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Meeting Report

Highlights from the 3rd International Conference on Polyphenols and Health

Current trends in polyphenol research: from Mother Nature to molecular mechanisms

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Abstract

The 3rd International Conference on Polyphenols and Health (ICPH), held in Kyoto, Japan, on November 25-28, 2007, focused on recent advances in polyphenolic research in different fields, from natural characterization, chemistry, bioavailability, metabolism, biological effects, formulations, epidemiological and interventional studies to clinical trials. The main focus of the conference was the molecular mechanism underlying pharmaceutical application of polyphenols in a plethora of disease conditions, including inflammation, cancer, metabolic syndrome, diabetes, allergy, cognition and oxidative stress-related pathologies.

Introduction

In recent years, much attention has been devoted around the world to polyphenols and health. Augustin Scalbert initiated the International Conference on Polyphenols and Health (ICPH) in Vichy, France, in 2004. This stimulated and encouraged many people engaged in research on polyphenols in human health. The second conference, organized by Andrew Waterhouse and Cesar Fraga in Davis, California, was also a true success. This year, Junji Terao organized the 3rd International Conference on Polyphenols and Health, held on November 25-28, 2007, in Kyoto (Japan). More than 600 scientists from over 30 countries engaged in polyphenolic research participated in the conference. The themes of the conference included: basic mechanisms of biological function, clinical effects in cancer and other lifestyle-related diseases, epidemiological and interventional studies, characterization as foods and pharmaceuticals, benefits and risks.

Nowadays, polyphenols are recognized as essential functional food factors prevailing from the dining table to medicinal uses. Polyphenols are a large group of phytochemicals that are gaining acceptance as being responsible for the health benefits associated with fruits and vegetables. Because of their chemical structure, plant polyphenols can scavenge free radicals and inactivate other pro-oxidants, and can also interact with a number of molecules of biological relevance. The main classes of polyphenols are phenolic acids (mainly caffeic acid) and flavonoids (the most abundant in the diet are flavanols, *i.e.*, catechins plus proanthocyanidins, anthocyanins and their oxidation products), which account for one- and two-thirds, respectively. Polyphenols are reducing agents, and together with other dietary reducing agents, such as vitamin C, vitamin E and carotenoids, referred to as antioxidants, protect the body's tissues against oxidative stress and associated pathologies, such as cancer, coronary heart disease and inflammation.

A number of reports were presented on polyphenols, as well as diets rich in fruits and vegetables, that promoted health and attenuated or delayed the onset of various disorders, including cardiovascular and neurodegenerative diseases, diabetes, cancer and several other age-related disorders. The chemical components involved,

and the physiological and molecular mechanisms by which fruits and vegetables reduce the risk of disease, were also thoroughly discussed. Table I summarizes the entire research work presented at the 3rd ICPH.

Epidemiological studies of polyphenols

Epidemiological studies are the main contributors to elucidating the potential of polyphenols in prophylaxis and therapy. These studies have indicated a significant difference in the incidence of various diseases among ethnic groups which have different lifestyles and have been exposed to different environmental factors. The well-known French paradox and Mediterranean diet are good examples to cite for epidemiological evidence proving the efficacy of polyphenolic antioxidants in preventing disease. The French paradox refers to the low cardiovascular mortality despite high fat intake in the French population, due to the antioxidant properties of red wine (1-4). The Mediterranean diet is also rich in antioxidant content, which results in protection from heart diseases. Many of the benefits derived from the intake of such diets may be the result of synergy between natural antioxidants and the better known vitamin antioxidants (5, 6).

Epidemiological studies are useful for evaluating the effects of long-term exposure to physiological concentrations of polyphenols on human health, but reliable data on the polyphenol content of foods are still scarce. Available epidemiological data on the flavonoid subclass of flavanols, flavones, catechins and lignans suggested beneficial effects for both flavonoids and lignans on cardiovascular disease and oxidative stress-related pathologies. Interventional studies have been performed only with polyphenol-rich products, such as chocolate, wine, tea, berries and fruit juices, which mainly showed favorable effects on markers of endothelial function, such as blood pressure and flow-mediated dilatation. Although these studies suggest a beneficial effect for polyphenols, the positive effects may also have been caused by nonpolyphenolic compounds (7). Interventions with pure polyphenols are needed to advance research on polyphenols and health. A prospective study among 26,311 residents in Miyagi Prefecture in Japan suggested that green tea consumption is not associated with a substantially lower risk of cancer. However, a possible protective association for cardiovascular disease observed in 40,530 residents needs confirmation in large-scale studies (8). Furthermore, the Kuopio Ischemic Heart Disease Risk Factor study in 2,590 middle-aged Eastern Finnish men concluded that high intake of flavonoids may be associated with a decreased risk of lung cancer in this population (9).

Chemistry of polyphenols

The biological properties, bioavailability, antioxidant activity and specific interactions with cell receptors and enzymes are related to the chemical structure of polyphenols. It is therefore essential to determine the nature of the main polyphenols ingested, their dietary origin, the amounts consumed in different diets, their bioavailability and the factors controlling their bioavailability.

Understanding how environment, production and cultivation practices influence the composition and quality of food crops is fundamental to the production of high-quality nutritious foods. Flavonoids are secondary plant metabolites (SPMs) that function in plant defense mechanisms. Environmental stress, including nutrient deficiency, wounding, pathogens and ultraviolet radiation, activates the biosynthesis of flavonoids. Fundamental differences between organic and conventional production systems, particularly in terms of pest control and soil management, have the potential to impact the nutritional composition of plants and, in particular, SPMs (10). The accumulation of SPMs in different plant organs is theoretically feasible by breeding or molecular engineering and by using various growth conditions. Although many structural and regulatory genes of the pathway have been identified, some proteins involved in the specific branches and responsible for flavonoid diversity have yet to be characterized. In addition, the complex regulation of the pathway by biotic, abiotic and developmental factors remains largely unknown (11). *In vivo* animal and *in vitro* molecular studies have revealed diverse pathological functions of procyanidins and have suggested that these functions are related to the chemical structures of the compounds, degree of polymerization, stereochemistry, bioavailability and interaction with proteins (12).

Bioavailability and metabolism of polyphenols

The health effects of polyphenols are dependent on numerous processes, including absorption, transport, metabolism and differential effects on cellular targets and signaling pathways. The elucidation of specific metabolic pathways, as well as the genetic and environmental factors that affect their regulation, is essential to understand the mechanism of action of phytochemicals in the context of specific diseases. The metabolism and disposition of flavonoids has been an area of active research in the last decade. The data indicate considerable differences among the different types of flavonoids. Passive diffusion, enzymatic hydrolysis of glycosides and interaction with various transporters regulate their absorption, disposition and elimination. Absorbed flavonoids undergo extensive first-pass metabolism in the small intestine and liver, and metabolite conjugates with methyl, glucuronate and sulfate groups are the predominant forms present in plasma and tissues. Ultimately, most flavonoids, whether absorbed or not, reach the large intestine, where they are metabolized to low-molecular-weight phenolic acid and excreted. These findings should be considered in the design and interpretation of studies investigating the mechanisms and potential health effects of flavonoids (13).

The absorption, metabolism and excretion of flavonoids and how they vary according to the number of meals and subject variables were investigated in a series of randomized, crossover trials. The relevance of micro-

Table I: Summary of studies on polyphenols presented at the 3rd International Conference on Polyphenols and Health.

Ref.	Polyphenols/plants/ natural interventions	Study design	Outcome
EPIDEMIOLOGICAL & INTERVENTIONAL STUDIES			
47	Cocoa	In a randomized, double-blind study, 10 patients with type 2 diabetes received either high-flavanol cocoa drinks containing 963 or 371 mg or a low-flavanol control drink containing 75 mg of total flavanols. Endothelial function was measured as flow-mediated dilatation of brachial artery using high-resolution ultrasound	The ingestion of flavanol-rich cocoa significantly increased flow-mediated dilatation in a dose-dependent fashion from 3.7 ± 0.2% at baseline to peak values of 4.6 ± 0.2% (371 mg) and from 3.7 ± 0.3% to 5.5 ± 0.4% (963 mg). Flavanol-rich cocoa was sufficiently absorbed and reversed endothelial dysfunction in type 2 diabetes
48	Epicatechin & procyanidin	The effect of oral ingestion of chemically pure (–)-epicatechin (EC) and procyanidin dimer (DB1) on fibrinolytic markers was studied in a randomized, double-masked, crossover study in healthy humans	The consumption of EC and DB1 can modulate components of the fibrinolytic system, suggesting another mechanism by which diets rich in these compounds may reduce the risk of cardiovascular disease
49	Flavonoids	In a cross-sectional study, the relationship between the intake of 26 flavonoids from 5 subclasses –flavanols, flavones, flavanones, flavan-3-ols and anthocyanidins– and the mean common carotid artery intima-media thickness (CCA-IMT) was assessed in middle-aged Finnish men	Of the different flavonoid subclasses, flavan-3-ols were inversely associated with CCA-IMT. High intake of flavonoids was associated with decreased carotid atherosclerosis in middle-aged Finnish men
50	Fruits & vegetables	The urinary excretion of polyphenols and the antioxidant capacity of fruit and vegetable intake were studied in a randomized, crossover study	The level of total polyphenol excretion and the antioxidant capacity of urine can be used as biomarkers to describe the effect of different types of diets with different polyphenol content
51	Dietary quercetin	The association between quercetin intake and plasma circulating oxidized LDL was investigated in a cross-sectional study	Quercetin contributed to the suppression of oxidized LDL in postmenopausal women with LDL hypercholesterolemia
52	Apple juice	Polyphenols reaching the colon after the oral intake of cloudy apple juice were studied for their chemo-preventive potential	Besides radical-scavenging potential, apple juice polyphenols reaching the colon possess little direct chemopreventive activity
FOOD CHEMISTRY			
53	Xanthohumol (XN) & isoxanthohumol (IXN) from hop plant	The development of an analytical method for the determination of XN and IXN in different hop products and in beer to investigate the impact of the extraction process of the hop product (pellets, ethanolic extract and supercritical CO_2 extract) on the amount of XN and IXN	The chemopreventive role of XN and IXN is of growing interest. The ethanolic extract was revealed to be the hop product richest in XN. It was possible to produce beers enriched in XN (5-fold increase) and IXN (20-fold increase) by changing the use of supercritical CO_2 extract for the ethanolic hop extract or hop pellets
54	Oil palm (*Elaeis guineensis*) frond methanolic extract (OPFME)	The effect of OPFME treatment on rat liver tissue was examined in an L-NAME-induced hypertension model	OPFME attenuates hepatocyte damage in rats with nitric oxide (NO) deficiency due to its protective effect against increasing blood pressure
55	*Strobilanthes cripus*	Major flavonoid compounds of *S. cripus* leaves obtained by supercritical fluid extraction and solvent extraction were identified in order to evaluate process efficiency	The solvent extract contained more flavonoid compounds, including catechin, epicatechin, rutin, quercetin and naringin (supercritical fluid extract contained catechin, epicatechin and rutin)
56	*Viburnum dilatatum* pomance (Thunb. fruits)	Male KKA^y mice, a model of non-insulin-dependent diabetes, were fed a 0.2% and 1% *V. dilatatum* pomance flesh and peel powdered diet for 4 weeks	*V. dilatatum* dose-dependently suppressed plasma glucose levels, along with plasma, hepatic and renal oxidative stress. Cyanidin 3-sambubioside (C3S) and chlorogenic acid (5CQA) are major polyphenols in *V. dilatatum* pomance having antioxidant and α-glucosidase-inhibitory activities

Continuation

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FOOD CHEMISTRY			
57	Tea catechins & dibenzyl-butyrolactone lignan	Matrix metalloproteinases (MMPs) are considered to be involved in tumor metastasis and invasion, and potent and safe MMP inhibitors have been sought for tumor therapy. The inhibitory effect of tea catechins and lignans on human MMP-7 was evaluated	Catechin (epicatechin gallate) and lignan (5-hydroxypluviatolide) were shown to bind MMP-7 and inhibit its activity, and could be suitable lead compounds for developing MMP-7 inhibitors
58	*Syzygium polyanthum* (Salam leaf)	The radical-scavenging activity of 9 tannins and 8 flavonoids isolated from *S. polyanthum* was evaluated using three assays: the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical, superoxide radical and the ORAC assay	In the DPPH assay, tannins showed very strong activity, especially pentagalloylglucose, tellimagrandin II, casuarictin, casuarinin and petrocarinin A, which have 5-*O*-trihydroxy-phenyl groups, and alienanin B, a dimer of ellagic tannin. In the superoxide radical assay, ellagic tannins and epigallocatechin, and in the ORAC assay, quercetin and quercetin rhamnoside showed the strongest activities
59	Cocoa	Naturally occurring polyphenols in cocoa beans and pH have been reported to reduce the concentration of flavor compounds, primarily pyrazines, after cocoa roasting. The combined role of polyphenol concentration and pH was determined on cocoa flavor	A polyphenol concentration of 43-58 g/kg and a pH of 7.0-7.5 were found to be optimal for the production of flavor precursors. It is suggested that remaining high concentrations of polyphenols can be extracted to be used in other food and pharmaceutical products
60	*Micromeria cristata*	The inhibitory effect of *M. cristata* extracts (diethyl ether, ethyl acetate and *n*-butanol) on DPPH and hydroxyl radicals and protection in the β-carotene-linoleic acid model system were evaluated	The *M. cristata* extracts showed strong radical-scavenging activity, with an IC_{50} of 20-50 ng/ml, and can be used as natural antioxidants
61	*Ecklonia stolonifera* (brown algae with strong fertility from Japanese sea)	Male KKA^{y} mice (see above) were fed 0%, 0.2% and 1% water, methanolic and ethanolic extracts of *E. stolonifera* for 4 weeks	*E. stolonifera* methanolic and ethanolic extracts dose-dependently suppressed plasma glucose levels due to their α-glucosidase-, maltase- and glucoamylase-inhibitory activities
62	Catechins	The antioxidant activity of catechins was affected by metal ions. The complexation reactions of catechins (epicatechin, epigallocatechin, epicatechin gallate & epigallocatechin gallate) with metal ions (Cu^{2+}, Fe^{2+} & Fe^{3+}) were examined by UV-Vis spectrometry, cyclic voltametry, H^{1}-NMR and electrospray ionization mass spectroscopy (ESI-MS)	The metal ions promote the acid dissociation of catechins, and then combine on the B-ring for the catechins without a galloyl group, and on the D-ring for the catechins with a galloyl group. The complexation reaction can be assumed to occur more easily on the D- than the B-ring of catechins
63	Chinese medicinal herbal materials	Chrysanthemum, hawthorn, licorice root, hibiscus, cassia seed and Chinese wolfberry were evaluated *in vivo* for their antioxidant activity and activity against oxidized LDL	Chinese medicinal herbs are a good source of antioxidants against free radical species and useful for preventing atherosclerosis and other degenerative diseases
64	Propolis	An ethanolic extract of red propolis (Cuba, Brazil & China) was prepared and total polyphenol & flavonoid content and its antioxidant potential were determined	An ethanolic extract of red propolis (China) had relatively strong antioxidant activity, which was correlated with the total polyphenol and flavonoid contents
65	Sweet potato (*Ipomoea batatas* L.)	The sweet potato polyphenol 3,4,5-tri-*O*-caffeoylquinic acid exhibits selective inhibition of HIV replication. A new analytical method was developed to analyze the highest contents of 3,4,5-tri-*O*-caffeoylquinic acid in 1,400 genotypes of sweet potato	Two types of 3,4,5-tri-*O*-caffeoylquinic acid polyclonal antibodies were produced and characterized for measuring the difference in the 3,4,5-tri-*O*-caffeoylquinic acid content among the sweet potato genotypes

