prior, R.L. 1998. Serum antioxidant capacity is increased by consumption of strawberries, spinach, red wine or vitamin C in elderly women. *J. Nutr.*, **128**:2383–2390.

[8] Ghiselli, A., Serafini, M., Maiani, G., Azzini, E., and Ferro-Luzzi, A. 1995. A fluorescence-based method for measuring total plasma antioxidant capability. *Free Radic. Biol. Med.*, **18**:29–36.

[9] Benzie, I.F. and Strain, J.J. 1996. The ferric reducing ability of plasma (FRAP) as a measure of "antioxidant power": The FRAP assay. *Anal. Biochem.*, **239**:70–76.

[10] Velioglu, Y.S., Mazza, G., Gao, L., and Oomah, B.D. 1998. Antioxidant activity and total phenolics in selected fruits, vegetables, and grain products. *J. Agric. Food Chem.*, **46**:4113–4117.

[11] Rice-Evans, C.A., Miller, N.J., Bolwell, P.G., Bramley, P.M., and Pridham, J.B. 1995. The relative antioxidant activities of plant-derived polyphenolic flavonoids. *Free Radical Res.*, **22**:375–383.

[12] Rice-Evans, C.A., Miller, N.J., and Paganga, G. 1996. Structure-antioxidant activity relationships of flavonoids and phenolic acids. *Free Rad. Biol. Med.*, **20**:933–956.

[13] Guo, C., Cao, G., Sofic, E., and Prior, R.L. 1997. High-performance liquid chromatography coupled with coulometric array detection of electroactive components in fruits and vegetables: Relationship to oxygen radical absorbance capacity. *J. Agric. Food Chem.*, **45**:1787–1796.

[14] Manach, C., Morand, C., Crespy, V., Demigné, C., Texier, O., Régérat, F., and Rémésy, C. 1998. Quercetin is recovered in human plasma as conjugated derivatives which retain antioxidant properties. *FEBS Lett.*, **426**:331–336.

[15] Cavalieri, E.L., Stack, D.E., Devanesan, P.D., Todorovic, R., Dwivedy, I., Higginbotham, S., Johansson, S.L., Patil, K.D., Gross, M.L., Gooden, J.K., Ramanathan, R., Cerny, R.L., and Rogan, E.G. 1997. Molecular origin of cancer: Catechol estrogen-3,4-quinones as endogenous tumor initiators. *Proc. Natl. Acad. Sci. USA*, **94**:10937–10942.

[16] Bachur, N.R., Gordon, S.L., and Gee, M.V. 1978. A general mechanism for microsomal activation of quinone anticancer agents to free radicals. *Cancer Res.*, **38**:1745–1750.

[17] Baez, S., Segura-Aguilar, J., Widersten, M., Johansson, A.S., and Mannervik, B. 1997. Glutathione transferases catalyse the detoxication of oxidized metabolites (o-quinones) of catecholamines and may serve as an antioxidant system preventing degenerative cellular processes. *Biochem. J.*, **324**:25–28.

[18] Zhu, B.T., Ezell, E.L., and Liehr, J.G. 1994. Catechol-*O*-methyltransferase-catalyzed rapid *O*-methylation of mutagenic flavonoids. Metabolic inactivation as a possible reason for their lack of carcinogenicity *in vivo*. *J. Biol. Chem.*, **269**:292–299.

[19] Dangles, O., Dufour, C., Manach, C., Morand, C., and Rémésy, C. 2001. Binding of flavonoids to plasma proteins. *Methods Enzymol*., **335**:319–333.

[20] Laranjinha, J. 2001. Redox cycles of caffeic acid with alpha-tocopherol and ascorbate. *Methods Enzymol.*, **335**:282–295.

[21] Haddad, J.J. 2002. Antioxidant and prooxidant mechanisms in the regulation of redox(y)-sensitive transcription factors. *Cell Signal*, **14**:879–897.

[22] Whitehead, T.P., Robinson, D., Allaway, S., Syms, J., and Hale, A. 1995. Effect of red wine ingestion on the antioxidant capacity of serum. *Clin. Chem.*, **41**:32–35.

[23] Miyazawa, T., Fujimoto, K., Suzuki, T., and Yasuda, K. 1994. Determination of phospholipid hydroperoxides using luminol chemiluminescence—high-performance liquid chromatography. *Methods Enzymol*., **233**:324–332.

[24] Leenen, R., Roodenburg, A.J., Tijburg, L.B., and Wiseman, S.A. 2000. A single dose of tea with or without milk increases plasma antioxidant activity in humans. *Eur. J. Clin. Nutr.*, **54**:87–92.

[25] Serafini, M., Ghiselli, A., and Ferro-Luzzi, A. 1996. *In vivo* antioxidant effect of green and black tea in man. *Eur. J. Clin. Nutr.*, **50**:28–32.

[26] Maxwell, S., and Thorpe, G. 1996. Tea flavonoids have little short term impact on serum antioxidant activity. *British Medical Journal*, **313**:229.

[27] Serafini, M., Laranjinha, J.A., Almeida, L.M., and Maiani, G. 2000. Inhibition of human LDL lipid peroxidation by phenol-rich beverages and their impact on plasma total antioxidant capacity in humans. *J. Nutr. Biochem.*, **11**:585–590.

[28] Serafini, M., Maiani, G., and Ferro-Luzzi, A. 1998. Alcohol-free red wine enhances plasma antioxidant capacity in humans. *J. Nutr.*, **128**:1003–1007.

[29] Fuhrman, B., Lavy, A., and Aviram, M. 1995. Consumption of red wine with meals reduces the susceptibility of human plasma and low-density lipoprotein to lipid peroxidation. *American Journal of Clinical Nutrition*, **61**:549–554.

[30] Maxwell, S., Cruickshank, A., and Thorpe, G. 1994. Red wine and antioxidant activity in serum. *Lancet*, **344**:193–194.

[31] Carbonneau, M.A., Leger, C.L., Monnier, L., Bonnet, C., Michel, F., Fouret, G., Dedieu, F., and Descomps, B. 1997. Supplementation with wine phenolic compounds increases the antioxidant capacity of plasma and vitamin E of low-density lipoprotein without changing the lipoprotein Cu(2+)-oxidizability: Possible explanation by phenolic location. *Eur. J. Clin. Nutr.*, **51**:682–690.

[32] Ghiselli, A., Natella, F., Guidi, A., Montanari, L., Fantozzi, P., and Scaccini, C. 2000. Beer increases plasma antioxidant capacity in humans. *J. Nutr. biochem.*, **11**:76–80.

[33] Nakagawa, K., Ninomiya, M., Okubo, T., Aoi, N., Juneja, L.R., Kim, M., Yamanaka, K., and Miyazawa, T. 1999. Tea catechin supplementation increases antioxidant capacity and prevents phospholipid hydroperoxidation in plasma of humans. *J. Agric. Food Chem.*, **47**:3967–3973.

[34] Young, J.F., Nielsen, S.E., Haraldsdottir, J., Daneshvar, B., Lauridsen, S.T., Knuthsen, P., Crozier, A., Sandstrom, B., and Dragsted, L.O. 1999. Effect of fruit juice intake on urinary quercetin excretion and biomarkers of antioxidative status. *Am. J. Clin. Nutr.*, **69**:87–94.

[35] Rein, D., Lotito, S., Holt, R.R., Keen, C.L., Schmitz, H.H., and Fraga, C.G. 2000. Epicatechin in human plasma: In vivo determination and effect of chocolate consumption on plasma oxidation status. *J. Nutr.*, **130**:2109S–2114S.

[36] Sharpe, P.C., McGrath, L.T., McClean, E., Young, I.S., and Archbold, G.P. 1995. Effect of red wine consumption on lipoprotein (a) and other risk factors for atherosclerosis. *Q. J. Med.*, **88**:101–108.

[37] Hodgson, J.M., Puddey, I.B., Croft, K.D., Mori, T.A., Rivera, J., and Beilin, L.J. 1999. Isoflavonoids do not inhibit in vivo lipid peroxidation in subjects with high-normal blood pressure. *Atherosclerosis*, **145**:167–172.

[38] Laughton, M.J., Halliwell, B., Evans, P.J., and Hoult, J.R. 1989. Antioxidant and pro-oxidant actions of the plant phenolics quercetin, gossypol and myricetin. Effects on lipid peroxidation, hydroxyl radical generation and bleomycin-dependent damage to DNA. *Biochem. Pharmacol.*, **38**:2859–2865.

[39] Shirahata, S., Murakami, H., Nishiyama, K., Yamada, K., Nonaka, G., Nishioka, I., and Omura, H. 1989. DNA breakage by flavan-3-ols and procyanidins in the presence of cupric ion. *J. Agric. Food Chem.*, **37**:299–303.

[40] Sakagami, H., Kuribayashi, N., Iida, M., Sakagami, T., Takeda, M., Fukuchi, K., Gomi, K., Ohata, H., Momose, K., Kawazoe, Y., Hatano, T., Yoshida, T., and Okuda, T. 1995. Induction of DNA fragmentation by tannin- and lignin-related substances. *Anticanc. Res.*, **15**:2121–2128.

[41] Vance, R.E. and Teel, R.W. 1989. Effect of tannic acid on rat liver S9 mediated mutagenesis, metabolism and DNA binding of benzo[a]pyrene. *Cancer Lett.*, **47**:37–44.

[42] Wood, A.W., Huang, M.T., Chang, R.L., Newmark, H.L., Lehr, R.E., Yagi, H., Sayer, J.M., Jerina, D.M., and Conney, A.H. 1982. Inhibition of the mutagenicity of bay-region diol epoxides of polycyclic aromatic hydrocarbons by naturally occurring plant phenols: Exceptional activity of ellagic acid. *Proc. Natl. Acad. Sci. USA*, **79**:5513–5517.

[43] Sayer, J.M., Yagi, H., Wood, A.W., Conney, A.H., and Jerina, D.M. 1982. Extremely facile reaction between the ultimate carcinogen benzo[*a*]pyrene-7,8-diol 9,10-epoxide and ellagic acid. *J. Am. Chem. Soc.*, **104**:5562–5564.

[44] Mukhtar, H., Das, M., Del Tito, B.J., and Bickers, D.R. 1984. Protection against 3-mehtylcholanthrene-induced skin tumorigenicity in BALB/c mice by ellagic acid. *Biochem. Biophys. Res. Commun.*, **119**:751–757.

