

RECENT ADVANCES IN POLYPHENOL RESEARCH: HIGHLIGHTS FROM THE 4TH INTERNATIONAL CONFERENCE ON POLYPHENOLS AND HEALTH HELD DECEMBER 7-11, 2009, AT HARROGATE INTERNATIONAL CENTRE, HARROGATE, UK

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CONTENTS

Summary	869
Introduction	869
Botanical phenolics and intracellular signaling pathways	870
Bioavailability and metabolism of polyphenols	870
Cancer preventive effects of polyphenols	872
Polyphenols and oxidative stress	873
Polyphenols and cardiovascular disease	873
Polyphenols, adipose tissue and obesity	874
Flavonoids and brain health	875
Personalized nutrition: opportunities and challenges	875
Conclusions	875
References	876

SUMMARY

The 4th International Conference on Polyphenols and Health (ICPH) focused on recent advances in polyphenolic research, with special emphasis on key issues such as polyphenol uptake and bioavailability, bioactivity and interventional studies to clinical trials. This conference followed the truly successful trend of the previous three meetings. The contribution from the stalwarts engaged in polyphenol research led to extensive discussion and development of key themes, such as potential mechanisms of action in the prevention and therapy of cardiovascular diseases, obesity, diabetes, inflammation and neurological disorders.

INTRODUCTION

The International Conference on Polyphenols and Health (ICPH) is a biennial conference initiated by Augustin Scalbert in 2003, and the first, highly successful meeting was held in Vinchy, France. It stimulated and encouraged many people engaged in research on polyphenols in human health. The 2nd ICPH, organized by Andrew Waterhouse and Cesar Fraga at Davis, California, U.S., was also a true success. The 3rd ICPH was organized by Junji Terao at Kyoto, Japan. Recently, Gary Williamson and Andrea Day organized the 4th ICPH, December 7-11, 2009, in Harrogate (U.K.). More than 650 scientists from over 28 countries engaged in polyphenolic research participated in the conference. The themes of the conference included mechanisms and factors affecting the health benefits of berry fruits, and the absorption, bioavailability and health benefits of polyphenols, with the main emphasis on cardiovascular diseases, obesity, diabetes, inflammation and neurological disorders.

The recent surge in research interest in polyphenols has led to major advances in understanding the chemistry, biology and cellular biology of this large class of compounds, and progress has been made in the fields of nutritional science and clinical medicine. The current focus is on methods and strategies on how to translate results from nutritional studies into perspectives on human health. The issues involved appear to be straightforward at first glance, but upon scrutiny, it turns out that a number of major research topics need to be tackled in the future. These include establishing appropriate methods for studying bioavailability, biokinetics, metabolism and toxicology.

Polyphenols are divided into different groups depending on the number of phenol rings and the chemical groups attached to the rings. Flavonoids make up the largest and the most important single group of polyphenols and can be divided into subgroups, such as flavanols (catechin, epicatechin), flavonols (quercetin, myricetin,

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kaempferol), flavanones (hesperetin, naringenin), flavones (apigenin, luteolin), isoflavonoids (genistein, daidzein) and anthocyanins (cyanidin, malvidin). The capacity of flavonoids to act as antioxidants is dependent upon their molecular structure, the position of the hydroxyl groups and other substitutions in the chemical structure of these polyphenols. A number of excellent reviews dealing with their structure, absorption, metabolism and pharmacokinetics have been published (1-3). Besides scavenging free radicals, many phenolics also exhibit multiple biological properties, e.g., anti-inflammatory, anticancer, antiviral, antimicrobial, vasorelaxant and anticlotting activities (4). In general, these phenolic compounds are rapidly converted to their glucuronide derivatives upon ingestion and are transported to the circulatory system and different body organs, including the brain. In recent years, a number of reviews have reported on the neuroprotective effects of polyphenols in cellular systems and animal models (5-7).

BOTANICAL PHENOLICS AND INTRACELLULAR SIGNALING PATHWAYS

It is becoming recognized that, in addition to their antioxidant and anti-inflammatory properties, many phenolics may also have a specific effect on intracellular signaling pathways. These signaling pathways are interrelated and are evolved from reactive oxygen species (ROS) from NADPH oxidase and mitochondria. In particular, these signaling pathways are downstream elements in response to ROS production from NADPH oxidase in response to cerebral ischemia, β -amyloid ($A\beta$) and excitotoxicity. Studies further link these kinases to activation of cytosolic phospholipase A_2 (cPLA₂) and release of arachidonic acid. There is also evidence that ROS produced from NADPH oxidase is linked to transcriptional pathways, such as the nuclear factor NF- κ B pathway and the NF-E2-related factor/antioxidant response element (Nrf/ARE) pathway for induction of antioxidant and inflammatory genes (8), and subsequently triggering the apoptotic pathway. Successful identification of these compounds and their action on intracellular signaling pathways will be important for effective use to combat neurodegenerative diseases.

A number of reports were presented on polyphenols, as well as diets rich in fruit and vegetables, which promoted health and attenuated or delayed the onset of various diseases, including cardiovascular and neurodegenerative diseases, diabetes and several other age-related disorders. The chemical components, bioavailability and metabolism of polyphenols, along with physiological and molecular mechanisms by which fruits and vegetables reduce the risk of disease, were thoroughly discussed. This report and Table I (available in the online version only) summarize the entire research work presented at the 4th ICPH-2009.

BIOAVAILABILITY AND METABOLISM OF POLYPHENOLS

Flavonoids, the most extensively studied class of polyphenols, show large variations in bioavailability: isoflavones have the highest bioavailability, whereas anthocyanins are only poorly available in the body. The very low bioavailability of anthocyanins, their rapid appearance in plasma and the presence of intact glycosides in the circulation all point to absorption from the stomach. The most efficient absorption, as compared to the stomach or colon, occurs from the small intestine. Flavan-3-ols are absorbed from the small intestine.

Information on proanthocyanidins is lacking, but it appears that only dimers are absorbed, whereas higher oligomers were not detected in plasma. However, the absorption of dimers is much less efficient than that of flavanol-3-ol monomers, as evidenced by 6- to 50-fold lower C_{max} values for the dimers. All other flavonoids occur as glycosides in foods, and only glucosides can be absorbed from the small intestine. Flavonoids that are not absorbed here are transported to the colon, where they are subjected to metabolism by microbiota. As a result, the bioavailability of these flavonoids is generally much lower than that of flavonoids absorbed from the small intestine. The notable exception is the isoflavones, which are absorbed from the colon but have the highest bioavailability of all flavonoids. Phenolic acids are quite well absorbed from the small intestine. Esterification (e.g., chlorogenic acid) markedly reduces absorption. *trans*-Resveratrol is quickly absorbed and its bioavailability is higher than that of catechin. Upon absorption, only conjugated forms are present in blood. Methylation of catechol units may also occur. It is important to realize that conjugation and methylation profoundly change the biological activity of polyphenols, a fact that has not been addressed in most in vitro studies, which have mainly been performed only with aglycones (9).

Grapes and related products contain a wide and complex variety of polyphenolic compounds. Various health benefits, such as cardiovascular protection, anticarcinogenic effects, antioxidant properties and protection against cognitive decline, have been reported with their regular consumption. Purple grape juice made from Concord grapes possesses high in vitro antioxidant activity, which is attributed to its high polyphenolic content of procyanidins, flavonols, flavan-3-ols, esters of hydroxycinnamates, phenolic acids and anthocyanins. Although anthocyanins comprise 50% of total polyphenolics, their bioavailability is usually low, with urinary levels typically less than 1% of intake. Recently, interest has arisen from studying the microbial production of metabolites from anthocyanins, with an emphasis on their beneficial effects on colonic health. Purple grape juice also contains high levels of caftaric and coutaric acids, tartaric esters of hydroxycinnamates. Little information is currently available regarding their bioavailability in humans other than that they appear in the circulatory system as free and conjugated hydroxycinnamates. Previous studies on the bioavailability of quinic esters of hydroxycinnamates have shown that they are highly bioavailable and present in plasma and urine as a wide range of free and conjugated metabolites derived from metabolism both in the small and large intestine (10).

Epidemiological studies suggested that dietary flavonoids are closely related to the prevention of degenerative diseases such as atherosclerosis and central nervous system (CNS) disorders. Numerous studies discovered diverse functions of flavonoids in cellular systems, which can be attributed to their antioxidant activity and "beyond" antioxidant activity. These biological activities have been explained as the mechanism of action for disease prevention by dietary flavonoids, which are mostly converted to their conjugated metabolites during intestinal absorption. Lower concentrations of inactive metabolites in the circulation are unlikely to participate in disease prevention. Thus, this "flavonoid paradox" should be resolved to evaluate their role in disease prevention. Terao et al. have focused on the function of quercetin, a typical flavonol from plant foods and studying the relationship between its metabolic conver-

sion and biological activity (11). Kawai et al. found that quercetin-3-glucuronide (Q3GA), one of the major quercetin metabolites, retains antioxidant activity and may act as a precursor of active aglycone when vascular targets are exposed to inflammation (12). Conversion of Q3GA to quercetin aglycone undoubtedly elevates its lipophilicity, resulting in the acceleration of its cellular uptake. On the other hand, immunochemical analysis implied that Q3GA accumulates in the CNS, although the pathway across the blood–brain barrier has not yet been clarified. A study in rats demonstrated that dietary quercetin suppressed the stress-induced increase in plasma corticosterone levels by attenuating hypothalamic–pituitary–adrenal (HPA) axis activation (13). Conjugated metabolites of flavonoids may concentrate at the target site as their aglycones and exert their functions in an unfavorable environment, such as intolerable oxidative stress. This idea may be helpful to resolve the “flavonoid paradox”.