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66	Anthocyanin-pyruvic acid adducts & portisins	Anthocyanin-pyruvic acid adducts & portisins are polyphenolic pigments used in the food industry as colorants with antioxidant activity. Their antiradical activity and reducing power were determined	These anthocyanin-derived pigments, especially portisins, protected the liposomal membrane against peroxyl radicals by increasing the time for induction of oxidation
67	Mulberry (*Morus alba* L.)	Component analysis and antioxidant activity of mulberry juice were examined. The concentration of polyphenols, anthocyanins and chlorogenic acid isomers was determined by the Folin-Denis method and HPLC, the radical-scavenging activity against DPPH, superoxide anion, hydroxyl and NO radical by absorbance and ESR, anti-HIV activity by the MTT method and lipid peroxidation by the d-ROMs test	Anthocyanins and chlorogenic acid isomers present in mulberry juice appear to be major contributors to antioxidant activity. Oral intake inhibited lipid peroxidation induced in mice by water immersion restraint stress
68	Lemon juice	The effect of addition of elderberry extract on the total polyphenolic contents and antioxidant potency of lemon juice was studied	The addition of elderberry extract improved the polyphenolic composition and the antioxidant activity of lemon juice by 3-4-fold. Stabilization of vitamin C content in beverages is the underlying protective mechanism
69	Red wine	The effect of red wine was studied on the adhesive properties of oral *Streptococcus mutans*, responsible for caries development in humans	Red wine anthocyanins and polymeric proanthocyanidins could have a beneficial effect on caries prevention by impeding the adhesion of cariogenic streptococci
70	Coffee beans	The antiperoxyl radical activity of roasted coffee beans was evaluated in an *ex vivo* system consisting of rat liver cell microsomes in which lipid peroxidation was induced by a xenobiotic	Coffee was able to completely inhibit lipid peroxidation
71	Sweet potato (*I. batatas* L.)	Antioxidant, antimutagenic and anticarcinogenic activity has been reported for anthocyanins. Anthocyanin pigments were purified from purple sweet potato by chlorogenate esterases	The chlorogenate extract was processed and caffeoylquinic acid derivatives were hydrolyzed to caffeic acid. Caffeic acid was separated by ODS column and purified anthocyanin without other polyphenolic components was obtained
72	Sweet potato (*I. batatas* L.)	The separation and purification of 3,4-*O*-dicaffeoylquinic acid, 3,5-*O*-dicaffeoylquinic acid and 4,5-*O*-dicaffeoylquinic acid from sweet potato leaf were performed	It was difficult to isolate each dicaffeoylquinic acid due to isomers of the same molecular weight. The isomers were separated by using ODS absorption column chromatography
73	Japanese cherry	Major anthocyanins and polyphenols contained in 15 species of cherries (13 sweet and 2 sour species) were identified, quantified and anthocyanin bioavailability was determined	The content of rutin identified in the cherries was 0.7-8.7 mg/100 g of fresh weight, and showed a higher correlation with cyanidin 3-*O*-rutinoside, identified as a major anthocyanin in 13 species of sweet cherries. C_{max} of cyanidin 3-*O*-rutinoside was measured 30 min after oral administration in rats
74	Strawberry	Phenolic compounds and antioxidant activity of fresh and stored strawberry puree, along with major components contributing to antioxidant activity in stored strawberries, were determined	Anthocyanins and ellagic acid derivatives, mainly ellagitannins, are major phenolic compounds in fresh strawberries. Upon storage, anthocyanins were severely damaged but ellagic acid contents were increased by 2.4-fold. Ellagic acid is the single most important contributor to the antioxidant activity of stored puree

Continuation

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FOOD CHEMISTRY			
75	Citriglu™	Citriglu™ is the main anthocyanidin fraction of black soybean skin extract. Anticarcinogenic, cytotoxic and antiinflammatory activities were evaluated	Citriglu™ showed strong cytotoxicity against MCF7 and SK-OV-3 cancer cell lines, with IC_{50} values of 9 and 25 μg/ml by the SRB method, and could also prevent ear and paw swelling
76	*Brassica oleracea sabellica* (curly kale)	Total phenols, flavonoid aglycones and antioxidant activity of kale were measured and native flavonoids with the highest antioxidant activity were isolated and characterized by LC-MS/MS	Major: quercetin (best antioxidant activity) and kaempferol; minor: myricetin and isorhamnetin were detected
77	Chlorogenic acids	Hypoglycemic, hepatoprotective, antiinflammatory, immunostimulant and antiviral activities of various medicinal plants have been attributed to chlorogenic acid content. Three brands of six dried plants were analyzed for chlorogenic acid content by HPLC	Green and toasted *Ilex paraguaiensis* (mate) presented the highest chlorogenic acid content (182.6 and 36.4 mg/200 ml cup, respectively). Average content of chlorogenic acid in *Baccharis genistelloides* (carqueja), *Pimpinella anisum* (anise), *Achyrocline satureoides* (macela), green and black *Camellia sinensis* and *Cymbopogon citratus* (lemon grass) was 20.6, 5.2, 4.5, 2.4, 3.4 and 2.3 mg/200 ml cup, respectively
78	Coffee	Antioxidant activity and the components responsible were determined and compared with other commonly used beverages	The antioxidant activity of coffee was found to be the highest compared to other beverages, including tea. Chlorogenic acid is the major antioxidant component in coffee
79	Dietary polyphenols	The effect of prolonged consumption (8 weeks) of dietary polyphenols (chlorogenic acid, epicatechin, naringin and rutin) on the overall antioxidant status was studied in rats	Prolonged ingestion of polyphenols did not exhibit marked effects on antioxidant status in rats fed a normal or modified (polyphenol-rich) diet
80	Green coffee beans, ginger, garlic, ling pepper & oregano	Antioxidant, antitumor and antiinflammatory activities were evaluated and compared	Coffee bean extract showed maximum radical-scavenging activity. All extracts, except garlic, exhibited antitumor activity but did not show antiinflammatory activity
81	Chocolate	The relationship between polyphenolic and nonfat cocoa solid (NFCS) content of chocolates (dark, milk chocolate with wafers or nuts) was predicted. Theobromine was used to estimate NFCS	It is assumed that higher NFCS contents are indicative of higher polyphenolic concentrations. In dark chocolate, NFCS is linearly related to total polyphenolic content (TPC) (r^2=0.73) but TPC appears to be slightly higher for milk chocolate
82	Cocoa & chocolate	The TPC of fermented and dried beans (Ecuador, Ivory Coast, Ghana) and resulting cocoa was measured by the Folin method	Ecuadorian beans had a higher content of polyphenols (TPC: 65.1 mg) than beans from Ghana (TPC: 57.9 mg) or Ivory Coast (TPC: 54.7 mg)
83	Polyphenolic compounds	An analytical method for the simultaneous quantitative analysis of 51 aglycones of phenolic and polyphenolic compounds in 150 food samples from Japan was developed	HPLC eluted 51 aglycones of phenolic and polyphenolic compounds with good resolution in 130 min
84	Tea catechins (ECG, EGCG, EC & EGC)	Solution NMR techniques were used to investigate the interaction between tea catechins and isotropic bicelles as a lipid bilayer model	^{1}H-NMR measurements indicated that signals from the B-ring and the galloyl moiety in ECG & EGCG were obviously shifted, and proton T_1 relaxation times were shortened upon interaction of the catechins with the bicelles. ECG and EGCG interact with the surface of lipid bilayers via the choline moiety
85	Barley & malt	The TPC of 10 different barley samples and their corresponding malts were measured by the Folin-Ciocalteau method	TPC ranged from 37.7 to 167.2 gallic acid eq/kg of dried material for barley and from 34.1 to 72.3 gallic acid eq/kg of dried material for malt. Catechin and ferulic acid were the most abundant polyphenolics contributing to its antioxidant activity

Continuation

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FOOD CHEMISTRY			
86	Hesperidin	The effect of hesperidin (0.5%) was studied on bone loss in ovariectomized aged mice	Histomorphometric analysis showed that bone volume and trabecular thickness in distal femoral cancellous bone were restored by hesperidin (after 8 weeks). Hesperidin prevented bone loss but had no effect on uterus
87	Chinese quince phenolics	The effect of heat treatment was studied on Chinese quince phenolics	Denaturation of Chinese quince phenolics by long-term heat treatment appears to be an effective method of increasing the antioxidant properties *in vitro* and *in vivo*. The change was related to a decrease in polymeric anthocyanidins and an increase in oligomers in solution
88	Malaysian plant extracts	Thirteen ethanolic and aqueous Malaysian plant extracts were prepared and evaluated in a variety of free radical-scavenging and lipid peroxidation assays	Ethanolic extracts were found to be better than aqueous extracts in both free radical-scavenging and lipid peroxidation assays, with lower pro-oxidant activity than ascorbic acid
89	Green tea catechins	Absorptional transport and secretory transport of catechins (EC & ECG) were determined in the rat distal colon, proximal colon and terminal ileum	Serosal and mucosal addition of catechins resulted in a time-dependent increase in the catechin flux to the opposite side. There is little difference in serosal and mucosal transport in distal and proximal colon, but serosal transport was higher in distal ileum. EC flux was greater than that of ECG
90	Green, black, rooibos & fruit teas	Green, black, rooibos & fruit teas from organic and conventional sources were analyzed for total polyphenols, antioxidant activity and total anthocyanin content	The organic teas had significantly higher antioxidant activity and higher anthocyanin content
91	Apple puree	Three organic and conventional apple puree preparations (fresh, after pasteurization and after 8 months) were analyzed for dry matter, total flavones and total phenols	Fresh organic apple puree contained significantly more flavones and also showed a tendency for higher levels of total polyphenols and dry matter than conventional products. Both pasteurization and storage decreased the nutritional value of apple products
92	*Lonicera caerulea*	Characterization of the phenolic fraction of *L. caerulea* for anthocyanins and phenolics by μLC-MS and assessment of antioxidant and cytoprotective activity	The phenolic fraction of *L. caerulea* displayed DPPH- and superoxide-scavenging activity (IC_{50} = 12.1 ± 0.1 and 115.5 ± 6.4 μg/ml, respectively), inhibited rat liver microsome peroxidation (IC_{50} = 160 ± 20 μg/ml) and exerted a cytoprotective effect on tBH-induced cell damage and LDL-induced oxidative damage in human umbilical vein endothelial cells (HUVEC)
93	Plant polyphenols	HPLC together with electrochemical detection and mass spectroscopy are the methods of choice to identify and quantify polyphenols from different plants. Conventional HPLC methodologies exceed 35 min	New and reliable methods for the rapid separation of several polyphenolic classes in a variety of sample matrices were developed
94	Blueberry, strawberry, raspberry & red leaf lettuce	Enhancement of polyphenols in crops (blueberry, strawberry, raspberry & red leaf lettuce) exposed to ultraviolet (UV) radiation during cultivation was studied	UV radiation has a greater effect on flavonoid biosynthesis in leaves than in fruits, with enhanced antioxidant activity and anthocyanin contents
95	Tea & coffee	Folin colorimetry was used to analyze total polyphenolic content in tea (prepared from leaf, bag, instant and bottle) & coffee (prepared from brewed and instant)	The order of antioxidant activity in tea is bag > leaf > bottle > instant, but no difference between instant and brewed coffee was seen. Coffee is the number one per capita beverage antioxidant source in the U.S.A., Europe and Japan. Tea is the number one beverage antioxidant in the U.K.