[45] Casalini, C., Lodovici, M., Briani, C., Paganelli, G., Remy, S., Cheynier, V., and Dolara, P. 1999. Effect of complex polyphenols and tannins from red wine (WCPT) on chemically induced oxidative DNA damage in the rat. *Eur. J. Nutr.*, **38**:190–195.

[46] Takagi, A., Sai, K., Umemura, T., Hasegawa, R., and Kurokawa, Y. 1995. Inhibitory effects of vitamin E and ellagic acid on 8-hydroxydeoxyguanosine formation in the liver nuclear DNA of rats treated with 2-nitropropane. *Cancer Lett.*, **91**:139–144.

[47] Giovannelli, L., Testa, G., De Filippo, C., Cheynier, V., Clifford, M.N., and Dolara, P. 2000. Effect of complex polyphenols and tannins from red wine on DNA oxidative damage of rat colon mucosa *in vivo*. *Eur. J. Nutr.*, **39**:207–212.

[48] Lodovici, M., Casalini, C., De Filippo, C., Copeland, E., Xu, X., Clifford, M., and Dolara, P. 2000. Inhibition of 1,2-dimethylhydrazine-induced oxidative DNA damage in rat colon mucosa by black tea complex polyphenols. *Food Chem. Toxicol.*, **38**:1085–1088.

[49] Huber, W.W., McDaniel, L.P., Kaderlik, K.R., Teitel, C.H., Lang, N.P., and Kadlubar, F.F. 1997. Chemoprotection against the formation of colon DNA adducts from the food-borne carcinogen 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) in the rat. *Mutat. Res.*, **376**:115–122.

[50] Lampe, J.W. 1999. Health effects of vegetables and fruit: Assessing mechanisms of action in human experimental studies. *Am. J. Clin. Nutr.*, **70**:475S–490S.

[51] Leighton, F., Cuevas, A., Guasch, V., Perez, D.D., Strobel, P., San Martin, A., Urzua, U., Diez, M.S., Foncea, R., Castillo, O., Mizon, C., Espinoza, M.A., Urquiaga, I., Rozowski, J., Maiz, A., and Germain, A. 1999. Plasma polyphenols and antioxidants, oxidative DNA damage and endothelial function in a diet and wine intervention study in humans. *Drugs Exp. Clin. Res.*, **25**:133–141.

[52] Boyle, S.P., Dobson, V.L., Duthie, S.J., Kyle, J.A., and Collins, A.R. 2000. Absorption and DNA protective effects of flavonoid glycosides from an onion meal. *Eur. J. Nutr.*, **39**:213–223.

[53] Lean, M.E., Noroozi, M., Kelly, I., Burns, J., Talwar, D., Sattar, N., and Crozier, A. 1999. Dietary flavonols protect diabetic human lymphocytes against oxidative damage to DNA. *Diabetes*, **48**:176–181.

[54] Beatty, E.R., O'Reilly, J.D., England, T.G., McAnlis, G.T., Young, I.S., Geissler, C.A., Sanders, T.A., and Wiseman, H. 2000. Effect of dietary quercetin on oxidative DNA damage in healthy human subjects. *Br. J. Nutr.*, **84**:919–925.

[55] Young, J.F., Dragstedt, L.O., Haraldsdottir, J., Daneshvar, B., Kal, M.A., Loft, S., Nilsson, L., Nielsen, S.E., Mayer, B., Skibsted, L.H., Huynh-Ba, T., Hermetter, A., and Sandstrom, B. 2002. Green tea extract only affects markers of oxidative status postprandially: Lasting antioxidant effect of flavonoid-free diet. *Br. J. Nutr.*, **87**:343–355.

[56] Collins, A.R. 1999. Oxidative DNA damage, antioxidants, and cancer. *Bioessays*, **21**:238–246.

[57] Liao, K. and Yin, M. 2000. Individual and combined antioxidant effects of seven phenolic agents in human erythrocyte membrane ghosts and phosphatidylcholine liposome systems: Importance of the partition coefficient. *J. Agric. Food Chem.*, **48**:2266–2270.

[58] daSilva, E.L., Piskula, M.K., Yamamoto, N., Moon, J.H., and Terao, J. 1998. Quercetin metabolites inhibit copper ion-induced lipid peroxidation in rat plasma. *FEBS Lett.*, **430**:405–408.

[59] Hayek, T., Fuhrman, B., Vaya, J., Rosenblat, M., Belinky, P., Coleman, R., Elis, A., and Aviram, M. 1997. Reduced progression of atherosclerosis in apolipoprotein E-deficient mice following consumption of red wine, or its polyphenols quercetin or catechin, is associated with reduced susceptibility of LDL to oxidation and aggregation. *Arteriosclerosis Thrombosis and Vascular Biology*, **17**:2744–2752.

[60] Miura, Y., Chiba, T., Tomita, I., Koizumi, H., Miura, S., Umegaki, K., Hara, Y., Ikeda, M., and Tomita, T. 2001. Tea catechins prevent the development of atherosclerosis in apoprotein E-deficient mice. *J. Nutr.*, **131**:27–32.

[61] Kaplan, M., Hayek, T., Raz, A., Coleman, R., Dornfeld, L., Vaya, J., and Aviram, M. 2001. Pomegranate juice supplementation to atherosclerotic mice reduces macrophage lipid peroxidation, cellular cholesterol accumulation and development of atherosclerosis. *J. Nutr.*, **131**:2082–2089.

[62] Yamakoshi, J., Kataoka, S., Koga, T., and Ariga, T. 1999. Proanthocyanidin-rich extract from grape seeds attenuates the development of aortic atherosclerosis in cholesterol-fed rabbits. *Atherosclerosis*, **142**:139–149.

[63] Zhu, Q.Y., Huang, Y., Tsang, D., and Chen, Z.Y. 1999. Regeneration of alpha-tocopherol in human low-density lipoprotein by green tea catechin. *J. Agric. Food Chem.*, **47**:2020–2025.

[64] Ishikawa, T., Suzukawa, M., Ito, T., Yoshida, H., Ayaori, M., Nishiwaki, M., Yonemura, A., Hara, Y., and Nakamura, H. 1997. Effect of tea flavonoid supplementation on the susceptibility of low-density lipoprotein to oxidative modification. *American Journal of Clinical Nutrition*, **66**:261–266.

[65] Kondo, K., Matsumoto, A., Kurata, H., Tanahashi, H., Koda, H., Amachi, T., and Itakura, H. 1994. Inhibition of oxidation of low-density lipoprotein with red wine. *Lancet*, **344**:1152.

[66] Kondo, K., Hirano, R., Matsumoto, A., Igarashi, O., and Itakura, H. 1996. Inhibition of LDL oxidation by cocoa. *Lancet*, **348**:1514.

[67] Aviram, M., Dornfeld, L., Rosenblat, M., Volkova, N., Kaplan, M., Coleman, R., Hayek, T., Presser, D., and Fuhrman, B. 2000. Pomegranate juice consumption reduces oxidative stress, atherogenic modifications to LDL, and platelet aggregation: Studies in humans and in atherosclerotic apolipoprotein E-deficient mice. *Am. J. Clin. Nutr.*, **71**:1062–1076.

[68] Osakabe, N., Natsume, M., Adachi, T., Yamagishi, M., Hirano, R., Takizawa, T., Itakura, H., and Kondo, K. 2000. Effects of cacao liquor polyphenols on the susceptibility of low-density lipoprotein to oxidation in hypercholesterolemic rabbits. *J. Atheroscler Thromb.*, **7**:164–168.

[69] de Rijke, Y.B., Demacker, P.N.M., Assen, N.A., Sloots, L.M., Katan, M.B., and Stalenhoef, A.F.H. 1996. Red wine consumption does not affect oxidizability of low-density lipoproteins in volunteers. *American Journal of Clinical Nutrition*, **63**:329–334.

[70] van het Hof, K.H., deBoer, H.S.M., Wiseman, S.A., Lien, N., Weststrate, J.A., and Tijburg, L.B.M. 1997. Consumption of green or black tea does not increase resistance of low-density lipoprotein to oxidation in humans. *American Journal of Clinical Nutrition*, **66**:1125–1132.

[71] van het Hof, K.H., Wiseman, S.A., Yang, C.S., and Tijburg, L.B. 1999. Plasma and lipoprotein levels of tea catechins following repeated tea consumption. *Proc. Soc. Exp. Biol. Med.*, **220**:203–209.

[72] Princen, H.M., van Duyvenvoorde, W., Buytenhek, R., Blonk, C., Tijburg, L.B., Langius, J.A., Meinders, A.E., and Pijl, H. 1998. No effect of consumption of green and black tea on plasma lipid and antioxidant levels and on LDL oxidation in smokers. *Arterioscler. Thromb. Vasc. Biol.*, **18**:833–841.

[73] Abu-Amsha Caccetta, R.A., Croft, K.D., Beilin, L.J., and Puddey, I.B. 2000. Ingestion of red wine significantly increases plasma phenolic acid concentrations but does not acutely affect ex vivo lipoprotein oxidizability. *Am. J. Clin. Nutr.*, **71**:67–74.

[74] Kaamanen, M., Adlercreutz, H., Jauhiainen, M., and Tikkanen, M.J. 2003. Accumulation of genistein and lipophilic genistein derivatives in lipoproteins during incubation with human plasma *in vitro*. *Biochim. Biophys. Acta*, **1631**:147–152.

[75] Maeda, K., Kuzuya, M., Cheng, X.W., Asai, T., Kanda, S., Tamaya-Mori, N., Sasaki, T., Shibata, T., and Iguchi, A. 2003. Green tea catechins inhibit the cultured smooth muscle cell invasion through the basement barrier. *Atherosclerosis*, **166**:23–30.

[76] Lu, L.H., Lee, S.S., and Huang, H.C. 1998. Epigallocatechin suppression of proliferation of vascular smooth muscle cells: Correlation with c-jun and JNK. *Br. J. Pharmacol.*, **124**:1227–1237.

[77] Tebib, K., Besancon, P., and Rouanet, J.M. 1994. Dietary grape seed tannins affect lipoproteins, lipoprotein lipases and tissue lipids in rats fed hypercholesterolemic diets. *J. Nutr.*, **124**:2451–2457.

[78] Montforte, M.T., Trovato, A., Kirjavainen, S., Forestieri, A.M., Galati, E.M., and Lo Curto, R.B. 1995. Biological effects of heperidin, a Citrus flavonoid. Hypolipidemic activity on experimenal hypercholesterolemia in rat. *Il. Farmaco.*, **50**:595–599.