Polyphenols in dietary and botanical matrices are usually present as simple and complex O-glycosides. In fermented dietary materials, the glycosidic moiety is removed and accompanied in some cases by more complex changes to the polyphenol. As for most xenobiotics, polyphenols undergo phase II conjugation in the intestinal wall during their absorption from the gut. In contrast, a few, such as puerarin in the kudzu vine, are C-glycosides and are stable in the gut and during absorption and distribution. Large bowel bacteria reduce polyphenol aglycones and cause ring opening and ring cleavage. The products are mostly absorbed and enter the bloodstream. Phase I and II metabolism events occur in the liver, where polyphenols mostly circulate as β -glucuronides and sulfate esters, with very little as the aglycones, the presumed active forms. Metabolism can occur in nonhepatic tissues. Breast tumor cells have variable amounts of cytochrome P450, sulfatase and sulfotransferase activities. Polyphenols can react with chemical oxidants (HOCl, HOBr, ONO_2) produced by inflammatory processes. The isoflavones daidzein and genistein and the flavanol quercetin form chlorinated products. Genistein is converted to 3'-nitrogenistein in the lung tissue of lipopolysaccharide-treated rats. Polyphenols that can be converted to quinones react with glutathione to form adducts. Chlorinated isoflavones do not react with glutathione, but instead they are converted to β -glucuronides and are excreted in bile. Analysis of polyphenols and their metabolites is routinely carried out with great sensitivity, specificity and quantification by LC–tandem mass spectrometry (14).

Orange beverages are a rich source of flavanones, which are present both in soluble and insoluble forms. Beverage processing affects the flavonoid composition and bioavailability. Flavanones were evaluated by HPLC–MS–MS in plasma samples collected at 0, 1, 2, 3, 4, 5, 7, 8, 9, 10 and 11 h after intake. Naringenin and hesperetin sulfates and glucuronides were detected in plasma. Flavanone excretion was also evaluated in urine collected during 24 and 48 h after intake. The same metabolites detected in plasma were observed, together with diglucuronides and glucuronide sulfates of naringenin and hesperetin. A large interindividual variability in flavanone absorption and excretion was observed. Some volunteers absorbed and excreted less flavanones than others in all the interventions. This could be due to genetic variability affecting the intestinal absorption and metabolism of flavanones, or to gut microbiota metabolism of flavanones, leading to C-ring cleavage metabolites (phenylpropionic, phenylacetic derivatives), therefore leaving less intact flavanones for

absorption. The way flavanones are present in the beverages affects their bioavailability. Beverages with a larger amount of soluble flavanones show a higher bioavailability than those that are richer in precipitated flavanones in the cloud. Flavonoid-enriched beverages showed an increased flavonoid bioavailability. The relative bioavailability was higher for the flavonoid extract dissolved in water, showing a clear effect of the orange juice matrix on flavanone absorption and metabolism (15).

Quercetin reduces blood pressure in hypertensive animals. However, quercetin (aglycone) is not usually present in plasma, but is rapidly metabolized by methylation, glucuronidation and sulfation. Unlike quercetin, its glucuronide metabolites lack direct vasodilating effects. Perez-Vizcaino et al. analyzed the effects on blood pressure of the conjugated metabolites of quercetin (quercetin-3-glucuronide, Q3G; isorhamnetin-3-glucuronide, I3G; and quercetin-3'-sulfate, Q3'S) in spontaneously hypertensive rats (SHR) and on vascular function in mesenteric arteries from Wistar rats (16). Diastolic blood pressure was measured in conscious SHR. Mesenteric arteries from Wistar rats were mounted for isometric force recording. Q3G progressively and dose-dependently reduced mean blood pressure (MBP) in SHR (maximum effect observed at 3 h: $14.9 \pm 1.8\%$ decrease at 1 mg/kg i.p.). I3G also reduced MBP ($11.4 \pm 1.8\%$ at 3 h), while Q3'S was without effect. Interestingly, the hypotensive effect of Q3G was abolished in SHR treated with a specific inhibitor (glucuronidase, saccharic acid 1,4-lactone [SAL]). In mesenteric arteries, unlike quercetin, Q3G (10 μM) had an inhibitory effect on the contractile response to phenylephrine after 30 min. However, after 2 h, Q3G had a similar inhibitory effect to quercetin, which was also suppressed by incubation with SAL (1 mM). These data indicate that the glucuronidated metabolites are involved in the in vivo antihypertensive effect of quercetin, acting as carrier molecules for the plasma transport of quercetin, which releases glucuronidase in the target tissues.

Chlorogenic acids (CGAs) and related compounds are the main components of the phenolic fraction of green coffee beans, commonly reaching levels up to 9 g% (dry matter basis) in *Coffea canephora* species. CGAs are esters of *trans*-cinnamic acids with (–)-quinic acid. The main classes include caffeoylquinic acids, dicaffeoylquinic acids, feruloylquinic acids, *p*-coumaroylquinic acids and mixed diesters. During roasting, CGAs may be isomerized, hydrolyzed, epimerized or degraded into low-molecular-weight compounds. A fraction of CGAs may also be transformed into quinolactones and, along with other compounds, incorporated into the backbone of melanoidins. In addition to 12 major isomers, more than 60 minor CGAs and other related compounds have been observed in both green and roasted coffee (17). Human subjects drank coffee containing 412 μmol of chlorogenic acids and plasma and urine were collected at 0–24 h after ingestion and analyzed by HPLC–PDA–MSn. Within 1 h, some of the components in the coffee reached low nmol/L peak plasma concentrations (C_{max}), while chlorogenic acid metabolites, including caffeic acid 3-O-sulfate and ferulic acid 4-O-sulfate, and sulfates of 3- and 4-caffeoylquinic acid lactones, had higher C_{max} values. The short time to reach C_{max} (t_{max}) indicates absorption of these compounds in the small intestine. In contrast, dihydroferulic acid, its 4-O-sulfate and dihydrocaffeic acid 3-O-sulfate exhibited much higher C_{max} values (145–385 nM), with t_{max} values in excess of 4 h, indicating absorption in the large intestine and the probable involvement of catabolism by colonic bacteria.

These three compounds, along with ferulic acid 4-*O*-sulfate and dihydroferulic acid 4-*O*-glucuronide, were also major components excreted in urine (8.4–37.1 μmol) after coffee intake. Feruloylglycine, which is not detected in plasma, was also a major urinary component (20.7 μmol excreted). Other compounds not accumulating in plasma but excreted in smaller quantities included the 3-*O*-sulfate and 3-*O*-glucuronide of isoferulic acid, dihydro(iso)ferulic acid 3-*O*-glucuronide and dihydrocaffeic acid 3-*O*-glucuronide. Overall, the 119.9 μmol excretion of the chlorogenic acid metabolites corresponded to 29.1% of intake, indicating that, in addition to being subject to extensive metabolism, chlorogenic acids in coffee are well absorbed. Pathways for the formation of the various metabolites within the body are proposed. Urinary dihydrocaffeic acid 3-*O*-sulfate and feruloylglycine are potentially very sensitive biomarkers for the consumption of relatively small amounts of coffee (18).

Despite 20 years of rigorous research on the relationship between soy and breast cancer, questions regarding the absorption, metabolism and distribution of isoflavones in breast tissue remain unanswered. The potential health effects of isoflavone consumption on breast tissue, the concentration and nature of metabolites and biodistribution were assessed and compared to 17 β -estradiol (E_2) exposure. In this dietary intervention study, healthy women were randomized to soy milk ($n = 11$; 16.98 mg genistein and 5.40 mg daidzein aglycone equivalents per dose), soy supplement ($n = 10$; 5.27 mg genistein and 17.56 mg daidzein aglycone equivalents per dose) or control ($n = 10$). After a run-in of 4 days, three doses of either soy milk or soy supplements were taken daily during 5 days before an aesthetic breast surgery. Blood and breast biopsies (adipose and glandular tissue) were collected during surgery and analyzed using LC–ESI–MS/MS. Genistein and daidzein concentrations ranged between 135.1 and 2831.2 nmol/L and 23.9 and 917.7 nmol/L, respectively, in hydrolyzed serum, and between 49.2 and 431.3 pmol/g and 24.2 and 175.1 pmol/g, respectively, in hydrolyzed breast tissue. The major metabolites in hydrolyzed serum and breast tissue were identified as genistein 7-*O*-glucuronide ($91.8 \pm 2.5\%$ and $67.0 \pm 8.1\%$, respectively) and daidzein 7-*O*-glucuronide ($89.0 \pm 1.7\%$ and $65.3 \pm 9.7\%$, respectively). The isoflavone-derived E_2 equivalents towards the estrogen receptor β (ER β equivalents) were nearly equally distributed between adipose and glandular tissue (49/51; $P < 0.001$). After both soy milk and soy supplement intake, the exposure to ER β equivalents in glandular tissue (0.846 and 0.680 pmol/g, respectively) exceeded the unconjugated E_2 concentrations (0.348 and 0.134 pmol/g, respectively; $P = 0.033$ and $P = 0.007$, respectively). These findings show that, upon soy milk or soy supplement intake, isoflavones can reach exposure levels in breast tissue with potential beneficial health effects (19).