Continuation

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Ref.	Polyphenols/plants/ natural interventions	Study design	Outcome
FOOD CHEMISTRY			
96	Sea buchthorn, flowering quince, rowanberry, hawthorn	The content of proanthocyanidins and antioxidant activity of sea buchthorn (*Hippophae rhamnosides* L.), flowering quince (*Chaenomeles japonica*), rowanberry (*Sorbus aucuparia* L.), hawthorn (*Crataegus oxyacanta*) in pulp, juice and pomace was compared	The pulp of flowering quince and hawthorn contained the highest quantity of epicatechin and catechin (1994.71 and 922.97 mg/100 g). Proanthocyanidins remained in the pomace. The antioxidant activity of pulp, juice and pomace was strongly correlated with proanthocyanidin content
97	Strawberry	The effect of the addition of sugar, pectin and L-ascorbic acid to Elkat, Kent and Sengana strawberries was studied on the phenolic compounds of conventional and liquid-frozen products	The greatest influence of the applied treatments was observed for Kent strawberries. Microwave thawing significantly increased ellagic acid derivatives in comparison with thawing over 20 h at 20 °C
98	Rosemary (*Rosmarinus officinalis* L.)	The effect of different drying methods (freeze drying, convective drying, vacuum microwave drying) on the antioxidant activity and polyphenolic content of rosemary was studied	The total polyphenolic content in fresh rosemary was 1101.61 mg/100 g dry weight. The total polyphenolic content and antioxidant activity were reduced to half in all the processes. Freeze drying was the least destructive
99	Japanese apricot (*Prunus mume* Sibe. et Zucc.)	Inhibition of *Helicobactor pylori* motility by unripe Japanese apricot was studied	A methanolic extract of unripe Japanese apricot showed inhibitory activity against *H. pylori* motility. The inhibitory compound was isolated and identified as (+)-syringaresinol by spectroscopic method
100	Quercetin	Nasal administration of quercetin liposomes (containing 0.5 mg of quercetin in 20 μl daily for 4 weeks) was evaluated for protection against lipid peroxidation and increased survival of neurons in rat brain	Nasal administration of quercetin liposomes significantly decreased lipid peroxidation and increased the survival of neurons both in cortex and hippocampus
101	Buckwheat	Buckwheat sprouts have a much greater rutin content than buckwheat seeds. Changes in nutritional components of buckwheat during germination in the dark were studied	The conversion of buckwheat seeds to sprouts through germination in the dark results in a physically different final product, higher content of rutin, generation of vitamin C, abundance of essential amino acids and no fagopyrin
102	Oriental medicinal herbs	Ten oriental medicinal herbs were evaluated for total polyphenolic content and antioxidant activities	*Cornus officinalis* showed maximum polyphenolic content and antioxidant activity
103	Crowberry (*Empetrum nigrum*)	Analysis of the polyphenol content and antioxidant activity of crowberry was done and compared with bilberry, blackberry, black currant, blueberry, cranberry, mulberry, raspberry, red currant and strawberry	The major polyphenols in crowberry were anthocyanins, such as delphinidin-3-galactoside, cyanidin-3-galactoside, peonidin-3-glucoside and malvidin-3-galactoside. Crowberry extract showed strong antioxidant activity in each assay compared with other berry fruits
104	Asiaticoside (*Centella asiatica*)	The effect of asiaticoside (0.1 and 1 mg/kg/day for 21 days) after sciatic nerve crush injury in steptozotocin-induced diabetic rats was studied	Asiaticoside at the dose of 1 mg/kg can facilitate the functional recovery of sciatic nerve after crush injury in diabetic rats
105	*Scutellaria baicalensis* Georgi & rosemary	The effect of *S. baicalensis* Georgi (5000 and 10,000 ppm) & rosemary (200 ppm) on lipid peroxidation during storage of turkey hamburgers was evaluated	Products prepared with rosemary had a strong rosemary flavor and taste. Scullcap polyphenols effectively inhibited lipid peroxidation in turkey hamburgers without adverse effects on their sensory quality
106	Red wine	The impact of cork *versus* synthetic seals on polyphenol composition, antioxidant and vasorelaxant activities in bottled Portuguese red wine was evaluated	Wine sealed with cork presented the highest content of anthocyanins and oligomeric procyanidins and the lowest degree of polymerization, suggesting a lower degree of oxidation. However, vasorelaxant properties remained unaffected

Continuation

Table I (Cont.): Summary of studies on polyphenols presented at the 3rd International Conference on Polyphenols and Health.

Ref.	Polyphenols/plants/ natural interventions	Study design	Outcome
FOOD CHEMISTRY			
107	Quercetin	The effect of quercetin was studied on nerve crush injury	Quercetin could facilitate the recovery of both sensory and motor function of the sciatic nerve after crush injury
108	Birch twig	Characterization of polyphenols in the yellow birch twig extract	The natural extract contains eugenol, thymol, salicylic acid, salidroside, guiacol, epicatechin, vanillin and taxifolin
109	*Sargassum fulvellum*	Total polyphenolic and fatty acid contents of a crude extract from *S. fulvellum* were determined	Total polyphenolic content was 0.08 mg gallic acid eq/g along with 66.22% and 33.79% saturated and unsatured fatty acids, respectively
110	Pomegranate	Antioxidant and free radical-scavenging activity of pomegranate juice and its relationship with phenolic compounds were studied	Total polyphenolic compounds of pomegranate juice were comprised of 205 ± 5.0 mg gallic acid eq/100 ml and antioxidant activity was measured at 11.17 ± 0.3 mmol/l
111	*Phaseolus aureus* & *Cicer arietium*	The effect of *P. aureus* & *C. arietium* seed extracts on xanthine oxidase activity was studied	*P. aureus* was found to be superior in xanthine oxidase activity to *C. arietium*
ALLERGY & INFLAMMATION			
112	Polyphenols	The inhibitory activity of polyphenolic antioxidants on eosinophil peroxidase was determined. The assay measured conversion of tyrosine to dityrosine	Phenolic antioxidants strongly inhibited the formation of modified tyrosine and the inhibitory effects increased with increasing phenolic OH moieties
113	Parsley (*Petroselium crispum*)	The suppressive effect on allergic reactions and immune responses in mice of orally administered parsley was studied	A tendency for suppression of antigen-specific cell proliferation and cytokine and antibody production was observed in splenocytes from mice administered parsley
114	*Sasa quelpaertensis*	The antiinflammatory activity of the flavonoid tricin isolated from *S. quelpaertensis* was studied in lipopolysaccharide (LPS)-activated RAW 264.7 cells	Tricin significantly inhibited ROS, NO, PGE_2, IL-1β, IL-6, TNF-α and NF-κB production and inhibited iNOS and COX-2 protein expression
115	Quercetin	The effect of quercetin and its metabolites was studied on human vascular endothelial function	Quercetin significantly reduced the inflammation-induced overexpression of VCAM-1 and ICAM-1 in HUVEC and inhibited monocyte chemoattractant protein 1 (MCP-1). Quercetin metabolites were less effective than the parent aglycone
116	Cocoa flavanols (epicatechin)	The cocoa flavanol epicatechin was evaluated for its effects on arginase activity in HUVEC *in vitro* and in erythrocytes *in vivo*	Epicatechin reduced arginase activity and arginase-2 mRNA expression in HUVEC and erythrocytes
117	Catechin	The antiallergic activity of epigallo-catechin-3-*O*-(3-*O*-methyl)gallate was evaluated in mice	Epigallocatechin-3-*O*-(3-*O*-methyl)gallate strongly inhibited mast cell activation by preventing tyrosine phosphorylation of cellular protein and histamine release
118	Apple procyanidins	The antiallergic effect of apple procyanidins was studied in ovalbumin-sensitized W/Wv and B10A mice	Serum ovalbumin-specific IgE and IgG_1 titers, reduction in body temperature and increase in serum histamine were significantly inhibited by apple procyanidins
119	EGCG, myricetin & delphinidin	The cardioprotective mechanism of EGCG, myricetin & delphinidin was investigated in ischemia/reperfusion-induced myocardial injury	Biochemical and computer modeling analysis indicated that anti-STAT1 flavonoids specifically, directly and strongly interact with STAT1 near the SH2 domain and efficiently interfere with ischemia/reperfusion-elicited phosphorylation of tyrosine 701 and serine 727 on STAT1

Continuation

Table I (Cont.): Summary of studies on polyphenols presented at the 3rd International Conference on Polyphenols and Health.

Ref.	Polyphenols/plants/ natural interventions	Study design	Outcome
ALLERGY & INFLAMMATION			
120	Grape-derived polyphenols	The mechanisms involved in vascular protection by grape-derived polyphenols were investigated	Grape-derived polyphenols caused long-lasting production of endothelium-derived hyperpolarizing factor (EDHP) and NO due to sustained phosphorylation and upregulation of endothelial NOS, and prevented the expression of two major proangiogenic factors, vascular endothelial growth factor (VEGF) and MMP-2, in vascular smooth muscle cells
121	Polyphenols	Using human intestinal Caco-2 cells, the effects of standard polyphenols (50 μM) were investigated on cellular events associated with NF-κB activation	Chrysin and ellagic acid inhibited NF-κB activity, whereas genistein and resveratrol increased its activity. Among polyphenols, chrysin reduced IL-1β-induced IκBα phosphorylation. Ellagic acid, genistein and EGCG reduced IL-1β-induced IL-8 secretion, while resveratrol promoted secretion
BIOAVAILABILITY & METABOLISM			
122	Sesamin	The metabolism and excretion of sesame lignans were investigated	Sesame lignans were metabolized to enterolactone and no sesamin was detected, suggesting its complete transformation. Six intact lignans and 4 sesamin metabolites were identified in the first 4 h after challenge, indicating rapid absorption and metabolism of sesame lignans
123	Rutin	The effect of dietary fibers (pectin and cellulose) was studied on plasma quercetin and fecal flora in mice fed a rutin-supplemented diet	Plasma quercetin and isorhamnetin concentrations were significantly higher on the pectin-rutin than on the cellulose-rutin diet. The pectin-rutin diet greatly affected fecal flora. Moreover, pectin may enhance the bioavailability of quercetin from rutin by changing the metabolic activity of the intestinal flora
124	Red clover	Red clover isoflavones were tested for their ability to compete with estradiol and dihydrotestosterone for binding to and transactivation of estrogen receptors α and β, androgen and progestin receptors using *in vitro* test systems	3-Hydroxygenistein showed very interesting binding properties: it had the highest affinity for the estrogen receptor β apart from its natural ligand 17β-estradiol and its affinity for the estrogen receptor β was about 60 times higher than for the estrogen receptor α
125	Coffee	A method for the quantification of coffee-derived chlorogenic acids and their metabolites in human plasma was developed	A novel and very sensitive method for the quantification of chlorogenic acids and metabolites in human plasma using colorimetric detection and mass spectrometry was developed. Key to the method is sample preparation for very polar chlorogenic acids (using glucuronide and sulfate standards of coffee and ferulic acid)
126	Quercetin & genistein	Caco-2 cells were used as a model of the human small intestine to evaluate the suppressive effects of quercetin & genistein on LPS-induced NO generation	Basolateral medium showed a greater suppressive effect on NO generation than apical medium after 24 h of incubation
127	Quercetin	The contribution of each UDP-glucuronosyltransferase isoform to the glucuronidation of quercetin was studied	Quercetin glucuronidation towards the 3'- and 4'-hydroxyl moiety was catalyzed by several UGT isoforms (UGT1A1 > UGT1A9 > UGT2B1 > UGT2B7 > UGT1A8 > UGT1A10)
128	Anthocyanins	The bioactivity of anthocyanins was evaluated	The bioactivity of anthocyanins is the result of products formed from the degradation of the parent compound after deglycosylation in the intestine. The degradation products protocatechuic acid (PCA) and phloroglucinaldehyde (PGA) remained stable for a longer period of time

Continuation

Table I (Cont.): Summary of studies on polyphenols presented at the 3rd International Conference on Polyphenols and Health.

Ref.	Polyphenols/plants/ natural interventions	Study design	Outcome
BIOAVAILABILITY & METABOLISM			
129	Mulberry leaves	The ability of antioxidants from mulberry leaves (15 g% extract containing 135 μg rutin) and pure rutin (2 mg rutin) to protect rats from immobilization stress-induced injury was tested	Despite a much lower concentration of rutin, mulberry extract was more effective in protecting against inflammation and peroxidation than pure rutin
130	Luobuma (*Apocynum venetum* L.)	The antihypertensive effect of hyperoside (20 mg/kg) and isoquercetin (40 mg/kg) was studied alone and in combination in spontaneously hypertensive rats. Hyperoside and isoquercetin are the principal flavonoids in Luobuma leaf extract	A significant antihypertensive effect was observed in the combination treatment group. The antihypertensive effect of the combination is derived from the difference in the variation of the plasma concentrations of metabolites of hyperoside and isoquercetin between combined and single-agent administration
131	Genistein	The transport of intragastrically or intraduodenally administered genistein aglycone solubilized in propylene glycol (PEG) to the circulatory system was examined using unanesthetized thoracic lymph-cannulated rats	Simultaneous transport of genistein metabolites to both the portal vein and lymph was seen, with approximately 5 times higher concentrations in the plasma than in the lymph. Lymph was found to be a common pathway for quercetin and genistein to be absorbed from the stomach or the small intestine
132	Hesperitin & naringenin	The bioavailability and metabolism of hesperitin & naringenin from regular or rhamnosidase-treated orange juice was studied in a double-blind, randomized, crossover study in 16 volunteers	The consumption of rhamnosidase-treated orange juice containing glucosides compared to natural orange juice containing rutinosides resulted in greater absorption of both hesperetin and naringenin (conversion of rutinosides to glucosides resulting in higher bioavailability)
133	Flavonoid-rich diet	The metabolites of fresh strawberry (400 g), red onion (200 g), cocoa extract (3 g) and isoflavone-enriched cereal (160 mg) were measured in human plasma and urine	Intact favonoids and phenolic acids were detected in urine samples within 2 h of the consumption of a flavonoid-rich diet
134	Safflower seeds	A pharmacokinetic study of *N*-feruloylserotonin and *N*-(*p*-coumaroyl)serotonin was performed in rats. *N*-Feruloylserotonin and *N*-(*p*-coumaroyl)serotonin are major and unique polyphenols in safflower seeds	The plasma concentration profile of orally administered *N*-feruloylserotonin exhibited double peaks and was not dose-proportional, whereas following i.v. administration it was dose-proportional, and *N*-(*p*-coumaroyl)-serotonin exhibited a similar profile
135	Isoflavones & quercetin	The effect of 5 food lectins (SBA, CGA, RBA, WGA and AOL; 10-100 μg/day p.o. for 1 week) on the intestinal absorption of isoflavones (100 mg/kg p.o.) and quercetin (100 mg/kg p.o.) was investigated in rats	SBA and CGA increased quercetin absorption, whereas SBA and AOL increased isoflavone absorption. These lectins modulated sodium-dependent glucose transport (SGLT1)
136	EGCG	The effect of EGCG (20 mg/kg i.v.) on the pharmacokinetics of irinotecan (10 mg/kg i.v.) and its metabolite (SN-38) was studied in Sprague-Dawley rats	EGCG (a P-glycoprotein inhibitor) was found to inhibit the transport of irinotecan and SN-38 by biliary elimination and their half-lives in plasma could be substantially prolonged
137	Ferulic acid	The absorption and metabolism of ferulic acid were investigated using Caco-2 and HT-29-MTX co-cultures as an *in vitro* model of colonic epithelium	Ferulic acid was efficiently transported as the free form by passive diffusion, as judged by the linearity of the uptake over time and nonsaturable, linear concentration dependence. Less than 20% of ferulic acid was absorbed by facilitated diffusion

Continuation

Table I (Cont.): Summary of studies on polyphenols presented at the 3rd International Conference on Polyphenols and Health.