[79] Lee, S.H., Park, Y.B., Bae, K.H., Bok, S.H., Kwon, Y.K., Lee, E.S., and Choi, M.S. 1999. Cholesterol-lowering activity of naringenin via inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase and acyl coenzyme A: Cholesterol acyltransferase in rats. *Ann. Nutr. Metab.*, **43**:173–180.

[80] Bok, S.H., Lee, S.H., Park, Y.B., Bae, K.H., Son, K.H., Jeong, T.S., and Choi, M.S. 1999. Plasma and hepatic cholesterol and hepatic activities of 3-hydroxy-3-methyl-glutaryl-CoA reductase and acyl CoA: Cholesterol transferase are lower in rats fed citrus peel extract or a mixture of citrus bioflavonoids. *J. Nutr.*, **129**:1182–1185.

[81] Hodgson, J.M., Puddey, I.B., Burke, V., Beilin, L.J., Mori, T.A., and Chan, S.Y. 2002. Acute effects of ingestion of black tea on postprandial platelet aggregation in human subjects. *Br J. Nutr.*, **87**:141–145.

[82] Nestel, P.J., Yamashita, T., Sasahara, T., Pomeroy, S., Dart, A., Komesaroff, P., Owen, A., and Abbey, M. 1997. Soy isoflavones improve systemic arterial compliance but not plasma lipids in menopausal and perimenopausal women. *Arterioscler. Thromb. Vasc. Biol.*, **17**:3392–3398.

[83] Simons, L.A., von Konigsmark, M., Simons, J., and Celermajer, D.S. 2000. Phytoestrogens do not influence lipoprotein levels or endothelial function in healthy, postmenopausal women. *Am. J. Cardiol.*, **85**:1297–1301.

[84] Hodgson, J.M., Puddey, I.B., Beilin, L.J., Mori, T.A., and Croft, K.D. 1998. Supplementation with isoflavonoid phytoestrogens does not alter serum lipid concentrations: A randomized controlled trial in humans. *J. Nutr.*, **128**:728–732.

[85] Sagesaka-Mitane, Y., Miwa, M., and Okada, S. 1990. Platelet aggregation inhibitors in hot water extract of green tea. *Chem. Pharm. Bull (Tokyo)*, **38**:790–793.

[86] Russo, P., Tedesco, I., Russo, M., Russo, G.L., Venezia, A., and Cicala, C. 2001. Effects of de-alcoholated red wine and its phenolic fractions on platelet aggregation. *Nutr. Metab. Cardiovasc. Dis.*, **11**:25–29.

[87] Ruf, J.C., Berger, J.L., and Renaud, S. 1995. Platelet rebound effect of alcohol withdrawal and wine drinking in rats—Relation to tannins and lipid peroxidation. *Arterioscl. Thromb. Vasc. Biol.*, **15**:140–144.

[88] Wollny, T., Aiello, L., Di Tommaso, D., Bellavia, V., Rotilio, D., Donati, M.B., de Gaetano, G., and Iacoviello, L. 1999. Modulation of haemostatic function and prevention of experimental thrombosis by red wine in rats: A role for increased nitric oxide production. *Br. J. Pharmacol.*, **127**:747–755.

[89] Demrow, H.S., Slane, P.R., and Folts, J.D. 1995. Administration of wine and grape juice inhibits *in vivo* platelet activity and thrombosis in stenosed canine coronary arteries. *Circulation*, **91**:1182–1188.

[90] Osman, H.E., Maalej, N., Shanmuganayagam, D., and Folts, J.D. 1998. Grape juice but not orange or grapefruit juice inhibits platelet activity in dogs and monkeys. *J. Nutr.*, **128**:2307–2312.

[91] Rein, D., Paglieroni, T.G., Wun, T., Pearson, D.A., Schmitz, H.H., Gosselin, R., and Keen, C.L. 2000. Cocoa inhibits platelet activation and function. *Am. J. Clin. Nutr.*, **72**:30–35.

[92] Keevil, J.G., Osman, H.E., Reed, J.D., and Folts, J.D. 2000. Grape juice, but not orange juice or grapefruit juice, inhibits human platelet aggregation. *J. Nutr.*, **130**:53–56.

[93] Duffy, S.J., Vita, J.A., Holbrook, M., Swerdloff, P.L., and Keaney, J.F., Jr. 2001. Effect of acute and chronic tea consumption on platelet aggregation in patients with coronary artery disease. *Arterioscler. Thromb. Vasc. Biol.*, **21**:1084–1089.

[94] Janssen, K., Mensink, R., Cox, F., Harryvan, J., Hovenier, R., Hollman, P., and Katan, M. 1998. Effects of the flavonoids quercetin and apigenin on hemostasis in healthy volunteers: Results from an in vitro and a dietary supplement study. *Am. J. Clin. Nutr.*, **67**:255–425.

[95] Dent, S.B., Peterson, C.T., Brace, L.D., Swain, J.H., Reddy, M.B., Hanson, K.B., Robinson, J.G., and Alekel, D.L. 2001. Soy protein intake by perimenopausal women does not affect circulating lipids and lipoproteins or coagulation and fibrinolytic factors. *J. Nutr.*, **131**:2280–2287.

[96] Celermajer, D.S., Sorensen, K.E., Gooch, V.M., Spiegelhalter, D.J., Miller, O.I., Sullivan, I.D., Lloyd, J.K., and Deanfield, J.E. 1992. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. *Lancet*, **340**:1111–1115.

[97] Schächinger, V., Britten, M.B., and Zeiher, A.M. 2000. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease. *Circulation*, **101**:1899–1906.

[98] Andriambeloson, E., Magnier, C., Haan-Archipoff, G., Lobstein, A., Anton, R., Beretz, A., Stoclet, J.C., and Andriantsitohaina, R. 1998. Natural dietary polyphenolic compounds cause endothelium-dependent vasorelaxation in rat thoracic aorta. *J. Nutr.*, **128**:2324–2333.

[99] Honoré, E.K., Williams, J.K., Anthony, M.S., and Clarkson, T.B. 1997. Soy isoflavones enhance coronary vascular reactivity in atherosclerotic female macaques. *Fertility and Sterility*, **67**:148–154.

[100] Chen, C.K. and Paceasciak, C.R. 1996. Vasorelaxing activity of resveratrol and quercetin in isolated rat aorta. *General Pharmacology*, **27**:363–366.

[101] Karim, M., McCormick, K., and Kappagoda, C.T. 2000. Effects of cocoa extracts on endothelium-dependent relaxation. *J. Nutr.*, **130**:2105S–2108S.

[102] Duffy, S.J., Keaney, J.F., Jr., Holbrook, M., Gokce, N., Swerdloff, P.L., Frei, B., and Vita, J.A. 2001. Short- and long-term black tea consumption reverses endothelial dysfunction in patients with coronary artery disease. *Circulation*, **104**:151–156.

[103] Cuevas, A.M., Guasch, V., Castillo, O., Irribarra, V., Mizon, C., San Martin, A., Strobel, P., Perez, D., Germain, A.M., and Leighton, F. 2000. A high-fat diet induces and red wine counteracts endothelial dysfunction in human volunteers [In Process Citation]. *Lipids*, **35**:143–148.

[104] Peters, U., Poole, C., and Arab, L. 2001. Does tea affect cardiovascular disease? A meta-analysis. *Am. J. Epidemiol.*, **154**:495–503.

[105] Rotondo, S., Di Castelnuovo, A., and de Gaetano, G. 2001. The relationship between wine consumption and cardiovascular risk: From

epidemiological evidence to biological plausibility. *Ital. Heart J.*, **2**:1–8.

[106] Hertog, M.G.L., Sweetman, P.M., Fehily, A.M., Elwood, P.C., and Kromhout, D. 1997. Antioxidant flavonols and ischemic heart disease in a Welsh population of men: The Caerphilly Study. *American Journal of Clinical Nutrition*, **65**:1489–1494.

[107] Woodward, M. and Tunstall-Pedoe, H. 1999. Coffee and tea consumption in the Scottish Heart Health Study follow up: Conflicting relations with coronary risk factors, coronary disease, and all cause mortality. *J. Epidemiol. Community Health*, **53**:481–487.

[108] Knekt, P., Jarvinen, R., Reunanen, A., and Maatela, J. 1996. Flavonoid intake and coronary mortality in Finland: A cohort study. *British Medical Journal*, **312**:478–481.

[109] Hertog, M.G.L., Kromhout, D., Aravanis, C., Blackburn, H., Buzina, R., Fidanza, F., Giampaoli, S., Jansen, A., Menotti, A., Nedeljkovic, S., Pekkarinen, M., Simic, B.S., Toshima, H., Feskens, E.J.M., Hollman, P.C.H., and Katan, M.B. 1995. Flavonoid intake and long-term risk of coronary heart disease and cancer in the Seven Countries Study. *Archives of Internal Medicine*, **155**:381–386.

[110] Hirvonen, T., Pietinen, P., Virtanen, M., Ovaskainen, M.L., Hakkinen, S., Albanes, D., and Virtamo, J. 2001. Intake of flavonols and flavones and risk of coronary heart disease in male smokers. *Epidemiology*, **12**:62–67.

[111] Yochum, L., Kushi, L.H., Meyer, K., and Folsom, A.R. 1999. Dietary flavonoid intake and risk of cardiovascular disease in postmenopausal women. *Am. J. Epidemiol.*, **149**:943–949.

[112] Arts, I.C., Jacobs, D.R., Jr., Harnack, L.J., Gross, M., and Folsom, A.R. 2001. Dietary catechins in relation to coronary heart disease death among postmenopausal women. *Epidemiology*, **12**:668–675.

[113] Arts, I.C., Hollman, P.C., Feskens, E.J., Bueno de Mesquita, H.B., and Kromhout, D. 2001. Catechin intake might explain the inverse relation between tea consumption and ischemic heart disease: The Zutphen Elderly Study. *Am. J. Clin. Nutr.*, **74**:227–232.

[114] Yang, C.S., Landau, J.M., Huang, M.T., and Newmark, H.L. 2001. Inhibition of carcinogenesis by dietary polyphenolic compounds. *Annu. Rev. Nutr.*, **21**:381–406.

[115] Johnson, I.T., Williamson, G., and Musk, S.R.R. 1994. Anticarcinogenic factors in plant foods: A new class of nutrients?. *Nutr. Res. Rev.*, **7**:175–204.