CANCER PREVENTIVE EFFECTS OF POLYPHENOLS

Green tea (*Camellia sinensis*) and its major polyphenol, (–)-epigallocatechin-3-gallate (EGCG), have been extensively studied for the prevention of cancer. Preventive effects have been observed in animal models of cancer, including oral, gastrointestinal, lung, skin and prostate cancer. Based on studies with cancer cell lines and cell-free systems, many mechanisms of action have been proposed. In some cases, in vivo data support these proposed mechanisms, whereas in others no correlative in vivo data have been reported. Recently, laboratory studies have shown that green tea and EGCG may elicit can-

cer preventive effects through the modulation of carcinogen metabolism and DNA repair, via pro-oxidant effects or several other “high-affinity” targets, including vimentin and the proteasome. A recent area of interest that may be fruitful is the study of the cancer preventive effects of tea polyphenols in combination with other dietary components and pharmaceutical agents (e.g., atorvastatin). Studies in cell culture and animal models have been promising, but further studies are needed to clearly establish efficacy and mechanism of action. Although laboratory studies have been overwhelmingly positive, epidemiological studies remain mixed and there is a dearth of controlled interventional studies on tea and cancer prevention. In order to move beyond the conclusion that tea “may” prevent cancer to the conclusion that tea “does” prevent cancer, more such interventional studies are needed. Finally, although tea has a long history of safe use as a beverage and interventional studies have been conducted with relatively high doses of tea polyphenols, there are emerging case-study and laboratory reports of the potential toxicity of high oral doses of tea polyphenols (20).

Modulation of the aryl hydrocarbon receptor-mediated signaling pathway

The aryl hydrocarbon receptor (AhR) is a ligand-dependent transcription factor of the basic helix–loop–helix protein family and is involved in cell growth and differentiation. The AhR regulates the expression of various genes, including xenobiotic-metabolizing enzymes such as cytochrome P450 1A1 (CYP1A1). It is recognized that the polycyclic aromatic hydrocarbons, such as benzo[*a*]pyrene and 3-methylcholanthrene, and the halogenated aromatic hydrocarbons, including dioxins, are the exogenous classic ligands of this receptor. Moreover, benzo[*a*]pyrene and 3-methylcholanthrene are reported to undergo metabolic activation by the CYP1A subfamily and form ultimate carcinogens, resulting in an increase in the incidence of carcinogenicity. In addition to these classic ligands, certain natural products, especially dietary polyphenols, may also be AhR ligands. Although some polyphenols are reported to activate the AhR, they mostly exhibit an antagonist effect. In the case of flavonoids, these compounds are reported to be both agonists and antagonists of the AhR, and seem to act as antagonists at the dietary level. The molecular mechanisms of the antagonist effect depend on the subclass: flavones, flavonols and flavanones act as competitive antagonists of the AhR, whereas catechins do not. Flavonoids suppress not only AhR transformation, but also CYP1 enzymes directly. The mechanisms of action of dietary flavanoids should be further explored in vivo. Another effective polyphenol, curcumin, showed the following properties: inhibition of the binding of AhR ligands to the receptor and suppression of the transformation process by inhibiting phosphorylation of the AhR probably caused by protein kinase C (PKC). Thus, several molecular mechanisms underlie the modulation of AhR transformation by polyphenols, and these molecular mechanisms are involved in the anticarcinogenic effects of polyphenols (21).

Fecal deoxycholic acid and lithocholic acid as risk factors for colon cancer

Secondary bile acids such as deoxycholic acid and lithocholic acid have been considered to be cytotoxic for normal colonic crypt cells,

resulting in an increased compensatory proliferation of colonic epithelium cells, which is associated with an increased risk of colon cancer. The secondary bile acids cause DNA damage, oxidative stress and proinflammatory activity by activating nuclear factor NF- κ B. A high-fat diet stimulates the secretion of bile acids to the intestinal lumen, leading to a higher risk of colon cancer. Recent studies further suggest an association of bile acids with the development of colitis. The effect of dietary polyphenols on fecal secondary bile acids in rats fed a high-fat diet was evaluated. In experiment 1, rats were fed 30% beef tallow diet containing 0.5% polyphenols, including curcumin, caffeic acid, D-(+)-catechin, rutin, ellagic acid and quercetin, for 3 weeks. Dietary curcumin and caffeic acid significantly reduced fecal concentrations of deoxycholic acid. Dietary caffeic acid, catechin, rutin and ellagic acid significantly reduced fecal lithocholic acid. Fecal hyodeoxycholic acid, a metabolite of lithocholic acid, was markedly lowered by dietary curcumin, caffeic acid, catechin and rutin. In experiment 2, rats were fed 30% or 5% beef tallow diet with or without the addition of 0.5% curcumin. In the rats not receiving curcumin, the fecal level of deoxycholic acid was significantly higher in the high-fat diet group than in the low-fat diet group. Fecal deoxycholic acid was significantly reduced by dietary curcumin in animals on the high-fat diet, but not on the low-fat diet. The results suggested novel effects for some polyphenols favorable for colon health by reducing secondary bile acids in animals fed a high-fat diet (22).

Phytoestrogens and cancer risk

Phytoestrogens, polyphenolic plant metabolites, have estrogenic effects in humans. Epidemiological evidence has thus far been inconsistent and it is not clear whether these compounds are beneficial or detrimental to human health. Kuhnle et al. analyzed the phytoestrogen content of 500 foods commonly consumed in the U.K. to develop the most comprehensive database to date, with more than 10,000 food items. Using this database, we determined phytoestrogen consumption in the EPIC Norfolk cohort using two dietary assessment methods (food frequency questionnaire and 7-day food diary). Kuhnle et al. have also determined urinary and serum phytoestrogens as biomarkers of intake and compared the associations between phytoestrogen intake or concentration and their metabolism and breast and prostate cancer incidence in a nested case-control study (CCS; breast cancer: 244 cases/941 controls; prostate cancer: 204/812) (23). The food diary data were more strongly correlated with biomarker concentration than the Food Frequency Questionnaire (FFQ) data (correlation coefficient for daidzein: diary, 0.46; FFQ, 0.21). In the CCS, no significant association was found between phytoestrogen intake and breast cancer. Secoisolariciresinol intake was associated with an increased breast cancer risk in age-adjusted analysis (all odds ratios [OR] for doubling intake) (OR: 1.27; $P < 0.05$). However, this association was attenuated and became nonsignificant in the multivariate analysis. Prostate cancer risk was positively associated with intake of equol (OR: 1.43; $P < 0.005$), enterolactone (OR: 1.39; $P < 0.005$) and total enterolignans (OR: 1.41; $P < 0.005$). Although this association became nonsignificant after adjustment for multiple covariates, the OR remained within 10% of the original value. Similar results were obtained when using urinary and serum biomarkers to assess intake. The metabolism of phytoestrogens was assessed using the ratio of

urinary biomarker and intake. For glycitein, a strong association was found between differences in metabolism and the risk of breast (OR: 1.3; $P < 0.001$) and prostate cancer.

POLYPHENOLS AND OXIDATIVE STRESS

Mechanisms of protection against oxidative stress: direct, indirect and bifunctional antioxidant activities

Aerobic cells are chronically injured by: 1) electrophiles, including carcinogens; 2) oxidative stress from reactive oxygen intermediates; 3) inflammation; and 4) radiation, principally of solar origin. These processes are responsible for the pathogenesis of cancer and chronic degenerative diseases. Cells also contain endogenous networks of protective mechanisms, prominent among which is the Nrf2/ARE regulatory signaling system which controls the expression of a large number of cytoprotective phase II proteins (mostly enzymes). It is now well established in cells, animals and humans that phase II gene products exert a wide spectrum of protective functions, among which combating oxidants is prominent. Under basal conditions, these protective mechanisms operate at a fraction of their capacity. Their transcriptional upregulation is easily achieved by exposure to a variety of inducers, many of which are present in edible plants (e.g., sulforaphane). Elaborate cellular mechanisms for protection against oxidative stress depend on three types of small-molecule antioxidants: 1) direct antioxidants, which are redox-active, neutralize oxidants stoichiometrically and are short-lived; mechanisms involve sulfhydryl-disulfide conversions (e.g., glutathione, lipoic acid), diphenol-quinone conversions (e.g., vitamin K, tocopherols, ubiquinol) and ascorbic acid, bilirubin, Fe^{2+} ; 2) indirect antioxidants, which act by transcriptional induction of phase II enzymes, which act catalytically, are not consumed in antioxidant action and are long-acting; these include Michael reaction acceptors, isothiocyanates, oxidizable diphenols, divalent metals and trivalent arsenicals; their universal property is reactivity with SH groups and they target SH groups of highly reactive cysteine residues of Nrf2, release Nrf2 for migration to the nucleus and activate phase II gene transcription (24).