Ref.	Polyphenols/plants/ natural interventions	Study design	Outcome
BIOAVAILABILITY & METABOLISM			
138	Epicatechin	Intra- and interindividual variations in epicatechin plasma concentrations and metabolism were studied in humans	The inter- and intraindividual coefficients of variation of plasma epicatechin were found to be 23% and 10%, respectively
139	Hesperidin & naringin	The effect of hesperidin & naringin on bone metabolism was studied in male Wistar rats	Hesperidin & naringin intake significantly improved bone mineral density but not femoral strength, and bone resorption was slowed, whereas accretion remained unchanged, as did inhibition of serum IL-6
140	Epicatechin & catechin	The bacteria-dependent metabolism of epicatechin & catechin was investigated using a pH-controlled stirred batch culture fermentation system reflective of the distal region of the human large intestine	The distinct changes in microflora induced by catechin may be linked to the bacterial conversion of catechin to epicatechin, and flavanols may support gut health by acting as prebiotics
141	Berry polyphenols	The absorption and metabolism of phenolic compounds in bilberry-lingonberry puree administered with and without oat cereals were investigated	The content of phenolic compounds (anthocyanins, flavanols, catechins and phenolic acids) in puree and cereals was 767 mg (1800 μmol). After the puree and cereals, plasma concentrations of anthocyanins were < 20 nmol/l
142	Green tea catechins (EGCG)	The impact of dietary green tea catechins (GTCs) on folate status and mRNA levels of intestinal folate transporters *in vivo* and GTC-dependent changes in dihydrofolate reductase (DHFR) activity *in vitro* were studied	The highest intake of GTCs decreased total folate concentrations in serum and liver
143	Chokeberry (*Aronia arbutifolia*)	The bioavailability of cyanidin glucosides, the dominant anthocyanins from chokeberry juice, was studied in 13 volunteers following a dose of 0.8 mg anthocyanins/kg in 230-355 ml	The highest anthocyanin plasma concentration (32 nM) was found 1 h after challenge and during 24 h 0.3% of the ingested dose was excreted in the urine
144	Sesamol	The bioavailability of sesamol was determined in Sprague-Dawley rats following a dose of 30 mg/kg by tube feeding or by i.v. injection	The oral bioavailability of sesamol was 34.8% and sesamol was found to penetrate the blood-brain barrier and undergo hepatobiliary excretion
145	Lychee fruit extract (oligonol)	Oligonol lychee extract was processed to increase the content of monomers (20%), dimers (10%) and trimers (8%) to improve bioavailability	A dose of 100 mg/kg was associated with a significant decrease ($p < 0.05$) in body weight and a significant increase ($p < 0.05$) in protection against ROS-induced erythrocyte hemolysis
146	Geraniin	The urinary and intestinal microbial metabolites in rats after ingestion of geraniin, a typical ellagitanin isolated from *Geranium thunbergii*, an anti-diarrheal agent used in Japan, have been characterized	Four major metabolites were evaluated for antioxidant activity. Among them, M2 showed a potent radical-scavenging effect comparable to geraniin in the DPPH assay
147	Inhibition of α-amylase (flavonoids)	Structural requirements for inhibition of human salivary and pancreatic α-amylase isoforms (HAS and HPA) by flavonoids were investigated	The inhibitory activity of flavanols and flavones for both HAS and HPA depend on: 1) hydrogen bonds between the hydroxyl group of the polyphenols and the catalytic residue; and 2) the planar condensate ring structure
148	Quercetin 3-*O*-β-D-glucuronide (Q3GA)	The accumulation and antiarthero-sclerotic-like actions of Q3GA were studied in macrophage-derived cell lines	Q3GA and its aglycone decreased the mRNA and protein expression of scavenger receptors and inhibited foam cell formation

Continuation

Table I (Cont.): Summary of studies on polyphenols presented at the 3rd International Conference on Polyphenols and Health.

Ref.	Polyphenols/plants/ natural interventions	Study design	Outcome
BIOAVAILABILITY & METABOLISM			
149	Sesamin & episesamin	The pharmacokinetics of sesamin & episesamin were studied in rats and humans. Rats were orally administered a mixture of sesamin and episesamin (1:1) at a dose of 10 mg/kg	The bioavailability of sesamin & episesamin was 2% and 27%, respectively. They were mainly metabolized via a first-pass effect, and their pharmacokinetics in humans and rats were similar
150	Glucose, hesperetin & naringenin	The possible interaction between vitamin C and glucose and the citrus flavones hesperetin and naringenin was evaluated using human Caco-2 cells	The intracellular uptake of vitamin C was inhibited by glucose, hesperetin & naringenin
151	Q3GA	The inhibitory effect of Q3GA on LPS-induced COX-2 expression in macrophage cells was examined	Quercetin aglycone concentration-dependently suppressed COX-2 protein expression in LPS-treated RAW 264.7 cells, whereas even at higher concentrations, Q3GA scarcely suppressed COX-2 expression. These results showed that the extacellular deconjugation of Q3GA may be essential for LPS-induced COX-2 expression in macrophages
152	Olive oil	The effect of tyrosol and hydroxy-tyrosol on the decrease in bone mineral density in ovariectomized rats with or without chronic inflammation induced by talc injection was studied	Tyrosol and hydroxytyrosol prevented osteopenia by increasing bone formation
153	Polyphenols	The absorption profile of (+)-catechin, rosmarinic acid and cyanidin 3-glucoside through the gastrointestinal tract of rats was studied and related to their *in vivo* antioxidant activity	These polyphenols may contribute little to the *in vivo* antioxidant activity and exhibit health-promoting effects in the gastrointestinal tract
154	Hesperetin	UPLC-MS analysis of hesperetin in plasma and urine in rats fed a diet containing 0.1% or 0.5% hesperetin for 6 months was performed	Hesperetin plasma and urinary concentrations in rats were proportional to dose in the feed
155	Concentrated fruit juice	The effect of acute consumption of 400 ml of concentrated fruit juice shots on urinary metabolites of phytochemicals and the antioxidant status of plasma was investigated in 24 volunteers	The acute consumption of 400 ml of concentrated fruit juice shots can increase plasma antioxidant activity in humans
156	Quercetin & quercetin glycosides	The bioavailability of quercetin present in onion-based systems as either quercetin glycosides or quercetin alone was compared	Ingested quercetin appears rapidly in conjugated forms. A first peak appears at about 1 h after ingestion of onion-based meals, with a subsequent peak between 5 and 6 h
157	Quercetin	The events leading to the prevention of peroxynitrite-induced oxidation by its metabolites, as well as quercetin aglycone, were studied using an *in vitro* system. Oxidative hepato-toxicity was induced by i.p. treatment with galactosamine (Gal; 10 mg/kg) and LPS (10 mg/kg) 2 h after quercetin administration	Quercetin glycoside prevented hepatotoxicity and also reduced the induction of iNOS and increase in nitrotyrosine level
158	Anthocyanin	The gastrointestinal absorption site of anthocyanin was determined	The absorption of anthocyanin in the small intestine was greater than in the stomach and the site-dependent absorption efficiency showed the following order: ileum > duodenum > jejunum

Continuation

Table I (Cont.): Summary of studies on polyphenols presented at the 3rd International Conference on Polyphenols and Health.

Ref.	Polyphenols/plants/ natural interventions	Study design	Outcome
BIOAVAILABILITY & METABOLISM			
159	Red clove silage	Lactating ewes were fed a red clove silage diet containing 8 g/kg isoflavones for 1 month and the concentrations of isoflavones in different tissues were determined	Tissue concentrations varied widely and were lower than plasma concentration (26.8 M), except for kidney and liver (252 and 35 nmol/g, respectively). Higher concentrations in aorta (20 nmol/g) were related to its beneficial effect on endothelial function
160	Red grapes	Anthocyanin metabolites of red grapes were identified using large intestinal contents of pigs	Delphinidin-3-glucoside, petunidin-3-glucoside, peonidin-3-glucoside and malvidin-3-glucoside were identified as major anthocyanin metabolites and provided protection against colon cancer
161	Sesame lignan	The metabolism and distribution of sesame lignan metabolites were studied in rats. Furthermore, the detailed biological activity, especially antioxidant activity, was evaluated	The structure of the main sesamolin metabolite (compound A) was identified as sesamolin monocatechol by LC-MS, MS/MS and NMR. Compound A was found to be more potent than sesamolin
162	Rose hip & lactobacilli	Nine *Lactobacillus* strains were used together with *Rosa canina* and *Rosa pimpinellifolia* in mice to investigate their influence on ischemia/reperfusion-induced injury of the intestinal tract	Total antioxidant capacity and total phenolic content were higher in the groups fed rose hip in combination with bacteria than in those fed rose hip alone
COGNITIVE FUNCTION			
163	Curcumin	The effect of curcumin (60 mg/kg) on cognitive function, oxidative stress and inflammation was investigated in streptozotocin-induced diabetic rats	Curcumin improved cognitive function, cholinergic dysfunction, oxidative stress and inflammation in diabetic rats
164	Onion (*Allium cepa*)	The antidepressant-like effect of onion was examined in the forced swimming test in rats. Freeze-dried onion powder was orally administered to rats at a dose of 50 mg/kg/day for 2 weeks	Daily administration of freeze-dried onion powder reduced immobility time in the forced swimming test without affecting locomotor activity, indicating that daily consumption of onion exerts an antidepressant-like effect. Although the forced swimming test tended to increase serotonergic activity in rat hypothalamus, administration of freeze-dried onion powder suppressed the increase in the turnover of this neurotransmitter
165	*Ginkgo biloba* extract EGb-761	The efficacy of EGb-761 and its flavanol and terpenelactone fractions in modulating BACE-1 (β-secretase) enzyme activity and mRNA concentrations *in vitro* and in C57BL6 mice was investigated	The findings suggested that BACE-1 may not be a major molecular target of EGb-761 and its flavanol and terpenelactone fractions
166	Quercetin	The effects of quercetin on the mental stress response was investigated using two rat models (forced swimming and water immersion restraint)	Oral administration of quercetin before the stress session led to a marked decrease in corticosterone levels, whereas it had no effect on reduced glutathione
167	Pelargonidin & hesperetin	The effect of pelargonidin & hesperetin on 5-*S*-cysteinyldopamine (0-500 μM; 24 h)- and dihydrobenzothiazine (0-500 μM; 24 h)-induced neuronal injury was investigated	Pretreatment of cortical neurons with the flavonoids pelargonidin & hesperitin (0.1-3 μM; 18 h) resulted in significant protection against 5-*S*-cysteinyldopamine-induced injury. Thus, flavonoids may protect against neuronal injury induced by these endogenous neurotoxins via specific interactions within neuronal apoptotic signaling pathways
168	*Zingiber officinale*	The effect of *Z. officinale* on neuronal loss and brain dysfunction, including cognitive function, was studied in rats subjected to occlusion of the right middle cerebral artery	*Z. officinale* might serve as a natural source for the development of functional foods to attenuate neuronal deficits induced by stroke

Continuation

Table I (Cont.): Summary of studies on polyphenols presented at the 3rd International Conference on Polyphenols and Health.

Ref.	Polyphenols/plants/ natural interventions	Study design	Outcome
COGNITIVE FUNCTION			
169	*Kaempferia parviflora*	The potential of *K. parviflora* to enhance memory in both normal rats and animals with Alzheimer's disease was investigated following oral administration at doses of 150, 200 and 250 mg/kg for 2 weeks	The mechanism of the cognition-enhancing effect of *K. parviflora* may partly involve an increase in cholinergic activity via a decrease in the activity of acetylcholinesterase in hippocampus
170	*Bacopa monnieri*	The cognition-enhancing effect of *B. monnieri* extract in Alzheimer's disease was studied. Rats were pretreated with *B. monnieri* extract at a dose of 40 mg/kg/day 2 weeks before and 1 week after i.c.v. injection of AF64A	The extract significantly decreased escape latency and increased retention time. Thus, *B. monnieri* may attenuate the memory deficit and neuronal loss in Alzheimer's disease partly via the induction of an elevation in NGF-immunopositive neurons in the hippocampus
171	EGCG	The effect of EGCG on Aβ-induced apoptosis in neuronal cells and on memory impairment in rats was studied	EGCG treatment augmented the cellular antioxidant defense capacity through induction of heme oxygenase-1 and glutamate-cysteine ligase
172	*K. parviflora*	The cognition-enhancing effect of *K. parviflora* was studied in stress-exposed aged male rats. Rats were treated with the plant extract at a dose of 200 mg/kg once daily 45 min before exposure to 12-h restraint stress for 14 days	The extract produced a significant increase in neuronal density in CA1, CA2 and CA3 hippocampal regions and thus possesses memory-enhancing and neuroprotective effects
173	Green tea catechins	The effects of PE (polyphenol E) 0.5% w/v was studied in a rat model of Aβ-induced Alzheimer's disease	The preventive effects of PE on cognitive impairment in the rat model may involve amelioration of oxidative stress in conjunction with both repression of BACE-1 and augmentation of TTR gene expression in the hippocampus
174	*Z. officinale*	The effect of *Z. officinale* (400 & 800 mg/day) on the cognitive function of healthy elderly volunteers was studied	*Z. officinale* acts as a functional food to prevent or attenuate the age-related decline in cognitive function
PHARMACEUTICALS			
175	Cocoa	The effect of a crude extract prepared from cocoa powder (300, 600 & 800 mg/kg) was evaluated on atherosclerosis in hypercholesterolemic rabbits	Compared to the untreated group, cocoa could reduce by 50% the atherosclerotic lesion area in rabbits fed a cholesterol-enriched diet
176	Cocoa	Total polyphenolic contents and antioxidant activity of three fractions of crude cocoa extract were evaluated	The high antioxidant activity of fraction 3 was likely due to monomeric, dimeric and trimeric phenolic compounds. Theobromine and caffeine may contribute towards the beneficial effects of cocoa powder
177	Piperine	The effect of liposome-encapsulated piperine on cognitive function in young adult rats was evaluated	Liposome-encapsulated piperine improved memory and the survival of neurons in the hippocampus
METABOLIC SYNDROME			
178	Edible plants	The binding affinity of 70 herbs, spices and plants for the peroxisome proliferator-activated receptor (PPAR), a drug target for diabetes type 2, was assayed	The highest binding affinity was seen for quercetin, luteolin, rosmarinic acid and diosmetin. Strong eNOS activation by oregano, which contributed to its ability to ameliorate metabolic syndrome, was also observed
179	Red wine	The effect of chronic administration of red wine polyphenolic compounds on platelet aggregation and plasma lipid levels was studied in hypercholesterolemic rats	Red wine polyphenolic compounds inhibited platelet aggregation in rats with diet-induced hypercholesterolemia. This effect was not attributed to a decrease in plasma lipid levels

Continuation

Table I (Cont.): Summary of studies on polyphenols presented at the 3rd International Conference on Polyphenols and Health.