[116] Suschetet, M., Siess, M.-H., Le Bon, A.-M., and Canivenc-Lavier, M.-C. 1997. Anticarcinogenic properties of some flavonoids. In: *Polyphénols 96*, 165–204. Vercauteren, J., Chèze, C., and Triaud, J. ed. Paris, INRA Editions.

[117] Talalay, P., De Long, M.J., and Prochaska, H.J. 1988. Identification of a common chemical signal regulating the induction of enzymes that protect against chemical carcinogenesis. *Proc. Natl. Acad. Sci. USA*, **85**:8261–8265.

[118] Webster, R.P., Gawde, M.D., and Bhattacharya, R.K. 1996. Protective effect of rutin, a flavonol glycoside, on the carcinogen-induced DNA damage and repair enzymes in rats. *Cancer Letters*, **109**:185–191.

[119] Imanishi, H., Sasaki, Y.F., Ohta, T., Watanabe, M., Kato, T., and Shirasu, Y. 1991. Tea tannin components modify the induction of sister-chromatid exchanges and chromosome aberrations in mutagen-treated cultured mammalian cells and mice. *Mutation Res.*, **259**:79–87.

[120] Agullo, G., Gametpayrastre, L., Fernandez, Y., Anciaux, N., Demigne, C., and Remsey, C. 1996. Comparative effects of flavonoids on the growth, viability and metabolism of a colonic adenocarcinoma cell line (HT29 cells). *Cancer Letters*, **105**:61–70.

[121] Kuntz, S., Wenzel, U., and Daniel, H. 1999. Comparative analysis of the effects of flavonoids on proliferation, cytotoxicity, and apoptosis in human colon cancer cell lines. *Eur J. Nutr.*, **38**:133–142.

[122] Dong, Z., Ma, W., Huang, C., and Yang, C.S. 1997. Inhibition of tumor promoter-induced activator protein 1 activation and cell transformation by tea polyphenols, (−)-epigallocatechin gallate, and theaflavins. *Cancer Res.*, **57**:4414–4419.

[123] Barthelman, M., Bair, W.B., 3rd, Stickland, K.K., Chen, W., Timmermann, B.N., Valcic, S., Dong, Z., and Bowden, G.T. 1998. (−)-Epigallocatechin-3-gallate inhibition of ultraviolet B-induced AP-1 activity. *Carcinogenesis*, **19**:2201–2204.

[124] Lin, J.K., Chen, Y.C., Huang, Y.T., and Lin-Shiau, S.Y. 1997. Suppression of protein kinase C and nuclear oncogene expression as possible molecular mechanisms of cancer chemoprevention by apigenin and curcumin. *J. Cell Biochem. Suppl.*, **28–29**:39–48.

[125] Schneider, Y., Vincent, F., Duranton, B., Badolo, L., Gosse, F., Bergmann, C., Seiler, N., and Raul, F. 2000. Anti-proliferative effect of resveratrol, a natural component of grapes and wine, on human colonic cancer cells. *Cancer Lett.*, **158**:85–91.

[126] Gupta, S., Ahmad, N., Mohan, R.R., Husain, M.M., and Mukhtar, H. 1999. Prostate cancer chemoprevention by green tea: In vitro and in vivo inhibition of testosterone-mediated induction of ornithine decarboxylase. *Cancer Res.*, **59**:2115–2120.

[127] Metz, N., Lobstein, A., Schneider, Y., Gosse, F., Schleiffer, R., Anton, R., and Raul, F. 2000. Suppression of azoxymethane-induced preneoplastic lesions and inhibition of cyclooxygenase-2 activity in the colonic mucosa of rats drinking a crude green tea extract. *Nutr. Cancer*, **38**:60–64.

[128] Kuiper, G.G., Lemmen, J.G., Carlsson, B., Corton, J.C., Safe, S.H., van der Saag, P.T., van der Burg, B., and Gustafsson, J.A. 1998. Interaction of estrogenic chemicals and phytoestrogens with estrogen receptor beta. *Endocrinology*, **139**:4252–4263.

[129] Collins-Burow, B.M., Burow, M.E., Duong, B.N., and McLachlan, J.A. 2000. Estrogenic and antiestrogenic activities of flavonoid phytochemicals through estrogen receptor binding-dependent and -independent mechanisms. *Nutr. Cancer*, **38**:229–244.

[130] Lamartiniere, C.A., Cotroneo, M.S., Fritz, W.A., Wang, J. 2002. Mentor-Marcel, R., and Elgavish, A., Genistein chemoprevention: Timing and mechanisms of action in murine mammary and prostate. *J. Nutr.*, **132**:552S–558S.

[131] Ishikawa, Y. and Kitamura, M. 2000. Bioflavonoid quercetin inhibits mitosis and apoptosis of glomerular cells in vitro and *in vivo*. *Biochem. Biophys. Res, Commun.*, **279**:629–634.

[132] Gee, J.M., Hara, H., and Johnson, I.T. 2002. Suppression of intestinal crypt cell proliferation and aberrant crypt foci by dietary quercetin in rats. *Nutr. Cancer*, **43**:193–201.

[133] Spencer, J.P., Schroeter, H., Kuhnle, G., Srai, S.K., Tyrrell, R. M., Hahn, U., and Rice-Evans, C. 2001. Epicatechin and its in vivo metabolite, 3′-O-methyl epicatechin, protect human fibroblasts from oxidative-stress-induced cell death involving caspase-3 activation. *Biochem. J.*, **354**:493–500.

[134] Ishikawa, Y. and Kitamura, M. 2000. Anti-apoptotic effect of quercetin: Intervention in the JNK- and ERK-mediated apoptotic pathways. *Kidney Int.*, **58**:1078–1087.

[135] McCarty, M.F. 1998. Polyphenol-mediated inhibition of AP-1 transactivating activity may slow cancer growth by impeding angiogenesis and tumor invasiveness. *Med. Hypotheses*, **50**:511–514.

[136] Cao, Y. and Cao, R. 1999. Angiogenesis inhibited by drinking tea. *Nature*, **398**:381.

[137] Demeule, M., Brossard, M., Page, M., Gingras, D., and Beliveau, R. 2000. Matrix metalloproteinase inhibition by green tea catechins. *Biochim. Biophys. Acta* **1478**:51–60.

[138] Maeda-Yamamoto, M., Kawahara, H., Tahara, N., Tsuji, K., Hara, Y., and Isemura, M. 1999. Effects of tea polyphenols on the invasion and matrix metalloproteinases activities of human fibrosarcoma HT1080 cells. *J. Agric. Food Chem.*, **47**:2350–2354.

[139] Naasani, I., Oh-Hashi, F., Oh-Hara, T., Feng, W.Y., Johnston, J., Chan, K., and Tsuruo, T. 2003. Blocking telomerase by dietary polyphenols is a major mechanism for limiting the growth of human cancer cells in vitro and *in vivo*. *Cancer. Res.*, **63**:824–830.

[140] Flohe, L., Brigelius-Flohe, R., Saliou, C., Traber, M. G., and Packer, L. 1997. Redox regulation of NF-kappa B activation. *Free Radic. Biol. Med.*, **22**:1115–1126.

[141] Ahmad, N., Gupta, S., and Mukhtar, H. 2000. Green tea polyphenol epigallocatechin-3-gallate differentially modulates nuclear factor kappaB

in cancer cells versus normal cells. *Arch. Biochem. Biophys.*, **376**:338–346.

[142] Suganuma, M., Sueoka, E., Sueoka, N., Okabe, S., and Fujiki, H. 2000. Mechanisms of cancer prevention by tea polyphenols based on inhibition of TNF-alpha expression. *Biofactors*, **13**:67–72.

[143] Nomura, M., Ma, W., Chen, N., Bode, A.M., and Dong, Z. 2000. Inhibition of 12-O-tetradecanoylphorbol-13-acetate-induced NF-kappaB activation by tea polyphenols, (−)-epigallocatechin gallate and theaflavins. *Carcinogenesis*, **21**:1885–1890.

[144] Ferry, D.R., Smith, A., Malkhandi, J., Fyfe, D.W., de Takats, P.G., Anderson, D., Baker, J., and Kerr, D.J. 1996. Phase I clinical trial of the flavonoid quercetin: pharmacokinetics and evidence for *in vivo* tyrosine kinase inhibition. *Clin. Cancer Res.*, **2**:659–668.

[145] Jang, M., Cai, L., Udeani, G.O., Slowing, K.V., Thomas, C.F., Beecher, C.W.W., Fong, H.H.S., Farnsworth, N.R., Kinghorn, A.D., Mehta, R.G., and Pezzuto, J.M. 1997. Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. *Science*, **275**:218–220.

[146] Frankel, E.N., Waterhouse, A.L., and Teissedre, P.L. 1995. Principal phenolic phytochemicals in selected California wines and their antioxidant activity in inhibiting oxidation of human low-density lipoproteins. *J. Agric. Food Chem.*, **43**:890–894.

[147] Lutz, U., Lugli, S., Bitsch, A., Schlatter, J., and Lutz, W.K. 1997. Dose response for the stimulation of cell division by caffeic acid in forestomach and kidney of the male F344 rat. *Fundam. Appl. Toxicol.*, **39**:131–137.

[148] Hsieh, C.Y., Santell, R.C., Haslam, S.Z., and Helferich, W.G. 1998. Estrogenic effects of genistein on the growth of estrogen receptor-positive human breast cancer (MCF-7) cells *in vitro* and *in vivo*. *Cancer Res.*, **58**:3833–3838.

[149] Davis, J.N., Kucuk, O., and Sarkar, F.H. 2002. Expression of prostate-specific antigen is transcriptionally regulated by genistein in prostate cancer cells. *Mol. Carcinog.*, **34**:91–101.

[150] Levites, Y., Weinreb, O., Maor, G., Youdim, M.B., and Mandel, S. 2001. Green tea polyphenol (−)-epigallocatechin-3-gallate prevents N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced dopaminergic neurodegeneration. *J. Neurochem.*, **78**:1073–1082.

[151] Rucker, R. and Storms, D. 2002. Interspecies comparisons of micronutrient requirements: Metabolic vs. absolute body size. *J. Nutr.*, **132**:2999–3000.

[152] Kimira, M., Arai, Y., Shimoi, K., and Watanabe, S. 1998. Japanese intake of flavonoids and isoflavonoids from foods. *J. Epidemiol.*, **8**:168–175.