POLYPHENOLS AND CARDIOVASCULAR DISEASE

Epidemiological studies suggest a decreased cardiovascular risk in individuals with higher intake of flavonoid-containing foods, including grapes. Several potential mechanisms have been proposed to explain such a benefit. One possibility is a favorable effect on the vascular endothelium. The vascular endothelium regulates vascular homeostasis by producing factors that act locally in the vessel wall and lumen, including nitric oxide (NO), which has vasodilating, anti-inflammatory and antithrombotic effects. In atherosclerosis, effective release of NO is reduced and this change in endothelial function is accompanied by other changes in endothelial phenotype that promote atherosclerosis. Recent studies suggest that consumption of grape products improves the function of the endothelium, which might reduce cardiovascular risk. Reduced platelet aggregation might also account for a beneficial effect of grape products, and it is well established that antiplatelet drugs such as aspirin and clopidogrel have marked effects on cardiovascular risk. Several studies have demonstrated decreased platelet aggregation following consumption of grape juice and ex vivo studies have confirmed important bio-

logical effects of grape-derived flavonoids on platelet function. Other potential mechanisms include reduced blood pressure, protection of LDL against oxidation and an anti-inflammatory effect. Collectively, these studies provide a strong rationale for recommending consumption of grapes and grape products as part of a comprehensive strategy to improve vascular health and reduce the risk for cardiovascular disease. This recommendation fits well with the overall guidelines of the American Heart Association to increase the consumption of fruits and vegetables. Finally, these important mechanistic studies raise the interesting possibility that concentrated grape products or specific grape components might be developed as food supplements or drugs. Randomized clinical trials would be required to confirm the benefit of such interventions for the primary or secondary prevention of cardiovascular disease (25).

Dietary intervention studies in humans and animals indicate that flavanol-rich foods, wine, tea and chocolate may exert blood pressure (BP)-lowering effects and other cardiovascular benefits. However, the biochemical mechanisms mediating those benefits are still under debate. To advance the understanding of the effects of flavanols on BP, Fraga used a model of induced hypertension in rats by treatment with the NO synthase inhibitor L-NAME. The addition of (–)-epicatechin (EC) in the diet (0.2–4.0 mg/g diet) significantly modulated the L-NAME-dependent BP increase in a dose-dependent manner (26). The decrease in BP was associated with the presence of EC in plasma, decrease in markers of oxidative damage, i.e., malondialdehyde, nitrated proteins and oxidized glutathione, and an increase in plasma NO. Previous findings demonstrated that EC can not only trap radicals within the cells, but also act at the membrane level, decreasing Ca and NADPH oxidase-mediated ROS production. Integrating these results, we hypothesize that such a decrease in cell oxidants could lead to optimization of steady-state NO levels, resulting in EC-induced antihypertensive and cardioprotective effects.

The intake of tea and flavonoids found in tea has been associated with a reduced risk of cardiovascular disease in numerous population studies. These studies have led to the hypothesis that tea flavonoids protect against cardiovascular disease. A number of possible pathways for cardiovascular protection by tea and tea flavonoids have been investigated. Available evidence for many of the proposed mechanisms is limited, but there is growing evidence for a benefit on endothelial dysfunction, an early event in vascular disease. The endothelium, through the production and release of vasoactive factors such as NO, plays a vital role in the maintenance of vascular homeostasis and vascular tone. In vitro studies using isolated vessels have shown that tea flavonoids possess NO-dependent vasodilating activity. Randomized, controlled trials have shown that increased flavonoid intake from tea, as well as other dietary sources, can improve endothelial function. Isolated flavonoids present in tea have also been found to improve endothelial function and increase NO status. Tea intake has been inversely associated with BP in population studies. Blood pressure-lowering with regular consumption of tea has yet to be demonstrated in randomized, controlled trials. There is mounting evidence that tea flavonoids can increase NO status, cause vasodilatation and improve endothelial function, effects which could contribute to a reduced risk of cardiovascular disease (27).

The relationship between total polyphenol excretion (TPE) in urine, as a correlate of total polyphenol intake, and BP or with the prevalence of hypertension in an elderly population at high cardiovascular risk was assessed. A cross-sectional substudy with baseline data from the PREDIMED trial was designed. Participants included 263 men and 326 women aged 55–80 years and with a high risk of coronary heart disease. The anthropometric data and BP were measured. The volunteers were divided into quartiles according to their TPE, which was measured in spot urine samples by the Folin-Ciocalteu assay. A significant positive association between TPE in urine and daily intake of fruit and vegetables, coffee or wine was observed after adjusting for potential confounders. The intake of 100 g of fruits and vegetables ($\beta = 0.150$; $P < 0.001$) contributed more to TPE than 100 mL of coffee ($\beta = 0.141$; $P = 0.001$), and the latter two foods greater than the consumption of 100 mL of wine ($\beta = 0.120$; $P = 0.019$). An inverse association between urinary TPE and the prevalence of hypertension was observed; participants in the highest quartile of urinary TPE had a reduced prevalence of hypertension compared to the lowest quartile (OR: 0.64; 95% confidence interval [CI]: 0.45–0.92; $P = 0.016$). Systolic and diastolic BP were inversely associated with urinary TPE after adjustment for potential confounders ($P = 0.025$ and $P = 0.002$, respectively). Polyphenol intake, accessed via TPE in urine, was negatively associated with BP levels and prevalence of hypertension in an elderly Mediterranean population at high cardiovascular risk. A dietary intervention directed to increase polyphenol-rich food intake may be useful in the prevention and treatment of hypertension (28).

POLYPHENOLS, ADIPOSE TISSUE AND OBESITY

Adipose function is compromised in obesity. A shift occurs from oxidative to glycolytic metabolism. This is characterized by increased tissue lactate levels and reduced mitochondrial density, the first steps to adipose tissue failure. Keijer et al. have shown in dietary intervention experiments with marine long-chain polyunsaturated fatty acids that this condition can be reversed (29). In adipose tissue, but also in other organs, these fatty acids can stimulate increased mitochondrial density and metabolism under high fat conditions, resulting in reduced body weight and improved fitness. The increased mitochondrial density is the result of mitochondrial biogenesis, which is governed by peroxisome proliferator-activated receptor gamma coactivator 1- α (PGC-1- α). PGC-1- α activity is under the control of various biochemical sensors, including AMPK (which senses AMP/ATP ratios) and SIRT1 (which senses NAD^+/NADH ratios). These sensors are both sensitive to dietary components, i.e., AMPK is sensitive to marine fatty acids, and we and others have shown that SIRT1 is sensitive to various polyphenols, including resveratrol. Indeed, dietary intervention studies in rodents show that resveratrol can induce mitochondrial biogenesis in a number of tissues and increase metabolic fitness. Polyphenols thus have the potential to counteract the negative health effects associated with obesity. Rodent dietary intervention studies, including our own studies, also show that a number of other polyphenols, including quercetin, epigallocatechin gallate and cyanidin 3-O-D-glucoside, positively affect energy metabolism.

The global prevalence of obesity has increased in the last decades. A strategy for obesity management may be consumption of green tea catechins, to sustain energy expenditure by sustaining fat free

mass at the cost of fat mass, thereby counteracting the decrease in metabolic rate during weight loss. Short-term experiments show a significant increase of 4% in 24-h energy expenditure and fat oxidation upon consumption of epigallocatechin gallate plus caffeine (EGCG/caffeine, 3 x 90/50 mg) in comparison to caffeine (3 x 50 mg) or placebo capsules; similar effects occurred after three servings of a 250-mL thermogenic beverage per day during 3 days containing 94 mg EGCG and 100 mg caffeine, or with two capsules of 150 mg EGCG/day for 3 days or 2 h after a beverage containing 161 mg caffeine and 156 mg EGCG, showing thermogenic and fat oxidative properties beyond those explained by caffeine alone. Most long-term experiments with at least 270 mg EGCG and 150 mg caffeine per day show a relative decrease in body weight, waist circumference and fat mass, while sparing fat free mass in Caucasians and Asians, by meta-analysis. Weight maintenance was shown thereafter, with sustained energy expenditure and fat free mass sparing as the major factors. The meta-analysis revealed caffeine intake and ethnicity as the main moderators. Combination with relatively elevated protein intake does not show synergism with the body weight management effect of green tea. Catechins inhibit the enzyme catechol O-methyltransferase (COMT), which degrades norepinephrine and consequently stimulates the sympathetic nerve system, thereby increasing energy expenditure and fat oxidation. Caffeine affects thermogenesis by inhibiting the enzyme phosphodiesterase. Failing synergistic or even antagonistic effects may be due to a ceiling effect due to use of the same pathways (30).