Ref.	Polyphenols/plants/ natural interventions	Study design	Outcome
METABOLIC SYNDROME			
180	Polygonaceae	The antioxidant activity of certain species of Polygonaceae and the physiological activity of phenolic compounds in affecting lipid metabolism in mice were studied	Reduction in hepatic lipogenesis is the underlying mechanism for the hypolipidemic effect of quercetin
181	EGCG	Stimulation of glucose uptake and translocation of the insulin-sensitive glucose transporter 4 (GLUT4) to the plasma membrane in muscle cells was studied	EGCG activated PI3K and PKCγ, but not IRβ and Akt, in the insulin signal transduction pathway. Tea catechins improved hyperglycemia by reducing postprandial blood glucose levels
182	Flaxseed lignans (secoisolariciresinol diglucoside, or SDG)	The effect of SDG on the development of diet-induced obesity in mice and the effect of the SDG metabolite enterdiol (END) on adipogenesis in 3T3-L1 adipocytes were studied. Mice were fed 0.5% and 1% (w/w) SDG for 4 weeks	SDG reduced hypercholesterolemia, hyperinsulinemia and END induced PPAR-γ DNA binding activity in 3T3-L1 adipocytes
183	Polyphenols (oil palm leaves)	The antihypercholesterolemic effect of polyphenols from oil palm leaves was studied in cholesterol-fed rats	Rats fed a high-cholesterol diet supplemented with oil palm leaves showed a trend for increased plasma high-density lipoprotein (HDL) cholesterol and a lower artherogenic index compared to those without oil palm leave extract supplements
184	Tea catechin	The effect of tea was studied on the improvement of insulin resistance in mice and rats	After oral administration, tea or EGCG stimulates GLUT4 translocation from the endoplasmic reticulum to the plasma membrane in the skeletal muscle of mice or rats both *in vivo* and *ex vivo*
185	Cocoa powder	A comparative double-blind study was conducted in 160 subjects who ingested either cocoa powder containing low levels of polyphenolic compounds or cocoa powder containing high levels of polyphenolic compounds (13, 19.5 & 26 g/day for the low, middle and high cocoa groups, respectively) for 4 weeks	Polyphenolic compounds derived from cocoa powder may contribute to the reduction in LDL cholesterol, the elevation in HDL cholesterol and the suppression of LDL oxidation
186	Cacao liquor	0.5% cacao liquor, 1.0% cacao liquor or no cacao liquor (control) was provided to C57BL/KsJ-*db/db* (*db/db*) diabetic obese mice	Cacao liquor prevented the development of hyperglycemia in diabetic obese mice. These results indicated that cacao liquor reduced diabetes-induced oxidative stress and renal damage
187	Quercetin	The effect of quercetin and its metabolites was examined on the production of proinflammatory eicosanoids by human leukocytes	Quercetin inhibited leukotriene B_4 (LTB_4) formation in leukocytes. 3-*O*-Methylquercetin retained lipoxygenase-inhibitory activity while quercetin-3-*O*-glucuronide retained antioxidant but not lipoxygenase-inhibitory activity
188	Oligonol	The antioxidant and antiinflammatory effects of the lychee-derived polyphenol oligonol (100 mg/kg) converted to a low-molecular-weight form in white adipose tissue were investigated	Oligonol has antioxidant effects and attenuated the increase in the expression of genes for inflammatory adipokines induced by a high-fat diet
189	*Cleistocalyx operculatus*	The antihyperglycemic, antihyperlipidemic and antioxidant effects of *C. operculatus* were investigated *in vitro* and *in vivo*	Oral administration of *C. operculatus* to diabetic rats for 8 weeks resulted in a significant reduction in the levels of glucose, cholesterol and triglycerides in plasma, as well as the levels of glucose and sorbitol in lens

Continuation

Table I (Cont.): Summary of studies on polyphenols presented at the 3rd International Conference on Polyphenols and Health.

Ref.	Polyphenols/plants/ natural interventions	Study design	Outcome
METABOLIC SYNDROME			
190	Quercetin	The effect of quercetin on the expression of PPAR-γ, acetyl-CoA carboxylase, adiponectin levels and insulin sensitivity was studied in rats fed a high-fat diet	Quercetin may induce adiponectin via PPAR-γ-independent mechanisms. Quercetin did not affect body weight and serum leptin levels
191	Quercetin	The impact of quercetin (0.03%) on lipid metabolism and insulin resistance was investigated in rats fed a high-fat diet containing saturated long-chain fatty acids	In quercetin-fed rats, fasted glucose, triacylglycerols and plasma insulin concentrations were lower, whereas adiponectin was elevated
192	Resveratrol	Resveratrol was evaluated for PPAR activation	Resveratrol was found to be a dual agonist at PPAR-α and -γ
193	Apple polyphenol extract	The inhibitory effects of an apple polyphenol extract and procyanidins contained in the extract on pancreatic lipase activity *in vitro* and on triglyceride absorption in mice and humans *in vivo* were examined	The oligomeric procyanidins contained in apple polyphenol extract inhibited triglyceride absorption by inhibiting pancreatic lipase activity in mice and humans
194	Quercetin	The effects of enzymatically modified isoquercitrin (100 mg/kg), a water-soluble glycoside of quercetin, on collateral development in a murine hind limb ischemia model were investigated	Enzymatically modified isoquercitrin enhanced collateral development in ischemic tissues and plasma antioxidant activity
195	Red petal extract	Red petal extract was evaluated for its effects on metabolic syndrome	Red petal extract suppressed α-glucosidase (maltase) activity. The IC_{50} for inhibition of α-glucosidase activity by red petal extract containing 10%, 20% and 70% polyphenol was 4, 1.2 and 0.09 ppm, respectively
196	Phloretin	The effect of phloretin on adipocyte differentiation and adiponectin expression was investigated	Phloretin may be beneficial for reducing insulin resistance through its ability to regulate adipocyte differentiation and function
197	Naringenin chalcone	The effect of naringenin chalcone on the production of proinflammatory mediators in the interaction between adipocytes and macrophages was evaluated	Naringenin chalcone exhibited antiinflammatory properties in the interaction between adipocytes and macrophages by inhibiting TNF-α, MCP-1 and NO
198	Green tea	The *in vivo* effect of green tea (1 g/kg/day for 12 weeks) consumption on brain oxidative stress was studied using an experimental rodent model of diet-induced insulin resistance	Green tea protected against brain oxidative damage and may exert neuroprotective effects against early brain alterations and free radical-induced neurodegenerative disease in people with metabolic syndrome
199	Hesperidin	The hypoglycemic and hypolipidemic effects of hesperidin (10 mg/kg) in streptozotocin-induced diabetic rats were studied	Hesperidin normalized blood glucose and lipid levels in serum and liver
200	Mace (*Myristica fragrans*)	The antidiabetic and hypoglycemic efficacy of mace lignan isolated from *M. fragrans* was evaluated in *db/db* mice	Mace lignan enhances insulin sensitivity and improves lipid metabolic disorders by activating both PPAR-α and -γ and attenuating endoplasmic reticulum stress
201	*M. fragrans*	The PPAR-γ ligand-binding activity of lignan compounds (2-[4-allyl-2,6-dimethoxyphenoxy]-1-[4-hydroxy-3-methoxyphenyl]propane; 4-hydroxy-3-methoxy-3',4'-methylenedioxy-7', 7'-epoxylignan) isolated from the aril of *M. fragrans* was examined	The PPAR-γ ligand-binding activity of 2-(4-allyl-2,6-dimethoxyphenoxy)-1-(4-hydroxy-3-methoxyphenyl)propane and 4-hydroxy-3-methoxy-3',4'-methylenedioxy-7', 7'-epoxylignan increased 7.3- and 3.7-fold at 10 μM and significantly increased the expression of GLUT4. Both compounds can be developed as PPAR-γ agonists for improving insulin resistance

Continuation

Table I (Cont.): Summary of studies on polyphenols presented at the 3rd International Conference on Polyphenols and Health.

Ref.	Polyphenols/plants/ natural interventions	Study design	Outcome
METABOLIC SYNDROME			
202	Catechins & caffeine	The combined effects of catechins & caffeine were studied on enzymes related to lipid metabolism in the liver of mice	Combination of catechins & caffeine markedly suppressed fatty acid synthesis and activated lipid catabolism in liver. EGCG is strongly involved in the activation of lipid catabolism by catechins and caffeine
POLYMETHOXYFLAVONOIDS			
203	Chrysoeriol	The modulating effects of chrysoeriol, a methoxyflavonoid found in perilla seeds, were examined on 7-ethoxyresorufin *O*-deethylation (EROD) activity and 2- and 4-hydroxylation of E_2 catalyzed by human recombinant CYP1A1/1B1 microsomes	Chrysoeriol significantly inhibited EROD activity and 4-hydroxy-E_2 formation by human recombinant CYP1B1 microsomes under 0.1 μM. Chrysoeriol may be a potent chemoprotectant against human mammary carcinogenesis by selectively inhibiting enzymatic activity of CYP1B1
204	Leptin/nobiletin	Serum levels of leptin were determined in azoxymethane/dextran sulfate sodium-treated mice, a model of colon carcinogenesis, and the effect of nobiletin (100 ppm in the diet for 17 weeks) on colon carcinogenesis was evaluated	In azoxymethane/dextran sulfate sodium-treated mice, the incidence of colon adenocarcinoma was 40% and the serum leptin level was 6 times higher than in untreated mice. Nobiletin abolished colon malignancies and decreased serum levels of leptin by 75%
205	*G. biloba*	The hair growth-stimulating activity of bioflavones from *G. biloba* was studied in the anagen phase in C3H mice	Sciadopitysin, a triply methylated bioflavone from *G. biloba*, showed the greatest proliferative activity at a concentration of 50 μM, up to 170% of control, with induction of growth factors, Akt and ERK in the cells
206	Nobiletin	The effect of nobiletin was determined on 3T3-L1 preadipocyte differentiation and adipocyte lipolysis	Nobiletin may exert its antiobesity effect by inhibiting both preadipocyte differentiation of the marker proteins PPAR, C/EBP and AP-2, and promoting adipocyte lipolysis
207	Polymethoxyflavonoids	The biotransformation of the polymethoxyflavonoids sinesetin, nobiletin, pentamethoxyquercetin & tetramethoxykaempferol was studied in the fungus *Aspergillus niger* and in the larvae of *Spodoptera litura*	The metabolic conversion of these polymethoxyflavonoids by *A. niger* & larvae of *S. litura* involved demethylation at the C-4' position with regioselectivity & demethylation followed by glucosylation at the A-ring, respectively
208	Eupatilin	The cytostatic effect of eupatilin was examined in H-Ras-transformed human breast epithelial cells	The antiproliferative effect of eupatilin in MCF-10A-ras cells was associated with blockade of cell cycle progression, which appears to be attributable in part to inhibition of ERK1/2 activation
209	Epicatechin	The metabolism of epicatechin was evaluated in HUVEC	Epicatechin protected vascular endothelial cells after conversion to bioactive B-ring *O*-monomethyl ethers, which in turn suppressed NADPH oxidase-mediated superoxide and peroxynitrite generation
NUTRIGENOMICS			
210	Sesamin	The molecular mechanisms involved in the synergistic hypocholesterolemic activity of sesamin (0.2%) with tocopherol (0.5%) were studied	The cholesterol-lowering mechanism underlying the effects of co-ingestion of sesamin and vitamin E is attributable to upregulation of the gene for the cholesterol efflux transporter and downregulation of that involved in the secretion of apoprotein
211	Naringenin & hesperetin	Naringenin & hesperetin were evaluated against inflammation in glial cells	Naringenin & hesperetin may protect against LPS/interferon gamma-induced neuroinflammation by inhibiting iNOS and TNF-α induction. In particular, naringenin may achieve this by modulating signaling through the p38 and STAT1 pathways

Continuation

Table I (Cont.): Summary of studies on polyphenols presented at the 3rd International Conference on Polyphenols and Health.