[153] Shimoi, K., Saka, N., Nozawa, R., Sato, M., Amano, I., Nakayama, T., and Kinae, N. 2001. Deglucuronidation of a flavonoid, luteolin monoglucuronide, during inflammation. *Drug Metab. Dispos.*, **29**:1521–1524.

[154] Spencer, J.P., Schroeter, H., Crossthwaithe, A.J., Kuhnle, G., Williams, R.J., and Rice-Evans, C. 2001. Contrasting influences of glucuronidation and O-methylation of epicatechin on hydrogen peroxide-induced cell death in neurons and fibroblasts. *Free Radic. Biol. Med.*, **31**:1139–1146.

[155] Yoshizumi, M., Tsuchiya, K., Suzaki, Y., Kirima, K., Kyaw, M., Moon, J.H., Terao, J., and Tamaki, T. 2002. Quercetin glucuronide prevents VSMC hypertrophy by angiotensin II via the inhibition of JNK and AP-1 signaling pathway. *Biochem. Biophys. Res. Commun.*, **293**:1458–1465.

[156] Zhang, Y., Song, T.T., Cunnick, J.E., Murphy, P.A., and Hendrich, S. 1999. Daidzein and genistein glucuronides *in vitro* are weakly estrogenic and activate human natural killer cells at nutritionally relevant concentrations. *J. Nutr.*, **129**:399–405.

[157] Sturgeon, C. 2002. Practice guidelines for tumor marker use in the clinic. *Clin. Chem.*, **48**:1151–1159.

[158] Fujimoto, N., Sueoka, N., Sueoka, E., Okabe, S., Suganuma, M., Harada, M., and Fujiki, H. 2002. Lung cancer prevention with (−)-epigallocatechin gallate using monitoring by heterogeneous nuclear ribonucleoprotein B1. *Int. J. Oncol*, **20**:1233–1239.

[159] Urban, D., Irwin, W., Kirk, M., Markiewicz, M.A., Myers, R., Smith, M., Weiss, H., Grizzle, W.E., and Barnes, S. 2001. The effect of isolated soy protein on plasma biomarkers in elderly men with elevated serum prostate specific antigen. *J. Urol.*, **165**:294–300.

[160] Lu, L.J., Anderson, K.E., Grady, J.J., Kohen, F., and Nagamani, M. 2000. Decreased ovarian hormones during a soya diet: Implications for breast cancer prevention. *Cancer Res.*, **60**:4112–4121.

[161] Suganuma, M., Okabe, S., Kai, Y., Sueoka, N., Sueoka, E., and Fujiki, H. 1999. Synergistic effects of (−)-epigallocatechin gallate with (−)-epicatechin, sulindac, or tamoxifen on cancer-preventive activity in the human lung cancer cell line PC-9. *Cancer Res.*, **59**:44–47.

[162] Scambia, G., Ranelletti, F.O., Benedetti Panici, P., Bonanno, G., De Vincenzo, R., Piantelli, M., and Mancuso, S. 1990. Synergistic antiproliferative activity of quercetin and cisplatin on ovarian cancer cell growth. *Anticancer Drugs*, **1**:45–48.

[163] Cipak, L., Rauko, P., Miadokova, E., Cipakova, I., and Novotny, L. 2003. Effects of flavonoids on cisplatin-induced apoptosis of HL-60 and L1210 leukemia cells. *Leuk. Res.*, **27**:65–72.

[164] Sadzuka, Y., Sugiyama, T., and Hirota, S. 1998. Modulation of cancer chemotherapy by green tea. *Clin Cancer Res.*, **4**:153–156.

[165] Bracke, M.E., Depypere, H.T., Boterberg, T., Van Marck, V.L., Vennekens, K.M., Vanluchene, E., Nuytinck, M., Serreyn, R., and Mareel, M.M. 1999. Influence of tangeretin on tamoxifen's therapeutic benefit in mammary cancer. *J. Natl. Cancer Inst.*, **91**:354–359.

[166] Tavani, A. and La Vecchia, C. 2000. Coffee and cancer: A review of epidemiological studies, 1990–1999. *Eur. J. Cancer Prev.*, **9**:241–256.

[167] Sun, C.L., Yuan, J.M., Lee, M.J., Yang, C.S., Gao, Y.T., Ross, R.K., and Yu, M.C. 2002. Urinary tea polyphenols in relation to gastric and esophageal cancers: A prospective study of men in Shanghai, China. *Carcinogenesis.*, **23**:1497–1503.

[168] Su, L.J. and Arab, L. 2002. Tea consumption and the reduced risk of colon cancer—results from a national prospective cohort study. *Public Health Nutr.*, **5**:419–425.

[169] Blot, W.J., McLaughlin, J.K., and Chow, W.H. 1997. Cancer rates among drinkers of black tea. *Crit. Rev. Food Sci. Nutr.*, **37**:739–760.

[170] Yang, C.S., Maliakal, P., and Meng, X. 2002. Inhibition of carcinogenesis by tea. *Annu. Rev. Pharmacol. Toxicol.*, **42**:25–54.

[171] Hoshiyama, Y., Kawaguchi, T., Miura, Y., Mizoue, T., Tokui, N., Yatsuya, H., Sakata, K., Kondo, T., Kikuchi, S., Toyoshima, H., Hayakawa, N., Tamakoshi, A., Ohno, Y., and Yoshimura, T. 2004. A nested case-control study of stomach cancer in relation to green tea consumption in Japan. *Br. J. Cancer.*, **90**:135–138.

[172] Hartman, T.J., Tangrea, J.A., Pietinen, P., Malila, N., Virtanen, M., Taylor, P.R., and Albanes, D. 1998. Tea and coffee consumption and risk of colon and rectal cancer in middle-aged Finnish men. *Nutr. Cancer*, **31**:41–48.

[173] Gronbaek, M., Becker, U., Johansen, D., Tonnesen, H., Jensen, G., and Sorensen, T.I.A. 1998. Population based cohort study of the association between alcohol intake and cancer of the upper digestive tract. *Brit. Med. J.*, **317**:844–847.

[174] Prescott, E., Gronbaek, M., Becker, U., and Sorensen, T.I. 1999. Alcohol intake and the risk of lung cancer: Influence of type of alcoholic beverage. *Am. J. Epidemiol.*, **149**:463–470.

[175] Bosetti, C., La Vecchia, C., Negri, E., and Franceschi, S. 2000. Wine and other types of alcoholic beverages and the risk of esophageal cancer. *Eur. J. Clin. Nutr.*, **54**:918–920.

[176] Carpenter, C.L., Morgenstern, H., and London, S.J. 1998. Alcoholic beverage consumption and lung cancer risk among residents of Los Angeles County. *J. Nutr.*, **128**:694–700.

[177] Viel, J.F., Perarnau, J.M., Challier, B., and Faivre-Nappez, I. 1997. Alcoholic calories, red wine consumption and breast cancer among premenopausal women. *Eur. J. Epidemiol.*, **13**:639–643.

[178] Ferraroni, M., Decarli, A., Franceschi, S., and La Vecchia, C. 1998. Alcohol consumption and risk of breast cancer: A multicentre Italian case-control study. *Eur. J. Cancer*, **34**:1403–1409.

[179] Lopez-Carrillo, L., Lopez-Cervantes, M., Ramirez-Espitia, A., Rueda, C., Fernandez-Ortega, C., and Orozco-Rivadeneyra, S. 1998. Alcohol consumption and gastric cancer in Mexico. *Cad. Saude. Publica.*, **14**(Suppl 3):25–32.

[180] Rose, G. and Day, S. 1990. The population mean predicts the number of deviant individuals. *Brit. Med. J.*, **301**:1031–1034.

[181] Knekt, P., Kumpulainen, J., Jarvinen, R., Rissanen, H., Heliovaara, M., Reunanen, A., Hakulinen, T., and Aromaa, A. 2002. Flavonoid intake and risk of chronic diseases. *Am. J. Clin. Nutr.*, **76**:560–568.

[182] Knekt, P., Jarvinen, R., Seppanen, R., Heliovaara, M., Teppo, L., Pukkala, E., and Aromaa, A. 1997. Dietary flavonoids and the risk of lung cancer and other malignant neoplasms. *American Journal of Epidemiology*, **146**:223–230.

[183] Stefani, E.D., Boffetta, P., Deneo-Pellegrini, H., Mendilaharsu, M., Carzoglio, J.C., Ronco, A., and Olivera, L. 1999. Dietary antioxidants and lung cancer risk: A case-control study in Uruguay. *Nutr. Cancer*, **34**:100–110.

[184] Le Marchand, L., Murphy, S.P., Hankin, J.H., Wilkens, L.R., and Kolonel, L.N. 2000. Intake of flavonoids and lung cancer. *J. Natl. Cancer Inst.*, **92**:154–160.

[185] Hirvonen, T., Virtamo, J., Korhonen, P., Albanes, D., and Pietinen, P. 2001. Flavonol and flavone intake and the risk of cancer in male smokers (Finland). *Cancer Causes Control*, **12**:789–796.

[186] Garcia–Closas, R., Agudo, A., Gonzalez, C.A., and Riboli, E. 1998. Intake of specific carotenoids and flavonoids and the risk of lung cancer in women in Barcelona, Spain. *Nutr. Cancer*, **32**:154–158.

[187] Goldbohm, R.A., Hertog, M.G.L., Brants, H.A.M., van Poppel, G., and van den Brandt, P.A. 1997. Intake of flavonoids and cancer risk: A prospective cohort study, in *COST 916 Bioactive plant cell wall components in nutrition and health*, 159–166. Amado, R., Andersson, H., Bardocz, S., andSerra, F. European Communities, Aberdeen, Scotland,

[188] Garcia-Closas, R., Gonzalez, C.A., Agudo, A., and Riboli, E. 1999. Intake of specific carotenoids and flavonoids and the risk of gastric cancer in Spain. *Cancer Causes Control*, **10**:71–75.

[189] De Stefani, E., Ronco, A., Mendilaharsu, M., and Deneo-Pellegrini, H. 1999. Diet and risk of cancer of the upper aerodigestive tract–II. Nutrients. *Oral. Oncol.*, **35**:22–26.

[190] Arts, I.C., Hollman, P.C., Bueno De Mesquita, H.B., Feskens, E.J., and Kromhout, D. 2001. Dietary catechins and epithelial cancer incidence: The Zutphen elderly study. *Int. J. Cancer*, **92**:298–302.