FLAVONOIDS AND BRAIN HEALTH

Emerging evidence suggests that dietary phytochemicals, in particular flavonoids, may exert beneficial effects on the CNS by protecting neurons against stress-induced injury, suppressing neuroinflammation and improving cognitive function. Historically, they were believed to do this via an ability to express classic antioxidant activity in the brain. However, their poor brain bioavailability and extensive metabolism mean that this is unlikely. Instead, their actions on the brain appear to be mediated by two separate mechanisms. Firstly, they interact with critical protein and lipid kinase signaling cascades in the brain, leading to an inhibition of neurotoxin-induced apoptosis and the promotion of synaptic plasticity. For example, their ability to activate the extracellular signal-regulated kinase (ERK-1 and -2) and the protein kinase B (PKB/Akt) signaling pathways leads to activation of cAMP response element-binding protein (CREB), a transcription factor responsible for increasing the expression of a number of neurotrophins critical in memory processing. Secondly, they induce effects on the vascular system which lead to changes in cerebrovascular blood flow capable of causing angiogenesis, neurogenesis and changes in neuron morphology. Through these mechanisms, the consumption of flavonoid-rich foods throughout life holds the potential to limit neurodegeneration and to prevent or reverse age-dependent losses in cognitive performance (31).

Cocoa flavanols (CF) positively influence physiological processes in ways which suggest that their consumption may improve aspects of cognitive function. The first randomized, controlled, double-blind, balanced, three-period crossover study investigated the acute cognitive and subjective effects of CF consumption during sustained mental demand. Following baseline measurements, 30 healthy adults

consumed drinks containing 520 or 994 mg CF and a matched (low flavanol) control. Assessments included the State Anxiety Inventory and the Cognitive Demand Battery comprised of repeated cycles of two serial subtraction tasks (Serial Threes and Serial Sevens), a Rapid Visual Information Processing (RVIP) task and a "mental fatigue" scale over the course of an hour. Compared with controls, consumption 520 and 994 mg CF significantly improved Serial Threes performance. The 994-mg CF beverage significantly accelerated RVIP responses but also resulted in more errors during Serial Sevens. Increases in self-reported "mental fatigue" were significantly attenuated by consumption of the 520-mg beverage only. In a separate study, the same CF treatments had no acute effects on cognitive performance where there was little cognitive demand involved in task performance. This is the first report of acute cognitive improvements following CF consumption in young adults. While the mechanisms underlying the effects are unknown, they may be related to the known effects of CF on endothelial function and blood flow. The talk also briefly presented data from new studies describing the effects of other polyphenols (from tea and cocoa) on neurocognitive function, cerebral blood flow, endothelial function and brain bioelectrical activity (32).

PERSONALIZED NUTRITION: OPPORTUNITIES AND CHALLENGES

There is growing interest in the epigenetic mechanisms that influence cancer development, including the reversible acetylation of histones. Histone deacetylase (HD) inhibitors de-repress epigenetically silenced genes in cancer cells and some HD inhibitors show promise in the clinical setting. A growing body of evidence also suggests that dietary HD inhibitors may play a role in cancer prevention; sulforaphane, butyrate and various natural **organo sulfon** and organoselenium compounds exhibit HD-inhibitory activity. The literature is also replete with studies of tea polyphenols and their purported anticancer mechanisms, including effects on epigenetic endpoints. Dashwood et al. tested the isothiocyanate sulforaphane and the green tea polyphenol EGCG as inhibitors of polyp formation in the *Apc^{min}* mouse (33). Whereas each compound alone inhibited tumorigenesis, no suppression was observed for their combination. Mechanistic studies are in progress seeking to clarify the reason(s) for the loss of chemopreventive activity, and whether other tea polyphenols might be more effective. Although cooperative effects were not realized for sulforaphane and EGCG under these experimental conditions, further studies are warranted on alternative combinations of test agents and HD inhibitors.

Results from other studies presented at the meeting are summarized in Table I, published in the online version only.

CONCLUSIONS

The study of the relationship between diet and chronic disease in humans dates back more than 50 years, but the study of specific food components beyond vitamins and macronutrients in relation to chronic disease is relatively recent, showing a great re-emergence. There is a continued stream of new discoveries of compounds in foods or biological effects of such compounds. Scientists, nutritional experts and public health professionals felt that they have many challenges for the future, but ultimately they will need to work

together to create a more coherent message of our greatest strengths and their implications for improving human health. Of our many challenges, we need to continue to create or update food composition databases with the infrastructure in place to refine methods and document variability in foods and variability over time, as common varieties change and growing methods evolve. Related to this, we need accurate dietary assessment in large-scale human population studies. Methodologies are constantly being developed and improved upon and should be carefully considered with respect to phenolic compounds. All have strengths and biases, but the important issue is to assess and document how well each measures specific phenolic compounds and how they can be used in concert with other measures to obtain the best possible assessment of intake. The accurate assessment of biomarkers of intake may be the most challenging for the future decade, but also may be the most important for large-scale prospective studies. In many studies where thousands of samples are stored, specific biomarkers of phenolic compounds may be too unstable or may not give an accurate assessment of long-term exposure. Thus, there is a need to turn to metabolites or downstream markers related to oxidation and DNA damage. Finally, for some nutritional components there may be no effective and sufficiently stable marker. For these challenges, we may need to turn to the use of genetic markers related to the efficiency of nutrient absorption or metabolism as a marker of exposure before we can estimate the potential risks or benefits. Ultimately, in an era of evidence-based medicine, the final, most effective science will be that where we "reach across the aisle" and join food scientists with nutritional biochemists and nutritional epidemiologists to find those foods, nutritive compounds and biological pathways where there is the greatest potential to document and improve human health. The next International Conference on Polyphenols and Health in Europe in 2011 will be an excellent platform to discuss novel findings in the field of polyphenols.

DISCLOSURES

The authors state no conflicts of interest. This is not an official publication from ICPH2009, and this publication has not been endorsed by the conference organizers.

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Table I. Summary of studies on polyphenols presented at the 4th International Conference on Polyphenols and Health.

Ref.	Polyphenols/plants/natural interventions	Study design	Outcome
34	Anthocyanin metabolites: gallic acid, 3-O-methylgallic acid, 2,4,6-trihydroxybenzaldehyde and malvidin-3-glucoside	In this study gallic acid, 3-O-methylgallic acid, 2,4,6-trihydroxybenzaldehyde and malvidin-3-glucoside were incubated with Caco-2 cells and investigated for modulation of Caco-2 cell viability, cell cycle and apoptosis	Results suggested that anthocyanin metabolites are the basis for the protective effect of anthocyanin in colon cancer
35	Blueberry	The anticancer properties of an anthocyanin-pyruvic acid adduct were studied using the ER ⁻ MDA-MB-231 and ER α ⁺ MCF7 cancer cell lines	Anthocyanin-pyruvic acid adduct showed a more pronounced effect on MDA-MB-231 cells, suggesting an effect independent of the estrogen receptor
36	Strawberry fruit	Strawberry fruits of 8 different commercially available varieties were evaluated for standard nutritional parameters by measuring the total antioxidant capacity, total phenolic, total flavanoid and total anthocyanin contents of the strawberry extract. Three pilot studies were conducted in the screened participants and antioxidant status was evaluated by measuring the strawberry-dependent variations in plasma total antioxidant capacity (TAC)	The F1 and F2 crosses of <i>Fragaria ananassa</i> and <i>Fragaria virginiana</i> var. <i>glauca</i> were among the richest sources of antioxidants, the phenolic compounds and vitamin C. Pilot studies in the participants showed increases in plasma TAC and vitamin C concentration
37	Elderberry anthocyanins	In this parallel, randomized clinical trial the effect of 12-week consumption of 500 mg of anthocyanins on biomarkers of cardiovascular disease (CVD) risk and liver and kidney function were examined in 52 subjects	Daily consumption of physiologically relevant doses of elderberry extract did not induce detrimental changes in liver and kidney function and did not alter biomarkers of CVD risk
38	Black currant juice	In a randomized, double-blind study, the effect of 20% black currant juice on the vascular function, phytochemical metabolites, antioxidant status and risk factors for CVD were investigated in 20 volunteers. Blood samples were taken periodically for 8 h and urine samples were collected periodically for 24 h. Vascular reactivity was investigated by laser Doppler imaging with iontophoresis	The acute consumption of 20% black currant juice did not significantly alter the markers of endothelial function. Plasma vitamin C and insulin concentrations increased significantly. There were no significant treatment effects on the oxidative stability of plasma assessed by ORAC and FRAP
39	Bilberry extract	The effect of anthocyanins extracted from untreated bilberries (BE) and yeast-fermented bilberries (FBE) on the development of atherosclerosis was studied in apolipoprotein E-deficient (ApoE ^{-/-}) mice	BE contained 52% anthocyanins, whereas anthocyanins in FBE were largely condensed into polymeric pigments during fermentation. The atherosclerotic lesions were decreased by 15% and 30%, respectively, in BE- and FBE-supplemented ApoE ^{-/-} mice, suggesting that the fermentation may generate bioactive compounds with improved health-promoting properties
40	Bilberry-anthocyanin	This study aimed to explore the mechanisms involved in the antiatherosclerotic action of a bilberry-anthocyanin-rich extract in ApoE ^{-/-} mice by a high-throughput transcriptomic approach measuring gene expression in the aorta and liver	Bilberry-anthocyanin supplementation attenuated atherosclerotic lesion development by 15%. Anthocyanins significantly reduced plasma total cholesterol and hepatic triglyceride levels after 4 weeks of diet. Anthocyanin supplementation also modified the expression of 1,261 aortic genes and 2,289 hepatic genes
41	Bilberries (<i>Vaccinium myrtillus</i> L.)	The protective role of bilberry extract on ischemia/reperfusion injury in the isolated rat heart was studied. Postischemic myocardial injury during reperfusion was determined by changes in coronary flow rate, lactate dehydrogenase release rate, electrocardiogram analysis, incidence and duration of arrhythmias	The duration of arrhythmias was maximally shortened at 0.1 mg/L to 3.2 \pm 0.2% and at 1 mg/L to 4.4 \pm 0.3% of the control value from the untreated group. These results indicate that bilberry extract has anti-ischemic and antiarrhythmic activity in isolated rat hearts subjected to ischemia/reperfusion injury

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Table I. Cont. Summary of studies on polyphenols presented at the 4th International Conference on Polyphenols and Health.