Ref.	Polyphenols/plants/ natural interventions	Study design	Outcome
NUTRIGENOMICS			
212	Quercetin	The suppressive effect of dietary quercetin (0.1% or 0.5%) was evaluated on streptozotocin-induced diabetes in mice	The blood glucose levels of the group fed an AIN93G diet containing 0.1% quercetin were significantly lower than those of the group fed an AIN93G diet alone after 2 weeks. 0.5% quercetin significantly decreased serum insulin levels
213	Coffee	The ability of coffee to modulate NF-κB activation in transgenic NF-κB luciferase reporter mice was investigated	NF-κB activity was decreased by 63.2% in the LPS-treated mice receiving coffee extract
214	Hesperidin	The mechanism of action of the effect of hesperidin on bone mass and strength was evaluated in intact and ovariectomized female rats	The classification of genes showed significant effects on signaling pathways (MAPK, PPAR, Wnt and calcium), response to stress and bone metabolism-related functions (bone remodeling and mineralization)
215	Catechin	The protective effect of catechin (0.02%) was assessed in apoE$^{-/-}$ mice that spontaneously develop atherosclerosis	A 25% reduction in atherosclerotic lesion development by catechin was observed after 6 weeks of supplementation with catechin
216	Curcumin	The impact of curcumin consumption (0.25%) was studied in apoE-deficient mice	The classification of genes showed significant effects on signaling pathways (MAPK, JAK/ STAT), the immune system and lipid metabolism
217	Soy isoflavones	The effect of the soy isoflavones genistein and daidzein (100 & 750 mg/kg) on the mammary gland of female rats fed a high-fat diet was studied	The classification of genes showed significant effects on lipid metabolism and homeostasis, steroid hormone metabolism, insulin metabolism and the PPAR signaling pathway
218	Procyanidins	The effect of procyanidins on the regulation of gene expression was studied in human aortic endothelial cells	Grape seed procyanidins showed a marked reduction in the secretion of two abundant endothelial proteins, *e.g.*, connective tissue growth factor and thrombospondin-1
219	Catechins & proanthocyanidins	The aim of the study was to characterize the effect of different polyphenols and polyphenol-rich fruits (apples, grapes) on the development of atherosclerosis in apoE$^{-/-}$ mice and to decipher their mode of action *in vivo* and at the nutritional level	Modifications by catechin in the expression of a few hundred genes that are implicated in different biological functions associated with atherosclerosis development were identified. Modifications in the expression of these genes suggested an implication of different transcriptional factors, *e.g.*, c-Jun, PPARs and NF-κB
220	*I. paraguariensis*	*I. paraguariensis* (mate) extract (0.24-0.96%) was fed for 8 weeks to male SD rats fed a high-fat diet and the effect on gene expression was studied	Among the changes in the gene expression profile induced by mate extract, it was noticed that the genes for lipin-1 (4.78-fold) and hormone-sensitive lipase (4.66-fold) were upregulated, while those for interleukin-1 receptor antagonist (0.44-fold), stearoyl-CoA desaturase 1 (0.26-fold), chemokine (C-C motif) ligand 2 (0.16-fold), and annexin A1 (0.39-fold) were downregulated
221	Quercetin	The effect of quercetin on the gene expression profile in the intestine of BALB/c mice was studied	Microarray analysis showed that low-dose quercetin affected the expression of genes related to calcium signals, ribosomal proteins, lipid and drug metabolism. In *in vitro* assays, Grp78 expression induced by ER stress was downregulated by quercetin at both the mRNA and protein levels
OXIDATIVE STRESS & CELL SIGNALING			
222	EGCG	The cytoprotective effects of extracellular matrix (collagen, fibronectin or laminin) via blockade of receptor binding of EGCG and its internalization into cytosol were studied	Laminin pretreatment could protect cells from EGCG-induced cytotoxicity directly by preloading the cellular receptor for EGCG

Continuation

Table I (Cont.): Summary of studies on polyphenols presented at the 3rd International Conference on Polyphenols and Health.

Ref.	Polyphenols/plants/ natural interventions	Study design	Outcome
OXIDATIVE STRESS & CELL SIGNALING			
223	EGCG	The regulatory effect of EGCG (100 ppm) was investigated on cell cycle and gene expression in neonatal human tarsal fibroblasts	In normal fibroblasts, the cell cycle may be reversibly regulated by internalized EGCG, which would contribute to its cytoprotective effect
224	Ellagic acid	The effect of ellagic acid and its two methyl derivatives was studied on LDL nitratase activity	Ellagic acid, and to lesser extent 4,4'-methyl and 5,5'-methyl forms of ellagic acid, strongly inhibited nitratase activity, probably due to protein-ellagic acid/methylellagic acid interactions
225	Fruit extracts	The potential of polyphenolic fruit extracts (0-50 μg/ml) was studied in both an *in vitro* model of oxidative stress and in isolated muscle tissue	Fruits or derived functional foods may be beneficial in alleviating oxidative stress-induced muscle damage and function
226	EGCG	The effect of EGCG (5-20 μM) was studied on IL-13 mRNA expression induced in human basophilic KU812 cells	EGCG induced IL-13 mRNA expression via intracellular ROS generation and activation of JNK and NFATc1 in KU812 cells
227	Artichoke extract (*Cynara cardunculus*)	Artichoke extract was investigated for its antimutagenic, antioxidant, antiproliferative and apoptosis-inducing activities	Artichoke extract showed antimutagenic properties via direct inactivation of genotoxic agents (4-NQO), DPPH radical-scavenging and an antiapoptotic effect in murine and human leukemia cells
228	Curcumin	Curcumin was evaluated for dioxin receptor activity	Curcumin revealed antagonist effects on aryl hydrocarbon receptor (AhR) transformation induced by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in mouse hepatoma Hepa-1c1c7 cells
229	Quercetin	The critical value for the antioxidant effect of dietary 0.05-2% quercetin dehydrate (containing 31 mg/kg/day-1.3 g/kg/day quercetin aglycone) was evaluated in rats fed a high-cholesterol diet	The ingestion of up to 126 mg/kg/day quercetin is effective as a dietary antioxidant
230	*M. cristata*	The ability of diethyl ether, ethyl acetate and *n*-butanol extracts from *M. cristata* to inhibit both enzymatically and nonenzymatically induced microsomal lipid peroxidation was reported	*M. cristata* extracts exhibited a potent antioxidant effect on spontaneous and induced microsomal lipid peroxidation and protected microsomes against oxidative stress
231	EGCG, myricetin, delphinidin & robinetin	The molecular mechanism involved in the antiischemic effect of EGCG, myricetin, delphinidin & robinetin was evaluated	EGCG, myricetin, delphinidin & robinetin directly interacted with STAT1, thereby inhibiting interferon gamma-elicited STAT1 activation
232	Apple polyphenols	The antiaging effect of apple polyphenols was studied using heart/ muscle-specific manganese superoxide dismutase knockout mice	Oral administration of 0.1% apple polyphenols to the knockout mice significantly recovered growth retardation and significantly extended life span by 29% in males and 72% in females
233	Mao seed & marc extract	The effect of Mao seed & marc extract on H_2O_2- and phorbol ester-induced cytotoxicity and inflammation was investigated using human breast epithelial cells (MCF-10A)	Mao seed & marc extract inhibited 12-*O*-tetradecanoylphorbol-13-acetate-induced NF-κB activation by blocking the degradation of cytoplasmic IκBα and the subsequent nuclear translocation of p65, and also attenuated the activation of ERK, but not JNK and p38
234	EGCG	The putative molecular mechanism of action of EGCG (100 μM) was investigated	Tea may prevent dioxin toxicity through an AhR-dependent pathway by interacting with AhR complexes
235	Berry	The effect of bilberry-lingonberry puree and oat cereal meal was studied on plasma F2-isoprostane production *ex vivo*	Peak concentrations of phenolic compounds (767 mg) administered in bilberry-lingonberry puree decreased the copper-induced lipid peroxidation as measured by F2-isoprostane production

Continuation

Table I (Cont.): Summary of studies on polyphenols presented at the 3rd International Conference on Polyphenols and Health.

Ref.	Polyphenols/plants/ natural interventions	Study design	Outcome
OXIDATIVE STRESS & CELL SIGNALING			
236	Oligonol	The antioxidant effect of oligonol was studied. The oxidative product of creatinine by hydroxyl radical was measured as a marker of oxidative stress in urine	The antioxidant effect of oligonol is dependent on the level of initial oxidative stress in humans and its effect is stronger than the source of oligonol that contains less oligomer
237	EGCG & EGC	The antiproliferative effect of EGCG & EGC against HCT 116 colorectal carcinoma cells at various cell densities and the molecular mechanism underlying these activities were compared	EGCG & EGC had equivalent antiproliferative activities at relatively low cell densities. Furthermore, MAPK, ERK, JNK and p38 were activated by EGCG & EGC in the cells, although to a different extent
238	Apple procyanidins	The antiinflammatory effect of apple procyanidins was studied in HUVEC	Low concentrations of an apple procyanidin oligomer extract attenuated the TNF-α-induced upregulated expression of IL-6, MCP-1, ICAM-1 and VCAM-1 in HUVEC
239	Luteolin	The preventive effects of luteolin 7-*O*-glucoside and luteolin on CCl_4-induced liver injury were compared in mice to determine the relationship between chemical structure and activity	Luteolin was more effective than its 7-*O*-glucoside in mitigating liver injury induced by oxidative stress
240	Oligomeric proanthocyanidins	The possible mechanism by which oligomeric proanthocyanidins attenuate atherosclerosis was studied	Oligomeric proanthocyanidins directly disrupted lipid peroxidation, providing a likely mechanism by which they inhibit LDL oxidation
241	Catechin & epicatechin	The possible mechanism of action of the flavanols catechin & epicatechin and structurally related metabolites on endothelial function was studied using a model of TNF-α-induced inflammation	Catechin & epicatechin may modulate the activity of eNOS, as well as the expression of protein linked to endothelial inflammation, and thereby potentially improve endothelial function
242	Apple polyphenols	A crude apple polyphenol extract (0.75%) and low-viscosity apple fibers (16.7%) isolated from cider apples were administered to apoE-deficient mice	Apple polyphenols and fibers may reduce the risk of atherosclerosis
243	Resveratrol	The mechanism involved in the protective effect of resveratrol against peroxynitrite-induced endothelial cytotoxicity was investigated	Resveratrol provided protection against peroxynitrite-induced endothelial cytotoxicity by increasing the intracellular GSH pool
244	Chamomile, sage & green tea	The antioxidant effects of chamomile, sage & green tea (5%) were investigated in 15-month-old rats	Chamomile, sage & green tea improved the antioxidant capacity in rats and green tea powder was found to be the most effective
245	Quercetin & anthocyanin	The combined effect of quercetin & anthocyanin was evaluated against ferric nitrilotriacetate-induced nephrotoxicity	The combined juice significantly suppressed thiobarbituric acid-reactive substances (TBARS) and 8-OHdG by 98% and 84%, respectively
246	Bilberry anthocyanins	The antioxidant and antihyperglycemic effects of bilberry extract were investigated in a model of streptozotocin-induced diabetes in Wistar rats	The beneficial effect of bilberry extract resides in its ability to protect against oxidative stress produced secondary to the diabetic condition, such as by advanced glycation end products (AGEs), rather than by direct prevention of streptozotocin-induced oxidative damage in pancreatic β-cells
247	Red grape	The effect of red grape polyphenol extract was determined on oxidative stress in neoplastic Ehrlich ascites-infected mice	The administration of red grape polyphenol extract reduced oxidative stress produced by doxorubicin treatment in neoplastic Ehrlich ascites-infected mice

Continuation

Table I (Cont.): Summary of studies on polyphenols presented at the 3rd International Conference on Polyphenols and Health.

Ref.	Polyphenols/plants/ natural interventions	Study design	Outcome
OXIDATIVE STRESS & CELL SIGNALING			
248	Red grape seed extract	The effects of hydroethanolic red grape seed extract obtained from *Vitis vinifera*, variety Burgund Mare, Recas, Romania, on antioxidant activity and NO levels were compared with ascorbic acid during pregnancy in rats	*V. vinifera* at the chosen dose (3 x 0.79 mg/rat) did not influence NO levels in pregnant rats, although it did enhance plasma antioxidant activity
249	Tetrahydrocurcumin	The effect of tetrahydrocurcumin on the regulation of insulin/Akt/FOXO signal transduction was investigated	Tetrahydrocurcumin activated FOXO4 and increased the life span of mammals by regulating age-related gene expression
250	Wine phenols	The effect of wine phenols on glutathione levels in rat liver was evaluated	Red wine showed a slight protection against oxidative stress induced by *tert*-butylhydroperoxide and wine phenols did not show any pro-oxidant effect
251	Powergrape®	The effect of a whole-grape extract rich in flavanols –Powergrape® (400 mg/day)– on the antioxidant capacity of 20 professional sportsmen was studied during competition	The consumption of Powergrape® decreased oxidative stress generated in professional sportsmen during competition
252	Red wine & resveratrol	The effect and mechanism of action of red wine & resveratrol were determined in human NSCLC A549 cells	Red wine, similar to resveratrol, significantly inhibited A549 lung cancer cell proliferation, likely through inhibition of Akt and ERK activation
CANCER PREVENTION			
253	Propolis	The effect of propolis extract was investigated on the induction of phase 1 and 2 enzymes through AhR transformation and/or activation of NF-E2 p45-related factor 2 (Nrf2)	Propolis extract had the unique property of inducing drug-metabolizing enzymes, *i.e.*, it could suppress carcinogen-induced phase 1 enzymes while inducing phase 2 enzymes
254	Berry phytochemicals	The modulatory effect of berries (2% w/w) on CYP1A1 and 1B1, two key cytochrome P-450 enzymes involved in 17β-estradiol metabolism and oxidative DNA damage, was studied	The berry constituents inhibited the smoke-induced overexpression of CYP1A1 and 1B1, and the formation of oxidative adducts by catechol estrogens
255	*Elsholtzioa splendens*	The anticarcinogenic activity of *E. splendens* (1-50 μg/ml) was studied in human breast cancer MDA-MB-453 cells	*E. splendens* may be used as a functional food and has the potential to relieve and prevent diseases such as cancer and rheumatoid arthritis
256	Dietary flavonoids	The *in vivo* effects of selected flavonoids on glutathione *S*-transferase activity were studied in rats	The modulation of hepatic glutathione *S*-transferase by quercetin may affect the capacity of the liver to detoxify xenobiotics via glutathione conjugation
257	Ellagic acid	Alterations in gene expression in colon cancer Caco-2 cells by ellagic acid and its colonic microflora derivatives, urolithins, were studied	Dietary levels of these compounds could have an effect on the mRNA levels of genes involved in cell signaling and the regulation of cell proliferation (FGFR, KRAS, MYC, FOS, DUSP6, CD44) and xenobiotic metabolism. Dietary intake of ellagic acid could exert modulatory activities in the gastrointestinal epithelia leading to cancer prevention
258	Apple procyanidins	The effect of apple procyanidins on the expression of apoptosis-related genes and the sensitivity of apple procyanidins to TRAIL in human tumor cells were studied	Apple procyanidin treatment increased TRAIL sensitivity through the downregulation of Bcl-X_L in human tumor cells and effectively induced death receptor-mediated apoptosis in tumors that acquire TRAIL resistance due to Bcl-X_L expression

Continuation

Table I (Cont.): Summary of studies on polyphenols presented at the 3rd International Conference on Polyphenols and Health.