[191] Arts, I.C., Jacobs, D.R., Jr., Gross, M., Harnack, L.J., and Folsom, A.R. 2002. Dietary catechins and cancer incidence among postmenopausal women: The Iowa Women's Health Study (United States). *Cancer Causes Control*, **13**:373–382.

[192] Messina, M.J., Persky, V., Setchell, K.D.R., and Barnes, S. 1994. Soy intake and cancer risk: A review of the *in vitro* and *in vivo* data. *Nutr. Cancer*, **21**:113–131.

[193] Jacobs, D.R., Jr., Marquart, L., Slavin, J., and Kushi, L.H. 1998. Whole-grain intake and cancer: An expanded review and meta-analysis. *Nutr. Cancer*, **30**:85–96.

[194] Adlercreutz, H., Fotsis, T., Heikkinen, R., Dwyer, J.T., Woods, M., Goldin, B.R., and Gorbach, S.L. 1982. Excretion of the lignans enterolactone and enterodiol and of equol in omnivorous and vegetarian postmenopausal women and in women with breast cancer. *Lancet*, **2**:1295–1299.

[195] Murkies, A., Dalais, F.S., Briganti, E.M., Burger, H.G., Healy, D.L., Wahlqvist, M.L., and Davis, S.R. 2000. Phytoestrogens and breast cancer in postmenopausal women: A case control study. *Menopause*, **7**:289–296.

[196] Ingram, D., Sanders, K., Kolybaba, M., and Lopez, D. 1997. Case-control study of phyto-oestrogens and breast cancer. *Lancet*, **350**:990–994.

[197] den Tonkelaar, I., Keinan-Boker, L., Veer, P.V., Arts, C.J., Adlercreutz, H., Thijssen, J.H., and Peeters, P.H. 2001. Urinary phytoestrogens and postmenopausal breast cancer risk. *Cancer Epidemiol. Biomarkers Prev.*, **10**:223–228.

[198] Hulten, K., Winkvist, A., Lenner, P., Johansson, R., Adlercreutz, H., and Hallmans, G. 2002. An incident case-referent study on plasma enterolactone and breast cancer risk. *Eur. J. Nutr.*, **41**:168–176.

[199] Strom, S.S., Yamamura, Y., Duphorne, C.M., Spitz, M.R., Babaian, R.J., Pillow, P.C., and Hursting, S.D. 1999. Phytoestrogen intake and prostate cancer: A case-control study using a new database. *Nutr. Cancer*, **33**:20–25.

[200] Akaza, H., Miyanaga, N., Takashima, N., Naito, S., Hirao, Y., Tsukamoto, T., and Mori, M. 2002. Is daidzein non-metabolizer a high risk for prostate cancer? A case-controlled study of serum soybean isoflavone concentration. *Jpn. J. Clin. Oncol.*, **32**:296–300.

[201] Stattin, P., Adlercreutz, H., Tenkanen, L., Jellum, E., Lumme, S., Hallmans, G., Harvei, S., Teppo, L., Stumpf, K., Luostarinen, T., Lehtinen, M., Dillner, J., and Hakama, M. 2002. Circulating enterolactone and prostate cancer risk: A Nordic nested case-control study. *Int. J. Cancer*, **99**:124–129.

[202] McCann, S.E., Moysich, K.B., Freudenheim, J.L., Ambrosone, C.B., and Shields, P.G. 2002. The risk of breast cancer associated with dietary lignans differs by CYP17 genotype in women. *J. Nutr.*, **132**:3036–3041.

[203] Hertog, M.G.L., Hollman, P.C.H., Katan, M.B., and Kromhout, D. 1993. Intake of potentially anticarcinogenic flavonoids and their determinants in adults in The Netherland. *Nutr. Cancer*, **20**:21–29.

[204] Cantuti-Castelvetri, I., Shukitt-Hale, B., and Joseph, J.A. 2000. Neurobehavioral aspects of antioxidants in aging. *Int. J. Dev. Neurosci.*, **18**:367–381.

[205] Halliwell, B. 2001. Role of free radicals in the neurodegenerative diseases: Therapeutic implications for antioxidant treatment. *Drugs Aging*, **18**:685–716.

[206] Joseph, J.A., Shukitt-Hale, B., Denisova, N.A., Prior, R.L., Cao, G., Martin, A., Taglialatela, G., and Bickford, P.C. 1998. Long-term dietary strawberry, spinach, or vitamin E supplementation retards the onset of age-related neuronal signal-transduction and cognitive behavioral deficits. *J. Neurosci.*, **18**:8047–8055.

[207] Joseph, J.A., Shukitt-Hale, B., Denisova, N.A., Bielinski, D., Martin, A., McEwen, J.J., and Bickford, P.C. 1999. Reversals of age-related declines in neuronal signal transduction, cognitive, and motor behavioral deficits with blueberry, spinach, or strawberry dietary supplementation. *J. Neurosci.*, **19**:8114–8121.

[208] Martin, A., Prior, R., Shukitt-Hale, B., Cao, G., and Joseph, J.A. 2000. Effect of fruits, vegetables, or vitamin E–rich diet on vitamins E and C distribution in peripheral and brain tissues: Implications for brain function. *J. Gerontol. A Biol. Sci. Med. Sci.*, **55**:B144–B151.

[209] Matsuoka, Y., Hasegawa, H., Okuda, S., Muraki, T., Uruno, T., and Kubota, K. 1995. Ameliorative effects of tea catechins on active oxygen-related nerve cell injuries. *J. Pharmacol. Exp. Ther.*, **274**:602–608.

[210] Sun, G.Y., Xia, J., Draczynska-Lusiak, B., Simonyi, A., and Sun, A.Y. 1999. Grape polyphenols protect neurodegenerative changes induced by chronic ethanol administration. *Neuroreport*, **10**:93–96.

[211] Yan, J.J., Cho, J.Y., Kim, H.S., Kim, K.L., Jung, J.S., Huh, S.O., Suh, H.W., Kim, Y.H., and Song, D.K. 2001. Protection against beta-amyloid peptide toxicity *in vivo* with long-term administration of ferulic acid. *Br. J. Pharmacol*, **133**:89–96.

[212] Lim, G.P., Chu, T., Yang, F., Beech, W., Frautschy, S.A., and Cole, G.M. 2001. The curry spice curcumin reduces oxidative damage and amyloid pathology in an Alzheimer transgenic mouse. *J. Neurosci.*, **21**:8370–8377.

[213] Levites, Y., Amit, T., Youdim, M.B., and Mandel, S. 2002. Involvement of protein kinase C activation and cell survival/cell cycle genes in green tea polyphenol, (−)-epigallocatechin-3-gallate neuroprotective action Attenuation of 6-hydroxydopamine (6-OHDA)-induced nuclear factor-kappaB (NF-kappaB) activation and cell death by tea extracts in neuronal cultures. *J. Biol. Chem.*, **63**:21–29.

[214] Levites, Y., Youdim, M.B., Maor, G., and Mandel, S. 2002. Attenuation of 6-hydroxydopamine (6-OHDA)-induced nuclear factor-kappaB (NF-kappaB) activation and cell death by tea extracts in neuronal cultures. *Biochem. Pharmacol*, **63**:21–29.

[215] Choi, Y.T., Jung, C.H., Lee, S.R., Bae, J.H., Baek, W.K., Suh, M.H., Park, J., Park, C.W., and Suh, S.I. 2001. The green tea polyphenol (−)-epigallocatechin gallate attenuates beta-amyloid-induced neurotoxicity in cultured hippocampal neurons. *Life. Sci.*, **70**:603–614.

[216] Chang, H.C., Churchwell, M.I., Delclos, K.B., Newbold, R.R., and Doerge, D.R. 2000. Mass spectrometric determination of genistein tissue distribution in diet-exposed Sprague-Dawley rats. *J. Nutr.*, **130**:1963–1970.

[217] Tsai, T.H. 2002. Determination of naringin in rat blood, brain, liver, and bile using microdialysis and its interaction with cyclosporin

a, a p-glycoprotein modulator. *J. Agric. Food Chem.*, **50**:6669–6674.

[218] Mullen, W., Graf, B.A., Caldwell, S.T., Hartley, R.C., Duthie, G.G., Edwards, C.A., Lean, M.E., and Crozier, A. 2002. Determination of flavonol metabolites in plasma and tissues of rats by HPLC-radiocounting and tandem mass spectrometry following oral ingestion of [2-(14)C]quercetin-4′-glucoside. *J. Agric. Food Chem.*, **50**:6902–6909.

[219] Peng, H.W., Cheng, F.C., Huang, Y.T., Chen, C.F., and Tsai, T.H. 1998. Determination of naringenin and its glucuronide conjugate in rat plasma and brain tissue by high-performance liquid chromatography. *J. Chromatogr. B. Biomed. Sci. Appl.*, **714**:369–374.

[220] Orgogozo, J.-M., Dartigues, J.-F., Lafont, S., Letenneur, L., Commenges, D., Salamon, R., Renaud, S., and Breteler, M.B. 1997. Wine consumption and dementia in the elderly: A prospective community study in the Bordeaux area. *Rev. Neurol. (Paris)*, **153**:185–192.

[221] Lindsay, J., Laurin, D., Verreault, R., Hebert, R., Helliwell, B., Hill, G.B., and McDowell, I. 2002. Risk factors for Alzheimer's disease: A prospective analysis from the Canadian Study of Health and Aging. *Am. J. Epidemiol.*, **156**:445–453.

[222] Truelsen, T., Thudium, D., and Gronbaek, M. 2002. Amount and type of alcohol and risk of dementia: The Copenhagen City Heart Study. *Neurology*, **59**:1313–1319.

[223] Zuccala, G., Onder, G., Pedone, C., Cesari, M., Landi, F., Bernabei, R., and Cocchi, A. 2001. Dose-related impact of alcohol consumption on cognitive function in advanced age: results of a multicenter survey. *Alcohol Clin. Exp. Res.*, **25**:1743–1748.

[224] Commenges, D., Scotet, V., Renaud, S., Jacqmin-Gadda, H., Barberger-Gateau, P., and Dartigues, J.F. 2000. Intake of flavonoids and risk of dementia. *Eur. J. Epidemiol.*, **16**:357–363.

[225] Marles, R.J. and Farnsworth, N.R. 1995. Antidiabetic plants and their active constituants. *Phytomedicine*, **2**:137–189.

[226] Gray, A.M. and Flatt, P.R. 1997. Nature's own pharmacy: The diabetes perspective. *Proc. Nutr. Soc.*, **56**:507–517.