Ref.	Polyphenols/plants/natural interventions	Study design	Outcome
42	Raspberries	To identify the urinary excretion of urolithins and phenolic acids following a single intake of 300 g of raspberry smoothie in 10 human volunteers, urine was collected 24 h before intake and at 0-2, 2-8, 8-24, 24-32 and 32-48 h after the ingestion of raspberries and analyzed by HPLC-MS and GC-MS	HPLC-MS showed the presence of urolithin A glucuronide, two isomers of urolithin A glucuronide and urolithin B glucuronide. Urolithin A is the main microbial metabolite and the main excretion period was 24 h after raspberry intake. GC-MS showed the presence of phenolic acid derivatives, identified as 3-hydroxyphenylacetic acid, 4-hydroxyphenylacetic acid, 4-hydroxybenzoic acid, 3-methoxy-4-hydroxyphenyl acetic acid, 3-hydroxy-mandelic acid, hippuric acid 3-(3-hydroxy-phenyl)-3-hydroxypropionic acid
43	Elderberry anthocyanins	This study investigated whether chronic consumption of a high anthocyanin-supplemented diet affected the absorption or metabolism of a bolus anthocyanin dose in 26 subjects who received 500 mg elderberry anthocyanin daily for 12 weeks	The results showed that the chronic consumption of elderberry polyphenols does not significantly alter the absorption of anthocyanin, but has a moderate effect on their metabolism
44	Anthocyanins	The aim of this study was to assess (via HPLC-DAD-MS) the degradation and experimental recovery of anthocyanins and their phenolic acid constituents under simulated physiological (spiked bovine serum or 10 mM Na/K phosphate buffer at 37 °C, pH 7.4) and storage conditions (–80 °C)	The results showed that the disappearance of anthocyanins in buffer occurred at a rate of 3.3, 4.5 and 11.4 pM/h, respectively, for pelargonidin-3-glucoside, cyanidin-3-glucoside and delphinidin-3-glucoside, representing a loss of 20, 40 and 100%, respectively, over 12 h. However, the appearance of phenolic acid degradation products (protocatechuic, 4-hydroxybenzoic and gallic acid) only accounted for 12, 9 and 2%, respectively, of the loss of pelargonidin-3-glucoside, cyanidin-3-glucoside and delphinidin-3-glucoside. The recovery of anthocyanins from acidified serum samples was 80-95%, with the lowest recovery recorded for cyanidin-3-glucoside
45	Cyanidin-3-glycosides	This study was done to explore the bioavailability of anthocyanins following consumption of 720 mg cyanidin-3-glycosides	It was reported that the cumulative concentration of total parent and metabolite species over 7 h was 376 nmol and the total urinary excretion over 24 h was 1071 µg
46	Aglycone cyanidin	The aim of this study was to examine the absorption, distribution and metabolism of the aglycone cyanidin in rats. The concentrations of cyanidin and its metabolite were determined by LC-DAD-MS	Cyanidin was metabolized to methylated and glucuronidated derivatives, and the degradation products protocatechuic acid, vanillic and isovanillic acid. The total amount excreted corresponded to $0.08 \pm 0.01\%$ of cyanidin ingested
47	Bilberry	This study was done to determine the absorption and excretion fate of bilberry anthocyanins in mice	After oral administration of bilberry extract (100 mg/kg) both unmodified and methylated anthocyanins appeared in the plasma. The plasma concentration of total anthocyanins reached a maximum of $1.2 \pm 0.3 \mu\text{M}$ after 15 min and then sharply decreased. Bilberry anthocyanins were absorbed in the body and distributed in specific organs, particularly the liver, kidney and testis. The physiologically common anthocyanins were malvidin glycosides

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Table I. Cont. Summary of studies on polyphenols presented at the 4th International Conference on Polyphenols and Health.

Ref.	Polyphenols/plants/natural interventions	Study design	Outcome
48	Blueberries (<i>Vaccinium corymbosum</i> L.)	In a crossover design, 11 healthy human volunteers consumed either 200 g of blueberries plus 200 mL of water or 200 g of blueberry fruits plus 200 mL of whole milk. Venous samples were collected at baseline and at 1, 2 and 5 h postconsumption	When blueberries and milk were ingested there was no increase in plasma antioxidant capacity. There was a reduction in the peak plasma concentration of caffeic and ferulic acid, as well as the overall absorption (AUC) of caffeic acid ($P < 0.001$). The ingestion of blueberry together with milk thus impairs blueberry's in vivo antioxidant properties and reduces the absorption of caffeic acid
49	Anthocyanidins	This study was aimed at establishing the potential of anthocyanin phenolic acids to form glucuronide metabolites following hepatic metabolism. The cyanidin pelargonidin and its physiological degradation products procatechuic acid and 4-hydroxybenzoic acid, were incubated in the presence of human liver microsomes to assess their potential to form glucuronides	Results showed that the primary glucuronide metabolite of pelargonidin and its degradation product 4-hydroxybenzoic acid were likely to be acyl glucuronide species
50	Bilberry	In this study the antioxidant efficiency of an anthocyanin-rich bilberry extract was investigated in vitro in the human adenocarcinoma cell lines Caco-2 and HT-29. The reactive oxygen species (ROS) levels were investigated by the dichlorofluorescein assay. Oxidative DNA damage was monitored by single-cell gel electrophoresis (comet assay)	The data revealed that the bilberry extract decreased ROS levels in HT-29 and Caco-2 cells in a concentration-dependent manner. Slight decreases in induced DNA damage were detected in bilberry extract-treated cells by the comet assay. At a concentration of 10 µg/mL the extract significantly reduced ROS
51	Bilberry (<i>V. myrtillus</i> L.)	The preventive effect of bilberry extract and its major anthocyanins and inflammatory gene expression in specifically stimulated human colon epithelial cells was investigated by quantitative real-time PCR	The bilberry extract and associated anthocyanins modulated inflammatory genes in vitro and a transcription-based inhibition of proinflammatory gene expression was observed
52	Raspberry	To study the metabolic fate of raspberry polyphenols within the human gastrointestinal system, particularly the colon, the phenolic composition of fecal water samples was analyzed from 10 human subjects before and after supplementation of a normal diet with raspberry puree (200 g/day for 4 days) using gas chromatography-mass spectrometry	The majority of the subjects gave phenolic profiles consistent with model studies with fecal inocula, and supplementation increased levels of phenylacetic acid, 4-hydroxyphenylacetic acid and 3-hydroxyphenylacetic acid. The colonic microflora were not significantly altered
53	Black currants, blueberries and boysenberries	To identify the minor polyphenolic compounds (PC) in black currants, blueberries and boysenberries	Investigation detected 30-50 minor components in each berry species. Some of these compounds showed a large variation in concentration among cultivators
54	Blueberry and chokeberry	To study polyphenolic metabolism in blueberry- and chokeberry-fed mice with or without the addition of <i>Lactobacillus plantarum</i> HEAL19 subjected to intestinal oxidative stress by ischemia/reperfusion. Ischemia/reperfusion injury in mice was induced by clamping the superior mesenteric artery for 30 min followed by reperfusion for 240 min. Polyphenolic profiles in the cecum and colon content were determined by HPLC-MS-MS and lipid peroxidation levels were determined by measuring malondialdehyde (MDA)	Eleven anthocyanins were identified in the colon and 8 anthocyanins in the cecum of blueberry-treated groups. Three anthocyanins were found in both colon and cecum of the chokeberry-treated groups. It appears that blueberry prevents lipid peroxidation and oxidative stress more efficiently than chokeberry, and the addition of <i>L. plantarum</i> HEAL19 influenced the metabolism of polyphenols in both colon and cecum

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Table I. Cont. Summary of studies on polyphenols presented at the 4th International Conference on Polyphenols and Health.