Ref.	Polyphenols/plants/ natural interventions	Study design	Outcome
CANCER PREVENTION			
259	Apple procyanidins	The involvement of host immunity in the antitumor effect of apple procyanidins was studied	The increased number of activated $CD4^+$ and $CD8^+$ T-cells in treated mice indicated the involvement of host immunity in the antitumor effect of apple procyanidins
260	Apigenin	The potential of apigenin in cancer therapy was evaluated	Apigenin did not sensitize normal human peripheral blood mononuclear cells (PBMCs) to TRAIL-induced apoptosis. Combination of the dietary flavonoid apigenin and TRAIL may be promising as a new therapy against malignant tumors
261	Ampelopsin (*Myrica rubra*)	Ampelopsin induces concentration-dependent apoptosis in human leukemia cells (HL-60), as indicated by DNA fragmentation, activation of caspase-3, -8 and -9 and inactivation of PARP	Ampelopsin may induce apoptosis in HL-60 cells through a ROS-mediated mitochondrial dysfunction pathway
262	Daidzein & equol	The effect of the soybean isoflavone daidzein and its metabolite equol on the proliferation and invasion of AH109A cells was studied, as well as their mode of action	Daidzein & equol suppressed the secretion of hepatocyte growth factor (HGF), a known cell motility factor, from hepatoma cells, suggesting that decreased expression of HGF may be involved in their antiinvasive effect
263	Myricetin	Mouse JB6 cells, a validated model for screening cancer chemoprotective agents, were used to investigate the molecular mechanism of the inhibition of cell transformation by myricetin	Myricetin suppressed EGF-induced cell transformation through inhibition of JAK1- and p38-mediated STAT3 and AP1 pathways, suggesting that it may be useful for cancer prevention
264	Tea proanthocyanidins	The antiinflammatory effect of tea proanthocyanidins was studied in LPS-activated murine macrophage RAW 264.7 cells	Tea proanthocyanidins with the galloyl moiety may inhibit COX-2 and iNOS expression by blocking TAK1-mediated NF-κB and MAPK pathways, revealing a partial molecular basis for the antiinflammatory properties of tea proanthocyanidins
265	Horseradish (*Armaracia rusticana*)	The effects of horseradish leaf extract on detoxification enzymes were investigated for its use as a functional food	Administration of horseradish leaf extract increased glutathione *S*-transferase and quinine reductase in mouse liver
266	Quercetin	The metabolism and activity of quercetin (20 mg/kg) were studied after oral administration in rats	Inactive conjugates of dietary quercetin under healthy conditions were converted to aglycones (isorhamnetin) by β-glucuronidase, and isorhamnetin exhibited chemopreventive activity following the induction of carcinogenesis
267	Resveratrol	The antiproliferative effect of resveratrol was evaluated in human ovarian cancer PA-1 cells	Oncogenic eukaryotic elongation factor 1A2 upregulated via the PI3K/Akt signaling pathway is a potential target for ovarian cancer chemoprevention or treatment with resveratrol *in vitro* and *in vivo*
268	Oligonol	The antiinflammatory and antitumor activity of oligonol was investigated in mouse skin stimulated with phorbol ester	Topical oligonol significantly inhibited phorbol ester-induced COX-2 expression in mouse skin. Oligonol blunted phorbol ester-induced nuclear translocation and DNA binding to NF-κB by preventing phosphorylation and degradation of IκB
269	Curcumin	Basic information was derived for chemoprevention by curcumin	It was suggested that suppression by curcumin of *N*-nitroso compound-induced esophageal and hepatic carcinogenesis can be attributed to a decrease in metabolic activation by esophageal, but not liver, CYP2B1

Continuation

Table I (Cont.): Summary of studies on polyphenols presented at the 3rd International Conference on Polyphenols and Health.

Ref.	Polyphenols/plants/ natural interventions	Study design	Outcome
CANCER PREVENTION			
270	*V. vinifera*	The antitumor effects of the red grape seed extract from *V. vinifera*, variety Burgund Mare, Recas, Romania, were evaluated	Grape seed extract had tumor growth-inhibitory effects *in vitro* but not *in vivo*. The extract did not reduce the antitumor activity of doxorubicin
271	Curcumin	The ability of curcumin to inhibit NF-κB and STAT3 was investigated in three H-RS cell lines (KM-H2, L-428 & L-540)	The inhibition of NF-κB and STAT3 by curcumin (2.5-50 μM) led to a decreased expression of proteins involved in regulating cell proliferation and apoptosis (Bcl-2, Bcl-X_L, FLIP, XIAP, c-IAPI, survinin, c-myc, cyclin D1)
272	Canolol (rape seed oil)	The antiinflammatory effect of canolol was investigated using mouse peritoneal macrophages and its anticarcinogenic effect was investigated in gerbils infected with *H. pylori*, resulting in gastritis and cancer	Canolol suppressed NO, TNF-α and IL-12 production at above 10 μM *in vitro*. Suppression of carcinogenesis by 0.1% canolol appeared to parallel gastric inflammation rather than the disappearance of *H. pylori*
273	Brewed vinegars	The inhibitory effects of ethyl acetate extracts from 30 kinds of brewed vinegar on neoplastic transformation induced by phorbol ester in JB6 cells were evaluated	The ethyl acetate extracts decreased phorbol ester-induced soft agar colony formation with an IC_{50} of 4.7-39.7 μg/ml and without toxicity towards normal JB6 cells
PHYTOESTROGENS			
274	*Hijikia fusiforme*	The effects of *H. fusiforme* (50 & 100 mg/kg) were studied in ovariectomized rats	*H. fusifome* increased collagen content and the collagen cross-link pyridinoline of connective tissues in ovariectomized estrogen-deficient rats. Furthermore, *H. fusiforme* stimulated estrogenic activity
275	Phytoestrogens	The binding affinity for the androgen ligand binding domain of 16 phytoestrogenic flavonoids was investigated using surface plasmon resonance analysis	The order of binding affinity at 25 μM was as follows: for flavones, tangeretin < chrysin < apigenin < luteolin; for flavanols, isorhamnetin < galagin < kaempferol < quercetin; for flavanones, naringenin < eridictyol; for isoflavones and their metabolites, formononetin < diadzein < glycitein < equol < genistein < biochanin
276	Isoflavones	The effect of isoflavones on the lipid profile in diabetic rats was evaluated	Isoflavones may have beneficial effects in diabetic animals by improving plasma lipid profiles and lowering the atherogenic index and suppressing lipid peroxidation, indicating their efficacy in preventing macrovascular complications in diabetic animals
277	Isoflavones	The dose-response of isoflavones (0.2%, 0.4%, 1.0% and 2.0%) was determined on bone and uterine weight in ovariectomized mice	In ovariectomized mice, the bone mineral density of the femur and uterine weight was increased by isoflavones
278	Puerarin (*Pueraria labata*)	The effect of puerarin on bone metabolism was studied	When the murine preosteoclatic cell line RAW 264.7 was cultivated in the presence of puerarin and receptor activator of NF-κB ligand (RANKL), the expression and activity of TRAP, an osteoclast differentiation marker, were decreased with concomitant suppression of NFATc1, indicating that puerarin suppressed RANKL-induced osteoclast differentiation in RAW 264.7 cells by distributing the signal transduction processes, at least through an NF-κB-related step
279	Red clover extract	The total polyphenol content and radical-scavenging activity of an ethanol extract of red clover leaves and seeds were determined	The ethanol extract of red clover contains a high amount of polyphenols (153 mg/g in leaves; 16 mg/g in seeds) and marked DPPH-scavenging activity

bial transformation before absorption has been reported for many polyphenols, these being key steps in their absorption and bioavailability. Enzyme treatment using rhamnosidases and hesperidinases can increase the bioavailability of flavonoid glucosides from different food products, *e.g.,* citric flavonone glycosides, tea flavanols and black currant anthocyanins. Processing of cocoa beans, strawberries and pomegranates could enhance the bioavailability of catechins and ellagic acid (14). The next critical question is how to evaluate the flavonoids and their metabolites *in vivo*. Until now, liquid and gas chromatography techniques have been used. However, certain new approaches have been developed for the evaluation and characterization of plant polyphenols*, e.g.,* using monoclonal antibodies directed to the flavonoid (quercetin) and metabolites (15). The fate of the ingested flavonoid in the human body or *in vivo* system can be determined by using radiolabeled substrate (16).

Polyphenols and oxidative stress

Oxidative stress occurs when there is an imbalance between the generation of reactive oxygen species (ROS) and inadequate antioxidant defense systems. Oxidative stress can cause cell damage either directly or by altering signaling pathways. The oxidative breakdown of the membrane polyunsaturated fatty acids is known to be accompanied by the formation of a complex mixture of lipid hydroperoxides and secondary products. These compounds are highly reactive and are capable of rapid reaction with cellular nucleophiles such as phospholipids and proteins, and it was found that these reaction products are candidates as important biomarkers to evaluate the antioxidant activity of dietary antioxidants. Increased production of ROS is a feature of many human diseases, including cardiovascular disease, cancer, diabetes and neurodegenerative disorders. Researchers have developed immunochemical detection methods for oxidative stress by application of polyclonal and monoclonal antibodies. Dietary antioxidants may be especially important in protecting against human diseases associated with free radical damage to cellular DNA, lipids and proteins. Ascorbic acid is an effective water-soluble antioxidant and epidemiological studies suggest that increased ascorbate intake is associated with a reduced risk of some degenerative diseases, especially cancer and cataracts. Population studies have also shown that high vitamin E intake is associated with a decreased risk of coronary heart disease, possibly as a result of inhibition of atherogenic forms of oxidized low-density lipoprotein (LDL). Recent data suggest that β-carotene provides protection against lipid peroxidation in humans, as well as provitamin A activity. However, the available data are not sufficient to quantify the micronutrient requirements needed to protect against oxidative damage. The antioxidant roles of many food constituents, such as polyphenols, have not been clarified. The antioxidant properties of polyphenols have been widely studied, but it has become clear that the mechanisms of action of polyphenols go beyond the modulation of oxidative stress (17). Most antioxidants can act as pro-oxidants under certain conditions, and more research is needed to determine the occurrence and importance of this *in vivo*.. The few controlled interventional trials performed so far have shown mixed results as to the potential of antioxidant supplements for reducing the incidence of chronic diseases. Definitive recommendations on antioxidant intakes for disease prevention must await evidence from controlled studies and interventional trials. Overall, the available data suggest that protection against oxidative damage and related disease is best served by the variety of antioxidant substances found in fruits and vegetables.

Antiinflammatory effects of polyphenols

For more than 20 years, polyphenols, or food-derived bioactive compounds in fruits and vegetables, have been claimed to help prevent cancer, degenerative diseases and chronic and acute inflammation. Modern methods in cell and molecular biology allow us to understand the interactions of different polyphenols with basic mechanisms of the inflammatory response. The majority of studies deal with the effects of different antioxidants on the redox-sensitive transcription factor nuclear factor κB (NF-κB), inducible nitric oxide synthase (iNOS) expression and cyclooxygenase (COX) inhibition (18, 19). Understanding the regulatory steps and the multiple potential actions of polyphenols within the inflammatory cascade may help to define special polyphenols to be used for prevention and intervention in clinical conditions of inflammation. The relationship between the formation of advanced glycation end products (AGEs) as a consequence of high glucose and the activation of defense mechanisms through polyphenols opens up new fields in the prevention and treatment of oxidative stress and hyperglycemia. Polyphenols are promising compounds that may help to control oxidative stress and consequently the inflammatory response (20). To date, however, clinical studies have not been performed and should be carried out with specific polyphenols.

Polyphenols and cognitive function

Oxidative insults, whether overexcitation caused by the excessive release of glutamate or ATP caused by stroke, ischemia or inflammation, exposure to ionizing radiation, heavy metal ions or oxidized lipoproteins, may initiate various signaling cascades leading to apoptotic cell death and neurodegenerative disorders. Among the various ROS generated in the living organism, hydroxyl radical and peroxynitrite are the most potent and can damage proteins, lipids and nucleic acids. It appears that some natural antioxidants (tocopherol, ascorbic acid and glutathione) and defense enzyme systems (superoxide dismutase, catalase and glutathione peroxidase) may provide some protection against oxidative damage.

Recent findings indicate that several polyphenols and antioxidant drugs are effective in protecting cells from ROS attack. Further development of these antioxidant molecules may be of value in preventing the development of neurodegenerative diseases.

The onset of age-related neurodegenerative diseases superimposed on a declining nervous system function could exacerbate the motor and cognitive behavioral deficits that normally occur in senescence. It is likely that, in cases of severe deficits in memory or motor function, hospitalization and/or custodial care would be a likely outcome. This means that, unless we find a way to reduce these age-related reductions in neuronal function, healthcare costs will continue to rise exponentially. Thus, it is extremely important to explore methods to retard or reverse age-related neuronal deficits, as well as their subsequent behavioral manifestations. Applying molecular biological approaches to slow aging may be years away. It is therefore important to determine which methods can be used today to enhance healthy aging, forestall the onset of these diseases and create conditions favorable to obtain a "longevity dividend" in both financial and human terms. In this regard, epidemiological studies indicate that the consumption of diets rich in antioxidants and antiinflammatory compounds, such as those found in fruits and vegetables, may lower the risk of developing age-related neurodegenerative diseases, such as Alzheimer's disease or Parkinson's disease. Research suggests that the polyphenolic compounds found in fruits, such as blueberries, may exert their beneficial effects by altering stress signaling and neuronal communication, suggesting that interventions may exert protection against age-related deficits in cognitive and motor function (21). Supplementation with a blueberry diet improved the performance of aged animals on spatial working memory tasks within 3 weeks. In a follow-up acute human intervention trial, supplementation with a blueberry-rich drink induced a significant improvement in attentional performance, a measure of executive function (22).

Neurotrophic factors play key roles in the survival, differentiation and functional maintenance of nerve cells. Because of these properties, neurotrophic factors hold promise for the treatment of multiple neurological disorders. Since classical neurotrophic factors are not well suited for therapeutic purposes, the identification of small molecules that can mimic the properties of neurotrophic factors could have great value. Support for this idea comes from studies with the flavonoid fisetin. Fisetin can promote the survival and differentiation of nerve cells in culture. Furthermore, low doses of fisetin facilitate long-term potentiation in rat hippocampal slices, a cellular model of memory. In addition, oral administration of fisetin enhances memory in mice. Intravenous administration of fisetin reduced behavioral deficits in a rabbit stroke model and oral administration prevented striatal dopamine loss in the MPTP model of Parkinson's disease in mice. In an *in vitro* model of Alzheimer's disease, fisetin prevented both β-amyloid (Aβ) accumulation and cell death (23).