[227] Hsu, F.L., Chen, Y.C., and Cheng, J.T. 2000. Caffeic acid as active principle from the fruit of Xanthium strumarium to lower plasma glucose in diabetic rats. *Planta. Med.*, **66**:228–230.

[228] Liu, I.M., Hsu, F.L., Chen, C.F., and Cheng, J.T. 2000. Antihyperglycemic action of isoferulic acid in streptozotocin-induced diabetic rats. *Br. J. Pharmacol.*, **129**:631–636.

[229] Liu, I.M., Chi, T.C., Hsu, F.L., Chen, C.F., and Cheng, J.T. 1999. Isoferulic acid as active principle from the rhizoma of Cimicifuga dahurica to lower plasma glucose in diabetic rats. *Planta. Med.*, **65**:712–714.

[230] Matsui, T., Ebuchi, S., Kobayashi, M., Fukui, K., Sugita, K., Terahara, N., and Matsumoto, K. 2002. Anti-hyperglycemic effect of diacylated anthocyanin derived from Ipomoea batatas cultivar Ayamurasaki can be achieved through the alpha-glucosidase inhibitory action. *J. Agric. Food Chem.*, **50**:7244–7248.

[231] Geetha, B.S., Mathew, B.C., and Augusti, K.T. 1994. Hypoglycemic effects of leucodelphinidin derivative isolated from Ficus bengalensis (Linn). *Indian J. Physiol. Pharmacol*, **38**:220–222.

[232] Peungvicha, P., Temsiririrkkul, R., Prasain, J.K., Tezuka, Y., Kadota, S., Thirawarapan, S.S., and Watanabe, H. 1998. 4-Hydroxybenzoic acid: A hypoglycemic constituent of aqueous extract of Pandanus odorus root. *J. Ethnopharmacol.*, **62**:79–84.

[233] Matsumoto, N., Ishigaki, F., Ishigaki, A., Iwashina, H., and Hara, Y. 1993. Reduction of blood glucose levels by tea catechin. *Biosci. Biotechnol. Biochem.*, **57**:525–527.

[234] Shenoy, C. 2000. Hypoglycemic activity of bio-tea in mice. *Indian J. Exp. Biol.*, **38**:278–279.

[235] Peungvicha, P., Thirawarapan, S.S., and Watanabe, H. 1998. Possible mechanism of hypoglycemic effect of 4-hydroxybenzoic acid, a constituent of Pandanus odorus root. *Jpn. J. Pharmacol.*, **78**:395–398.

[236] Matsui, T., Ueda, T., Oki, T., Sugita, K., Terahara, N., and Matsumoto, K. 2001. Alpha-Glucosidase inhibitory action of natural acylated anthocyanins. 2. alpha-Glucosidase inhibition by isolated acylated anthocyanins. *J. Agric. Food Chem.*, **49**:1952–1956.

[237] Song, J., Kwon, O., Chen, S., Daruwala, R., Eck, P., Park, J.B., and Levine, M. 2002. Flavonoid inhibition of sodium-dependent vitamin C transporter 1 (SVCT1) and glucose transporter isoform 2 (GLUT2), intestinal transporters for vitamin C and Glucose. *J. Biol. Chem.*, **277**:15252–15260.

[238] Welsch, C.A., Lachance, P.A., and Wasserman, B.P. 1989. Effects of native and oxidized phenolic compounds on sucrase activity in rat brush border membrane vesicles. *J. Nutr.*, **119**:1737–1740.

[239] Gee, J.M., DuPont, M.S., Day, A.J., Plumb, G.W., Williamson, G., and Johnson, I.T. 2000. Intestinal transport of quercetin glycosides in rats involves both deglycosylation and interaction with the hexose transport pathway. *J. Nutr.*, **130**:2765–2771.

[240] Dimitrakoudis, D., Vranic, M., and Klip, A. 1992. Effects of hyperglycemia on glucose transporters of the muscle: Use of the renal glucose reabsorption inhibitor phlorizin to control glycemia. *J. Am. Soc. Nephrol.*, **3**:1078–1091.

[241] Cheng, J.T. and Liu, I.M. 2000. Stimulatory effect of caffeic acid on alpha1A-adrenoceptors to increase glucose uptake into cultured C2C12 cells. *Naunyn. Schmiedebergs Arch. Pharmacol.*, **362**:122–127.

[242] Anderson, R.A. and Polansky, M.M. 2002. Tea enhances insulin activity. *J. Agric. Food Chem.*, **50**:7182–7186.

[243] Shisheva, A. and Shechter, Y. 1992. Quercetin selectively inhibits insulin receptor function *in vitro* and the bioresponses of insulin and insulinomimetic agents in rat adipocytes. *Biochemistry*, **31**:8059–8063.

[244] Fiorentini, D., Hakim, G., Bonsi, L., Bagnara, G.P., Maraldi, T., and Landi, L. 2001. Acute regulation of glucose transport in a human megakaryocytic cell line: difference between growth factors and H(2)O(2). *Free Radic. Biol. Med.*, **31**:923–931.

[245] Vera, J.C., Reyes, A.M., Carcamo, J.G., Velasquez, F.V., Rivas, C.I., Zhang, R.H., Strobel, P., Iribarren, R., Scher, H.I., Slebe, J.C., et al. 1996. Genistein is a natural inhibitor of hexose and dehydroascorbic acid transport through the glucose transporter, GLUT1. *J. Biol. Chem.*, **271**:8719–8724.

[246] Waltner-Law, M.E., Wang, X.L., Law, B.K., Hall, R.K., Nawano, M., and Granner, D.K. 2002. Epigallocatechin gallate, a constituent of green tea, represses hepatic glucose production. *J. Biol. Chem.*, **277**:34933–34940.

[247] Arion, W.J., Canfield, W.K., Ramos, F.C., Schindler, P.W., Burer, H.J., Hemmerle, H., Schubert, G., Below, P., and Herling, A.W. 1997. Chlorogenic acid and hydroxynitrobenzaldehyde: new inhibitors of hepatic glucose 6-phosphatase. *Arch. Biochem. Biophys.*, **339**:315–322.

[248] Ohno, T., Kato, N., Ishii, C., Shimizu, M., Ito, Y., Tomono, S., and Kawazu, S. 1993. Genistein augments cyclic adenosine 3′5′-monophosphate(cAMP) accumulation and insulin release in MIN6 cells. *Endocr. Res.*, **19**:273–285.

[249] Johnston, K.L., Clifford, M.N., and Morgan, L.M. 2003. Coffee acutely modifies gastrointestinal hormone secretion and glucose tolerance in humans: glycemic effects of chlorogenic acid and caffeine. *Am. J. Clin. Nutr.*, **78**:728–733.

[250] Bonina, F.P., Leotta, C., Scalia, G., Puglia, C., Trombetta, D., Tringali, G., Roccazzello, A.M., Rapisarda, P., and Saija, A. 2002. Evaluation of oxidative stress in diabetic patients after supplementation with a standardised red orange extract. *Diabetes Nutr. Metab.*, **15**:14–19.

[251] Manuel y Keenoy, B., Vertommen, J., and De Leeuw, I. 1999. The effect of flavonoid treatment on the glycation and antioxidant status in Type 1 diabetic patients. *Diabetes Nutr. Metab.*, **12**:256–263.

[252] Suresh Babu, P. and Srinivasan, K. 1998. Amelioration of renal lesions associated with diabetes by dietary curcumin in streptozotocin diabetic rats. *Mol. Cell Biochem.*, **181**:87–96.

[253] van Dam, R.M. and Feskens, E.J. 2002. Coffee consumption and risk of type 2 diabetes mellitus. *Lancet*, **360**:1477–1478.

[254] Naismith, D.J., Akinyanju, P.A., Szanto, S., and Yudkin, J. 1970. The effect, in volunteers, of coffee and decaffeinated coffee on blood glucose, insulin, plasma lipids and some factors involved in blood clotting. *Nutr. Metab.*, **12**:144–151.

[255] Anderson, J.J.B. and Garner, S.C. 1997. The effects of phytoestrogens on bone. *Nutrition Research*, **17**:1617–1632.

[256] Nakajima, D., Kim, C.S., Oh, T.W., Yang, C.Y., Naka, T., Igawa, S., and Ohta, F. 2001. Suppressive effects of genistein dosage and resistance exercise on bone loss in ovariectomized rats. *J. Physiol. Anthropol. Appl. Human Sci.*, **20**:285–291.

[257] Ishimi, Y., Arai, N., Wang, X., Wu, J., Umegaki, K., Miyaura, C., Takeda, A., and Ikegami, S. 2000. Difference in effective dosage of genistein on bone and uterus in ovariectomized mice. *Biochem. Biophys. Res. Commun.*, **274**:697–701.

[258] Ishida, H., Uesugi, T., Hirai, K., Toda, T., Nukaya, H., Yokotsuka, K., and Tsuji, K. 1998. Preventive effects of the plant isoflavones, daidzin and genistin, on bone loss in ovariectomized rats fed a calcium-deficient diet. *Biol. Pharm. Bull.*, **21**:62–66.

[259] Picherit, C., Coxam, V., Bennetau-Pelissero, C., Kati-Coulibaly, S., Davicco, M.J., Lebecque, P., and Barlet, J.P. 2000. Daidzein is more efficient than genistein in preventing ovariectomy-induced bone loss in rats. *J. Nutr.*, **130**:1675–1681.

[260] Arjmandi, B.H., Birnbaum, R., Goyal, N.V., Getlinger, M.J., Juma, S., Alekel, L., Hasler, C.M., Drum, M.L., Hollis, B.W., and Kukreja, S.C. 1998. Bone-sparing effect of soy protein in ovarian hormone-deficient rats is related to its isoflavone content. *Am. J. Clin. Nutr.*, **68**:1364S–1368S.

[261] Picherit, C., Bennetau-Pelissero, C., Chanteranne, B., Lebecque, P., Davicco, M.J., Barlet, J.P., and Coxam, V. 2001. Soybean isoflavones dose-dependently reduce bone turnover but do not reverse established osteopenia in adult ovariectomized rats. *J. Nutr.*, **131**:723–728.

[262] Rassi, C.M., Lieberherr, M., Chaumaz, G., Pointillart, A., and Cournot, G. 2002. Down-regulation of osteoclast differentiation by daidzein via caspase 3. *J. Bone Miner Res.*, **17**:630–638.