Ref.	Polyphenols/plants/natural interventions	Study design	Outcome
55	Blueberry	The effect of chronic blueberry intervention on spatial working memory in both young (1 month) and aged (18 months) rats was investigated. Rats were fed with control or control plus blueberry (2% w/w) diets for a total of 6 weeks. Spatial memory was assessed in the 8-arm radial maze or the T-maze. Hippocampal gene expression was also tested using RT2 profiler PCR assays	The blueberry intervention significantly increased spatial working memory task performance in both young and aged animals. The chronic supplementation of aged animals with pure flavanol (catechin and [–]-epicatechin) or a purified blueberry extract revealed that the flavanol intervention resulted in a pattern of cognitive improvement very similar to that observed following blueberry intervention. Profile of 83 genes related to neuronal cell growth, differentiation, neuronal regeneration, apoptosis and survival supported the evidence linking flavanoid-rich food with improvement in memory and cognition
56	Black currant	PC which are abundant in black currant that could alleviate neurotoxicity were assessed using the cell culture model of Alzheimer's disease. Biochemical changes related to neuroprotection, cell survival and oxidative stress parameters were evaluated	The flavanoids quercetin and myricetin inhibited production of ROS in the cell lines. The observed neuroprotective function of quercetin and myricetin will help design special foods for elderly people who are at high risk for Alzheimer's disease
57	Mulberry (<i>Morus atropurpurea</i> L.)	The effect of mulberry extracts (ME) rich in phenolics and anthocyanins on the induction of antioxidant enzyme and the promotion of cognition in senescence-accelerated mice (SAMP) was evaluated. Six-month-old SAMP1 and SAMP8 mice were supplemented with 0.18% and 0.9% ME for 12 consecutive weeks	ME-treated mice showed significantly less β -amyloid protein and improved learning and memory ability in the conditioned avoidance response test. Biochemical evaluation showed higher antioxidant activity and less lipid oxidation in both the brain and liver. ME also decreased the levels of serum aspartate aminotransferase, alanine aminotransferase, triglycerides and total cholesterol, which increase with aging
59	Cranberry fruit powder	The objective of this study was to evaluate the efficacy and tolerability of cranberry fruit powder (CFP) in men at risk of prostate diseases with lower urinary tract symptoms (LUTS), elevated prostate-specific antigen (PSA), negative prostate biopsy and clinically confirmed chronic nonbacterial prostatitis. In a pilot randomized clinical study a cohort of 42 volunteers were enrolled to receive either 1500 mg/day of CFP containing 14.85% organic acids, 15.5% sugars, 0.11% anthocyanins, 1.95% tannins and 3.49% phenolics for 6 months or no treatment	In the CFP-treated subjects there were statistically significant improvements in International Prostate Symptom Score (IPSS), urinary parameters including rate of urine flow, average flow, total volume and postvoid residual urine volume, and lower PSA _{tot} levels on day 180 of the study. There was no influence on blood testosterone levels. No improvement was found in the control group (n = 21)
60	Raspberry and blackberry	Structure elucidation and quantification of native compounds was carried out using UPLC acquity and QTOF-HDMS synapt (waters). The 59 raspberry and 36 blackberry extracts were included in the study. Sanguin H6 and lambertianin C were quantified as respective standard equivalents	The presence of 14 ellagitannins and 8 ellagitannins in the raspberry extract and 17 ellagitannins and 5 ellagitannins in the blackberry extracts was confirmed. High variability among cultivators was observed

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Table I. Cont. Summary of studies on polyphenols presented at the 4th International Conference on Polyphenols and Health.

Ref.	Polyphenols/plants/natural interventions	Study design	Outcome
	Flavanoids	The ability of berry-derived flavanoids to protect against neuronal damage by attenuating the neuroinflammatory process and protecting against 5-S-cysteinyl-dopamine-induced neuronal injury was examined	The flavanols (+)-catechin and (–)-epicatechin, but not the anthocyanidins cyanidin and pelargonidin, attenuated lipopolysaccharide (LPS)/interferon gamma (IFN- γ)-induced TNF- α production in glial cells. The formation of 5-S-cysteinyl-dopamine and dihydro-benzothiazine species in the presence of peroxynitrite induced significant neuronal injury. The treatment of primary cortical neurons with pelargonidin and the 4'-O-Me derivative of catechin and ellagitannin (0.1–3.0 μ M) resulted in concentration-dependent protection against 5-S-cysteinyl-dopamine-induced neurotoxicity
62	Ascorbic acid	This study describes a simple, rapid and low-cost sensor based on the enzyme-less amperometric determination of ascorbic acid in black currant and strawberries using disposable platinized screen-printed electrodes	The study showed a good correlation when comparing ascorbic acid concentration as determined using a newly developed sensor to that measured with the standard HPLC coupled to UV detection
63	Strawberry	The qualities and the nutraceutical compounds in fresh and stored strawberry fruits were compared. Five Italian strawberry genotypes were selected: Onda, Unica, Zeta and selections 148.5 and 136.7, grown in the Cesena area, using cold-stored plants planted on fumigated soil	The results showed a lower antioxidant capacity of the stored fruits
64	Berries and rye porridge	Plasma kinetics and urinary excretion of the polyphenols in humans after ingestion of berries (1000 mg) and rye porridge (76 mg) were studied using a crossover study. Plasma and urine polyphenols were analyzed by GC-MS and HPLC and berry polyphenols by HPLC	Polyphenols were absorbed in humans, but there were large interindividual variations in the plasma concentrations of the compounds
65	Black currant	Temporal changes during ripening and storage in different genotypes of black currant were studied. Three different development stages –early ripe, fully ripe and overripe– were chosen when fruit was at commercial maturity	Anthocyanin concentration was nearly double in overripe berries compared to early ripe. Post-harvest storage led to enhanced synthesis of anthocyanins. Temperature during storage significantly affected anthocyanin concentration in fully ripe but not in early ripe berries
66	Blueberry flavanoids	This study investigated the behavioral and molecular actions of blueberry flavanoids on memory and cognition	It was suggested that the activation of extracellular signal regulated kinase (ERK1/2) and the protein kinase B (PKB/Akt) signaling pathway led to the activation of cAMP response element binding protein (CREB), a transcription factor responsible for increasing the expression of the number of neurotrophins critical in memory processing.
67	Blackberries (<i>Rubus fruticosus</i> L.)	Antioxidant capacity and some of the chemical properties of 58 wild blackberries and 7 commercial cultivars with foreign (Jumbo, Chester, Navaho, Waldo) and local origin (Bartin, Bursa1 and Bursa2) were compared in the study. Antioxidant capacity of fruits was determined by FRAP and Trolox [®] equivalent antioxidant capacity (TEAC) assays	The antioxidant capacity among wild varieties averaged 23.6 and 30 μ mol TE/gfw compared to cultivated blackberry displaying 9.2 and 14.1 μ mol TE/gfw, respectively, by the FRAP and TEAC methods. Total phenolic mean of wild blackberries was 6475 mg GAE/gfw compared to 4046 mg GAE/gfw in cultivated berries. Results indicate that wild blackberries may have higher phytonutrient content than cultivated blackberries

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Ref.	Polyphenols/plants/natural interventions	Study design	Outcome
68	European elderberry (<i>Sambucus nigra</i> L.)	The anthocyanin, total phenolic and antioxidant activity of three wild-grown elderberries was determined. Antioxidant activity was determined by FRAP assay	There were differences among genotype in terms of total anthocyanins (556-859 mg/100 gfw). The genotype with the highest total antioxidant capacity and total phenolic content was BSEA3 (7.01 mmol/100 gfw and 463 GAE/10 gfw). The cyanidin-based anthocyanins determined in the black elderberry genotype were cyanidin 3-sambubioside, followed by cyanidin 3-glucoside, cyanidin 3-sambubioside-5-glucoside, cyanidin 3,5-diglucoside and cyanidin 3-rutinoside. The most abundant anthocyanin was cyanidin 3-sambubioside
69	<i>Lonicera caerulea</i>	The antioxidant action of <i>L. caerulea</i> extract was evaluated in healthy rats. The total antioxidant capacity, lipid hydroperoxides, thiobarbituric acid reactive substances (TBARS), uric acid, albumin and ceruloplasmin were assayed in plasma drawn from the animals	<i>L. caerulea</i> berry extract induced a decrease in certain oxidative stress markers, including lipid peroxides, TBARS and ceruloplasmin
70	<i>L. caerulea</i> , <i>Aronea melanocarpa</i> and <i>Berberis vulgaris</i>	This study extending over 3 years investigated the anthocyanin and tannoid composition of 25 varieties and selections of honeysuckle, two selections of barberry and one variety of chokeberry	The total anthocyanins in honeysuckle genotype ranged in large limits from 10,183 mg% to 61,100 mg%; the richest of these compounds were the following selections: SL-6 (6110 mg%), SL-17 (55,397 mg%), SL-18 (51,324 mg%), SL-20 (51,230 mg%), SL-15 (50,052 mg%), SL-22 (45,621 mg%). The nero chokeberry variety was also rich in anthocyanin (50,916 mg%) and barberry selection B-V-5 and B-V-6/95 accumulated between 5906 mg% and 7943 mg%. The barberry selection and nero chokeberry contained high content of tannoids (0.640-0.673% and 0.762%, respectively)
71	Strawberry (<i>Arbutus unedo</i>)	The antioxidant and mellanoproteinase-inhibitory activities of polyphenol-enriched fractions of the fruit and leaves of <i>A. unedo</i> were investigated. The extract was fractionated using SPE column C18-E. Phenolic profiles were determined by HPLC-MS	Regarding the fruit extract, the polyphenol yield was < 20 when fractionated through SPE column and exhibited 200% antioxidant activity when compared with the crude extract. The polyphenol yield was 50% when fractionated through SPE column, while maintaining the antioxidant activity after fractionation. For the MMP-9-inhibitory activity, the respective IC ₅₀ values for fruit- and leaf-enriched fractions were 1681 and 1308 mg GAE/mL
72	Crowberry (<i>Corema album</i>)	Total phenolic content and in vitro antioxidant properties of the extract were evaluated by ORAC assay. The extract was also evaluated for intracellular radical-scavenging properties in an oxidative stress model of neurodegeneration in SK-N-MC cells using cell titer blue	The ratio of ORAC/total polyphenols is much higher for <i>C. album</i> fruit (2070 µmol TE/mgGAE) in comparison with <i>Rubus idaeus</i> fruit (1160 µmol TE/mgGAE). Pretreatment with the extract of <i>C. album</i> fruits protected the cell from oxidative stress injury, as detected by an increase in cell viability up to 75% with 175 µg/mL of GAE compared with 36% for 50 µg/mL of GAE for <i>R. idaeus</i> fruit

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Table I. Cont. Summary of studies on polyphenols presented at the 4th International Conference on Polyphenols and Health.