Polyphenols and chemoprevention

Oxidative stress and associated mechanisms involving inflammation, aberrant signaling pathways and gap junction intercellular communication are increasingly associated with the pathogenesis of various chronic degenerative disorders such as atherosclerosis, neurodegeneration and cancer. The ROS-induced development of cancer involves malignant transformation due to altered gene expression through epigenetic mechanisms, as well as DNA mutations. Considerable attention has been focused on identifying naturally occurring antioxidant phenolic phytochemicals that are able to decrease ROS levels, but the efficacy of antioxidant therapies has been equivocal at best. The consumption of fruits, vegetables and beverages like teas continues to be suggested to have the capacity to reduce the incidence of cancer. Bioactive compounds, including phenolics, may be responsible for the chemopreventive effects. While the free radical-scavenging and antioxidant properties of phenolics are well established, emerging literature reports suggest that their chemopreventive effects may also be ascribed to their ability to modulate components of cell signaling pathways (24).

A new horizon in chemoprevention research is the recent discovery of molecular links between inflammation and cancer. Components of the cell signaling network, especially those converging on the ubiquitous eukaryotic redox-sensitive transcription factor NF-κB, have been implicated in the pathogenesis of many inflammation-associated disorders. NF-κB may mediate tumorigenesis and thus could be used as a target for chemoprevention and for the treatment of cancer (25). Modulation of cellular signaling involved in chronic inflammatory responses hence provides a pragmatic strategy in molecular target-based chemoprevention and cytoprotection.

Induction of phase 2 detoxifying or antioxidant enzymes represents an important cellular defense in response to oxidative and electrophilic insults. Nuclear factor erythroid 2-related factor 2 (NF-E2-related factor 2, NRF2) plays a crucial role in regulating phase 2 detoxifying/antioxidant gene induction. Many antioxidants derived from dietary and medicinal plants have been found to activate this particular redox-sensitive transcription factor, thereby potentiating the cellular antioxidant or detoxifying capacity. It is noteworthy that there is a good correlation between the antiinflammatory activity of selected chemopreventive/cytoprotective agents and their ability to induce antioxidant gene expression (26).

Polyphenols and metabolic syndrome

Metabolic syndrome comprises a cluster of metabolic conditions, including hypertriglyceridemia, high LDL, low high-density lipoproteins (HDL), insulin resistance, abnormal glucose tolerance and hypertension, which, together with genetic susceptibility and abdominal obesity, are risk factors for type 2 diabetes, vascular inflammation, atherosclerosis and renal, liver and heart dis-

ease. One of the defects in metabolic syndrome and its associated diseases is excess cellular oxidative stress (mediated by ROS and reactive nitrogen species [RNS]) and oxidative damage to mitochondrial components, resulting in reduced efficiency of the electron transport chain (27). Recent evidence indicates that reduced mitochondrial function caused by ROS/RNS membrane oxidation is related to fatigue, a common complaint of metabolic syndrome patients. Lipid replacement therapy administered as a nutritional supplement with polyphenolic antioxidants can prevent excess oxidative membrane damage, restore mitochondrial and other cellular membrane functions and reduce fatigue. Recent clinical trials have shown the benefit of lipid replacement therapy plus polyphenolic antioxidants in restoring mitochondrial electron transport function and reducing moderate to severe chronic fatigue. Thus, lipid replacement therapy plus polyphenolic antioxidant supplements should be considered for metabolic syndrome patients who suffer various degrees of fatigue (27).

Green tea and cinnamon are effective in animals and humans and the beneficial effects are related to insulin sensitivity and antioxidant status (28). Black Oolong tea and sesamin improved lipid dysregulation and prevented metabolic syndrome (29). Cyanidin 3-glucoside significantly suppressed the development of obesity, normalized adipocyte hypertrophy in the epididymal white adipose tissue and ameliorated hyperglycemia and insulin sensitivity in mice (30).

In a double-blind, placebo-controlled study, the chronic effects of green tea polyphenols on vascular reactivity, blood pressure and blood lipids were evaluated in healthy men. Volunteers consumed 6 gelatin capsules per day containing an aqueous extract of *Camellia sinensis* (119 mg green tea polyphenols/day) for 3 weeks (n=17; BMI: 25.9 ± 3.2 kg/m^2; age: 41 ± 9 years) or placebo (n=16; BMI: 24.8 ± 3.0 kg/m^2; age: 40 ± 10 years). The results suggested that the consumption of green tea polyphenols for 3 weeks did not affect the elasticity of the vascular endothelium or other coronary heart disease risk factors in healthy men (31).

Polyphenols and pharmaceuticals

Although antioxidants are part of the diet, their bioavailability through dietary supplementation is reduced by several factors, such as poor solubility, inefficient permeability, instability due to storage of food, first-pass effect and gastrointestinal degradation. Conventional dosage forms may not result in efficient formulation owing to their poor biopharmaceutical properties. Principles of novel drug delivery systems need to be applied to significantly improve the performance of antioxidants. Novel drug delivery systems would also aid in the delivery of these antioxidants by the oral route, as this route is of prime importance when antioxidants are intended for prophylactic purposes. The implication of novel drug delivery systems for the delivery of antioxidants is largely governed by physicochemical characteristics, biopharmaceutical properties and pharmacokinetic parameters of the antioxidant to be formulated. Recently, chemical modifications, coupling agents, liposomes, microparticles, nanoparticles and gel-based systems have been explored for the delivery of these difficult-to-deliver molecules (32, 33). Nasal administration of quercetin liposomes (containing 0.5 mg quercetin) might serve as a novel therapeutic approach to enhance antidepressant and memory functions (33).

Tea and health

Since ancient times, green tea has been consumed by the Japanese and Chinese populations and is probably the most consumed beverage after water in Asian societies. Increasing interest in the health benefits of tea has led to the inclusion of tea extracts in dietary supplements and functional foods. However, epidemiological evidence regarding the effects of tea consumption on cancer and cardiovascular disease risk is conflicting. While tea contains a number of bioactive chemicals, it is particularly rich in catechins, of which epigallocatechin gallate (EGCG) is the most abundant. Catechins and their derivatives are thought to contribute to the beneficial effects ascribed to tea. Tea catechins and polyphenols are effective scavengers of ROS *in vitro* and may also function indirectly as antioxidants through their effects on transcription factors and enzyme activities. The fact that catechins are rapidly and extensively metabolized emphasizes the importance of demonstrating their antioxidant activity *in vivo*. In humans, modest, transient increases in plasma antioxidant capacity have been demonstrated following the consumption of tea and green tea catechins. The effects of tea and green tea catechins on biomarkers of oxidative stress, especially oxidative DNA damage, appear very promising in animal models, but data on biomarkers of *in vivo* oxidative stress in humans are limited. Larger human studies examining the effects of tea and tea catechin intake on biomarkers of oxidative damage to lipids, proteins and DNA are needed.

Epidemiological studies suggested that EGCG reduces cardiovascular risk. One potential mechanism for reduced cardiovascular risk is improved endothelial function, which may decrease inflammation, thrombosis, vasospasm and intimal growth in the arterial wall (34). Bettuzzi *et al.* described beneficial effects of green tea consumption in prostate cancer prevention (35). Studies with human cancer cell lines have demonstrated a number of potential cancer prevention mechanisms for tea polyphenols, including protection from induction of oxidative stress, inhibition of a vast array of enzymes (mitogen-activated protein [MAP] kinases, cyclin-dependent kinases [CDKs] and topoisomerase I) and inhibition of growth factor-related cell signaling. However, prospective studies did not provide support for the idea that increased consumption of green tea protects against cancer (36). Individuals consuming high levels of 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP) and a high-fat diet, white tea and caffeine showed promotion rather than sup-

pression of colon tumors via enhanced survival of cells with β-catenin mutations due to attenuation of apoptosis and increased cell proliferation, thereby further activating β-catenin signaling (37).

A crossover study in healthy males and females showed that Oolong tea (77.2 mg EGCG and 70.5 mg caffeine) intake for 4 weeks lowered fasting blood glucose and fructosamine levels, but not body mass index. Rodent studies have shown that green tea and EGCG (3.2 g/kg) might improve glucose homeostasis by increasing the affinity of insulin for its receptor in insulin-responsive tissues, increasing the expression of glucose transporters, decreasing carbohydrate absorption and inhibiting the hepatic expression of gluconeogenic enzymes. EGCG treatment attenuated obesity and metabolic syndrome, possibly by decreasing lipid absorption or inflammation, or by other mechanisms (38).

Polyphenols and nutrigenomics

Efforts to unveil the etiology of human disease often recapitulate the nature *versus* nurture debate. However, biologists now concede that neither nature nor nurture alone can explain the molecular processes that ultimately govern human health. The presence of a particular gene or mutation in most cases merely connotes a predisposition to a particular disease process. Whether that genetic potential will eventually manifest as a disease depends on a complex interplay between the human genome and environmental and behavioral factors. This understanding has helped spawn numerous multidisciplinary gene-based approaches to the study of health and disease.

One such endeavor is nutrigenomics, the integration of genomic science with nutrition and, when possible, other lifestyle variables such as cigarette smoking and alcohol consumption. Although genes are critical for determining function, nutrition modifies the extent to which different genes are expressed and thereby affects whether individuals attain the potential established by their genetic background. Nutrigenomics therefore initially referred to the study of the effects of nutrients on the expression of an individual's genetic makeup. More recently, this definition has been broadened to encompass nutritional factors that protect the genome from damage. Ultimately, nutrigenomics is concerned with the impact of dietary components on the genome, the proteome (the sum total of all proteins) and the metabolome (the sum of all metabolites) (39).

In one study, the physiological activity of sesame lignans (episesamin, sesamolin and sesamin) in affecting the gene expression profile in rat liver was compared using Affymetrics' Rat Genome 230 2.0 Array. Compared to a lignan-free diet, a diet containing 0.2% sesamin was associated with a 1.5-fold change in the expression of 188 genes (110 downregulated and 78 upregulated). A diet containing 0.2% episesamin and sesamolin caused a 1.5-fold change in 726 (529 downregulated and 197 upregulated) and 667 genes (467 downregulated and 200 upregulated), respectively. Episesamin and sesamolin greatly increased the mRNA levels of various hepatic fatty acid oxidation enzymes to similar levels (1.8-10-fold). Compared to episesamin and sesamolin, sesamin was much less effective in increasing these parameters (1.1-3.8-fold). These lignans also affect the expression of genes involved in lipogenesis, lipid transport and alcohol and glucose metabolism (40).

Current research has now moved to the characterization of genomic effects of polyphenols and the consequences for metabolism, which appears to extend far beyond the control of oxidative stress. Nutrigenomics offers new perspectives to characterize these effects in a global manner, to suggest new mechanisms of action more pertinent in a (supra) nutritional context, and to identify more robust markers of effects (41). Polyphenols modulate oxidative stress-related genes and genes of proinflammatory cytokines.

Anthocyanins

Anthocyanins are reddish pigments that are widely distributed in edible fruits and vegetables. Anthocyanins are especially abundant in bilberries, comprising 90% of the phenolic compounds. Moreover, the anthocyanin composition of bilberry is more diverse than that of most other berries, as a total of 15 different anthocyanins have been identified, including glycosides of delphinidin, cyanidin, petunidin, peonidin and malvidin. In particular, bilberry contains a greater amount of delphinidin glycosides, which is very low in other berries. These properties of bilberry anthocyanins provide the basis for the fact that bilberry has higher biological activities than other berries, because the structure-activity relationship (SAR) studies suggest that anthocyanins bearing hydroxyl moieties, such as delphinidin and cyanidin, in ring B have higher bioactivities than other anthocyanins without hydroxyl radical moieties. Hou presented the biological activities of bilberry anthocyanins with a focus on chemopreventive effects (*e.g.,* antioxidant, antiinflammatory and anticarcinogenic activities) and their molecular targets, including oncogenic signaling (*e.g.*, MAPK and epidermal growth factor receptor [EGFR] pathways), transcription factors (*e.g.,* AP-1, NF-κB, p53) and downstream genes (*e.g.,* COX-2, iNOS, Bax) (42). Ichiyanagi studied how structural diversity affected the biological behavior, such as absorption and metabolism, of anthocyanins. As a result, it was demonstrated that the attached sugar type was a modulator of anthocyanin absorption. The metabolism of anthocyanins was classified into three categories: 1) *O*-methylation of the B-ring; 2) glucuronidation of anthocyanins; and 3) glucuronidation of anthocyanidins. The metabolism of anthocyanins was modulated by the B-ring structure of aglycone (43). Furthermore, berry fruits and walnut anthocyanins inhibited overactivation of microglial cells in Alzheimer's disease and Parkinson's disease (44). *Vaccinium myrtillus* extract, a complex mixture of anthocyanosides, possesses potent anticancer activity (45).

Safety of polyphenols

Polyphenols are safe when consumed in amounts commonly found in foods. However, the risk of side effects may increase when they are consumed in excess amounts. Recently, abundant dietary supplements and beverages have emerged that contain large amounts of polyphenols and the safety assessment of polyphenols has therefore received considerable attention. Damage to DNA or chromosomes is important because it greatly influences cell functions, resulting in various diseases and aging. People sometimes use supplements with drugs and supplement-drug interactions are a matter of concern.

In a study where excess tea catechins (300 mg/kg) were given orally to mice, tea catechins did not induce microsomal damage, as evaluated by the micronucleus assay using peripheral blood. The results indicated that tea catechins have no genotoxicity even when an excess is consumed, and have the beneficial effect of minimizing chromosomal damage induced by ROS (46). *Ginkgo biloba* extract, which contains flavanols and terpenoids, attenuated the efficacy of co-administered drugs via the induction of hepatic drug-metabolizing enzymes (cytochrome P-450, or CYP). Some polyphenols in *G. biloba* influenced CYP activities in cell-free enzyme systems, but such findings were not observed in animal studies (46).

Conclusions

The increasing understanding of the role of free radicals in disease is opening new vistas for antioxidants in prevention and therapy in healthcare systems, along with a promising role as supportive remedies in many regimens of mainline therapy. However, more animal and human studies are required to unravel the complex links between polyphenols and health. The major concern of the scientific community is the low bioavailability of many of these agents, which may be due to poor preformulation research in this area. However, more scientific evidence is required for understanding the optimal levels of intake and safety, as well as their functionality. The next International Conference on Polyphenols and Health, to be held in London, U.K., in 2009, will be an excellent platform for discussing novel findings in the field of functional food factors.

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