[263] Fanti, P., Monier-Faugere, M.C., Geng, Z., Schmidt, J., Morris, P.E., Cohen, D., and Malluche, H.H. 1998. The phytoestrogen genistein reduces bone loss in short-term ovariectomized rats. *Osteoporos. Int.*, **8**:274–281.

[264] Tsuchida, K., Mizushima, S., Toba, M., and Soda, K. 1999. Dietary soybeans intake and bone mineral density among 995 middle-aged women in Yokohama. *J. Epidemiol.*, **9**:14–19.

[265] Chiechi, L.M., Secreto, G., D'Amore, M., Fanelli, M., Venturelli, E., Cantatore, F., Valerio, T., Laselva, G., and Loizzi, P. 2002. Efficacy of a soy rich diet in preventing postmenopausal osteoporosis: The Menfis randomized trial. *Maturitas*, **42**:295–300.

[266] Scheiber, M.D., Liu, J.H., Subbiah, M.T., Rebar, R.W., and Setchell, K.D. 2001. Dietary inclusion of whole soy foods results in significant reductions in clinical risk factors for osteoporosis and cardiovascular disease in normal postmenopausal women. *Menopause*, **8**:384–392.

[267] Kardinaal, A.F., Morton, M.S., Bruggemann-Rotgans, I.E., and van Beresteijn, E.C. 1998. Phyto-oestrogen excretion and rate of bone loss in postmenopausal women. *Eur. J. Clin. Nutr.*, **52**:850–855.

[268] Alekel, D.L., Germain, A.S., Peterson, C.T., Hanson, K.B., Stewart, J.W., and Toda, T. 2000. Isoflavone-rich soy protein isolate attenuates bone loss in the lumbar spine of perimenopausal women. *Am. J. Clin. Nutr.*, **72**:844–852.

[269] Yamori, Y., Moriguchi, E.H., Teramoto, T., Miura, A., Fukui, Y., Honda, K.I., Fukui, M., Nara, Y., Taira, K., and Moriguchi, Y. 2002. Soybean isoflavones reduce postmenopausal bone resorption in female Japanese immigrants in Brazil: A ten-wk study. *J. Am. Coll. Nutr.*, **21**:560–563.

[270] Uesugi, T., Fukui, Y., and Yamori, Y. 2002. Beneficial effects of soybean isoflavone supplementation on bone metabolism and serum lipids in postmenopausal japanese women: A four-wk study. *J. Am. Coll. Nutr.*, **21**:97–102.

[271] Morabito, N., Crisafulli, A., Vergara, C., Gaudio, A., Lasco, A., Frisina, N., D'Anna, R., Corrado, F., Pizzoleo, M.A., Cincotta, M., Altavilla, D., Ientile, R., and Squadrito, F. 2002. Effects of genistein and hormone-replacement therapy on bone loss in early postmenopausal women: A randomized double-blind placebo-controlled study. *J. Bone Miner. Res.*, **17**:1904–1912.

[272] Horcajada-Molteni, M.N., Crespy, V., Coxam, V., Davicco, M.J., Remesy, C., and Barlet, J.P. 2000. Rutin inhibits ovariectomy-induced osteopenia in rats. *J. Bone Miner. Res.*, **15**:2251–2258.

[273] Horcajada-Molteni, M.-N., and Coxam, V. 2001. Flavonols and isoflavones prevent bone loss in the ovariectomized rat: A model for postmenopausal osteoporosis. In: *Nutritional aspects of osteoporosis*. 325–340. Burckhardt, P., Dawson-Hugues, B., and Heaney, R.P., ed. San Diego, Academic Press.

[274] Muhlbauer, R.C. and Li, F. 1999. Effect of vegetables on bone metabolism. *Nature*, **401**:343–344.

[275] Hegarty, V.M., May, H.M., and Khaw, K.-T. 2000. Tea drinking and bone mineral density in older women. *Am. J. Clin. Nutr.*, **71**:1003–1425.

[276] Sakamoto, W., Nishihira, J., Fujie, K., Iizuka, T., Handa, H., Ozaki, M., and Yukawa, S. 2001. Effect of coffee consumption on bone metabolism. *Bone*, **28**:332–336.

[277] Clifford, M.N. and Scalbert, A. 2000. Ellagitannins, occurrence in food, bioavailability and cancer prevention. *J. Food Sci. Agric.*, **80**:1118–1125.

[278] Barotto, N.N., Lopez, C.B., Eynard, A.R., Fernandez Zapico, M.E., and Valentich, M.A. 1998. Quercetin enhances pretumorous lesions in the NMU model of rat pancreatic carcinogenesis. *Cancer Lett.*, **129**:1–6.

[279] Pereira, M.A., Grubbs, C.J., Barnes, L.H., Li, H., Olson, G.R., Eto, I., Juliana, M., Whitaker, L.M., Kelloff, G.J., Steele, V.E., and Lubet, R.A. 1996. Effects of the phytochemicals, curcumin and quercetin, upon azoxymethane-induced colon cancer and 7,12-dimethylbenz[a]-anthracene-induced mammary cancer in rats. *Carcinogenesis*, **17**:1305–1311.

[280] Breinholt, V. and Larsen, J.C. 1998. Detection of weak estrogenic flavonoids using a recombinant yeast strain and a modified MCF7 cell proliferation assay. *Chem. Res. Toxicol.*, **11**:622–629.

[281] Tamir, S., Eizenberg, M., Somjen, D., Stern, N., Shelach, R., Kaye, A., and Vaya, J. 2000. Estrogenic and antiproliferative properties of glabridin from licorice in human breast cancer cells. *Cancer Res.*, **60**:5704–5709.

[282] Ju, Y.H., Allred, C.D., Allred, K.F., Karko, K.L., Doerge, D.R., and Helferich, W.G. 2001. Physiological concentrations of dietary genistein dose-dependently stimulate growth of estrogen-dependent human breast cancer (MCF-7) tumors implanted in athymic nude mice. *J. Nutr.*, **131**:2957–2962.

[283] Petrakis, N.L., Barnes, S., King, E.B., Lowenstein, J., Wiencke, J., Lee, M.M., Miike, R., Kirk, M., and Coward, L. 1996. Stimulatory influence of soy protein isolate on breast secretion in pre- and postmenopausal women. *Cancer Epidemiol. Biomarkers. Prev.*, **5**:785–794.

[284] Shutt, D.A. 1976. The effect of plant oestrogens on animal reproduction. *Endeavour*, **35**:110–113.

[285] Whitten, P.L., Lewis, C., Russell, E., and Naftolin, F. 1995. Potential adverse effects of phytoestrogens. *Journal of Nutrition*, **125**:771S–776S.

[286] Doerge, D.R. and Chang, H.C. 2002. Inactivation of thyroid peroxidase by soy isoflavones, *in vitro* and *in vivo*. *J. Chromatogr. B Analyt. Technol. Biomed. Life Sci.*, **777**:269–279.

[287] Chang, H.C. and Doerge, D.R. 2000. Dietary genistein inactivates rat thyroid peroxidase *in vivo* without an apparent hypothyroid effect. *Toxicol. Appl. Pharmacol.*, **168**:244–252.

[288] Divi, R.L. and Doerge, D.R. 1996. Inhibition of thyroid peroxidase by dietary flavonoids. *Chemical Research in Toxicology*, **9**:16–23.

[289] Fort, P., Moses, N., Fasano, M., Goldberg, T., and Lifshitz, F. 1990. Breast and soy-formula feedings in early infancy and the prevalence of autoimmune thyroid disease in children. *J. Am. Coll. Nutr.*, **9**:164–167.

[290] Gaitan, E., Lindsay, R.H., Reichert, R.D., Ingbar, S.H., Cooksey, R.C., Legan, J., Meydrech, E.F., Hill, J., and Kubota, K. 1989. Antithyroid and goitrogenic effects of millet: Role of C-glycosylflavones. *J. Clin. Endocrinol. Metab.*, **68**:707–714.

[291] Hurrell, R.F., Reddy, M., and Cook, J.D. 1999. Inhibition of non-haem iron absorption in man by polyphenolic-containing beverages. *Brit. J. Nutr.*, **81**:289–295.

[292] Brune, M., Rossander, L., and Hallberg, L. 1989. Iron absorption and phenolic compounds: Importance of different phenolic structures. *Eur. J. Clin. Nutr.*, **43**:547–558.

[293] Gillooly, M., Bothwell, T.H., Torrance, J.D., MacPhail, A.P., Derman, D.P., Bezwoda, W.R., Mills, W., Charlton, R.W., and Mayet, F.

1983. The effects of organic acids, phytates and polyphenols on the absorption of iron from vegetables. *Brit. J. Nutr.*, **49**:331–342.

[294] South, P.K., House, W.A., and Miller, D.D. 1997. Tea consumption does not affect iron absorption in rats unless tea and iron are consumed together. *Nutr. Res.*, **17**:1303–1310.

[295] Temme, E.H. and Van Hoydonck, P.G. 2002. Tea consumption and iron status. *Eur. J. Clin. Nutr.*, **56**:379–386.

[296] Salonen, J.T., Nyyssonen, K., Korpela, H., Tuomilehto, J., Seppanen, R., and Salonen, R. 1992. High stored iron levels are associated with excess risk of myocardial infarction in eastern Finnish men. *Circulation*, **86**:803–811.

[297] Olthof, M.R., Hollman, P.C., Zock, P.L., and Katan, M.B. 2001. Consumption of high doses of chlorogenic acid, present in coffee, or of black tea increases plasma total homocysteine concentrations in humans. *Am. J. Clin. Nutr.*, **73**:532–538.

[298] Muller, T., Woitalla, D., Hauptmann, B., Fowler, B., and Kuhn, W. 2001. Decrease of methionine and S-adenosylmethionine and increase of homocysteine in treated patients with Parkinson's disease. *Neurosci. Lett.*, **308**:54–56.

[299] U.S. Department of Agriculture, N.D.L. 2003. USDA Database for the flavonoid content of selected foods (http://www.nal.usda.gov/fnic/foodcomp/).

[300] Wilson, T., Knight, T.J., Beitz, D.C., Lewis, D.S., and Engen, R.L. 1996. Resveratrol promotes atherosclerosis in hypercholesterolemic rabbits. *Life Sci.*, **59**:L15–L21.

[301] Jones, E. and Hughes, R.E. 1982. Quercetin, flavonoids and the life-span of mice. *Exp. Gerontol.*, **17**:213–217.