Ref.	Polyphenols/plants/natural interventions	Study design	Outcome
73	<i>Vaccinium</i> spp. fruit	The biochemical content of the blueberry fruit grown in Latvia, i.e., <i>V. myrtillum</i> L., <i>V. angustifolium</i> L., <i>V. corymbosum</i> L., <i>V. corymbosum</i> X and <i>V. angustifolium</i> were analyzed for phenolic, anthocyanin, vitamin C and total acid content	In cultivars of <i>V. corymbosum</i> L., <i>V. corymbosum</i> X and <i>V. angustifolium</i> total phenol content on average was 240 mg/100 g, total anthocyanin content was 79 mg/100 g and chlorogenic content was 18.1 mg/100g. In fruits of <i>V. angustifolium</i> L. the highest content of chlorogenic was found (on average 88.5 mg/g)
74	Black currant	The aim of the study was to evaluate the biochemical content of black currant varieties and hybrids grown in the Latvian State Institute. The study included 59 varieties which are mainly of Russian and Scandinavian origin, tested for the content of soluble solids, organic acids, phenolics, anthocyanins and vitamin C	The highest content of total polyphenols was found in the hybrids bred using varieties of Scandinavian origin. Six hybrids had total content of anthocyanin > 240 mg/100 g. Two varieties with total content of organic anthocyanin of < 2% and nine black currant varieties and hybrids with a content of soluble solids of 19-20% on average were selected
75	Strawberry and red raspberry	The objective of this project was to study the agricultural biodiversity of small berries, strawberry and red raspberry. The fruit nutritional quality and nutraceutical value were studied using the following analytical methods: TAC, TEAC, total phenolics (TP) by folin Ciocalteu's reagent method	The results showed a large variability among genotypes and the highest value of fruit nutritional quality and nutraceuticals was detected for some old accession. This variability was also influenced by the different cultivation locations and year of cultivation
76	Bilberries (<i>V. myrtillus</i> L.)	The antioxidant efficiency of bilberry anthocyanins was investigated in vitro in the human adenocarcinoma cell lines Caco-2 and HT-29. Modulation of intracellular ROS levels was investigated by the dichlorofluorescein assay. Oxidative DNA damage was monitored by single gel electrophoresis (comet assay)	Anthocyanins from bilberries decreased the intracellular ROS levels in HT-29 and Caco-2 cells in a concentration-dependent manner, with the greatest reduction achieved at the concentration of 10 µg/mL. A slight decrease in induced DNA damage was detected in anthocyanin-treated cells by the comet assay
77	Black currant juice	The study was designed to evaluate changes in black currant juice anthocyanins during storage in a refrigerator and at room temperature. The anthocyanin content was analyzed using HPLC	The decrease in the anthocyanin content was remarkably higher at room temperature than in the refrigerator. After 1 month of storage in the refrigerator it still had approximately 80% of the initial anthocyanins, while only 40% remained in the juice stored at room temperature
78	Black currant juices	Variations in the anthocyanin content among commercial juices purchased from Finland, Poland, Germany and the U.K. were analyzed by HPLC	There was 14-fold variation in the content of anthocyanins in the 12 analyzed European black currant juice trademarks (4.3-58 mg/2.5 dL), and the mean anthocyanin content varied widely among Finnish, British, Polish and German juices (11.9, 7.45, 32.0 and 38.6 mg/2.5 dL, respectively)
79	Black currant	Biochemical analysis of 4 perspective selections (10B, 2-96-51, 1-96) and 4 new cultivars (karri, Almo, Ats, Elo) from their own breeding program and 8 introduced cultivars (ojebyn, Zagadka, BenSarek, Intercontinental, Pamyati Vavilova, Titania, Pilenai) was presented	The highest anthocyanin content was found in cultivar Almo (1046.1 µg/kg) and the lowest in BenSarek (212.7 µg/kg)

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80	Siliceous lignin	The aim of the study was the assessment of the siliceous lignin at different berries cultivation	The positive effect of siliceous lignin application was observed in growing of strawberry and coffee from seeds, grapes and currant propagation by cutting and transplantation of strawberry and raspberry meristem seedling from in vitro to in vivo. The effect of siliceous lignin was explained by its elicitor properties, auxin-like activity, as well as activation of agronomically useful soil microbiota
81	<i>Pinus halepensis</i>	<i>P. halepensis</i> fresh, dry needles and bark water extract, as well as bayberry and blueberry extracts, were studied for their hypoglycemic effect in Skh:HR-2 mice	A marked and significant decrease in glucose levels was observed in both normal and diabetic mice
82	<i>P. halepensis</i> , tayberry and blueberry	The toxic effect of tobacco smoke was studied in vitro in murine keratinocytes and protection was also studied in vitro using rich phenolic antioxidant compounds <i>P. halepensis</i> bark extract, tayberry and blueberry extract. Cell viability was evaluated by microscopy and MTT assay and oxidative stress by fluorescence microscopy and fluorescence measurement	In vitro microscopy observation and MTT assay showed a toxic effect of cigarette smoke on keratinocytes. In vivo the results showed that UV light and cigarette smoke may act synergistically, as indicated by enhanced oxidative stress, transdermal water loss, squamous cell carcinoma and increased concentration of vitamin D ₃
83	Bioactive compounds in Indian foods	This study was designed to investigate the bioactive compounds in Indian foods commonly consumed in the U.K.	The database of the food components was elaborated and 109 bioactive compounds related to cardiometabolic effects were identified. Reported bioeffects of the components included in the study were largely related to dyslipidemia
84	Phenolic compounds	In this study a database of experimental and predicted phenolic compounds based on high-quality NMR data was presented	A molecule is considered a match if the mass is within 1-2 ppm deviation from that obtained from MS (and/or MS/MS) accurate mass and the predicted 1H-NMR spectrum correctly matches the 1H NMR experimental spectrum
85	Blueberry	The level of anthocyanins in the cortex, cerebellum, midbrain and diencephalogram at 18 h after feeding in pigs fed with 2% whole freeze-dried blueberries in the diet for 8 weeks was studied	Anthocyanins were measured in fm/g, with glucuronides at 1/10th levels of parent anthocyanins
86	Red wine polyphenolic extract	The aim of the study was to determine whether a red wine polyphenolic extract (RWP, a rich source of polyphenols; 2.9 g/L) induced apoptosis in human leukemia cells (Jurkat cells) and to determine the underlying mechanism	RWPs concentration-dependently reduced Jurkat cell viability and proliferation, and induced apoptosis. Cell cycle analysis indicated that RWPs arrested the cell cycle in the G ₀ /G ₁ phase. RWPs significantly increased the formation of ROS in Jurkat cells. Intracellular scavengers of superoxide anions (MnTMPyP, MnTBAP, PEG-SOD) prevented the RWP-induced formation of ROS and apoptosis, while native extracellular superoxide dismutase (SOD) was without effect. In addition, RWPs reduced the expression of UHRF1 and increased that of p73 and activated caspase-3; MnTMPyP prevented these responses

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87	Red wine polyphenols	This study investigated the effects of RWPs on the embryonal carcinoma cell line P19, which was grown in the same culture conditions as the most appropriate normal cell line counterpart, the pluripotent embryonic fibroblast cell line NIH/3T3	Findings indicate that RWPs inhibited the proliferation of P19 cells and induced G ₁ cell cycle arrest in a concentration-dependent manner, without affecting the growth of NIH/3T3 cells. Moreover, RWP treatment specifically triggered apoptosis of P19 cells, together with a marked upregulation of the tumor suppressor gene p53 and caspase-3 activation. Thus, a p53-dependent induction of apoptosis in cancer stem-like cells may contribute to the chemopreventive activity of RWPs on tumor development
88	Grape seed procyanidins	The aim of the study was to evaluate mechanisms of procyanidins (PROs) involved in modulation of doxorubicin (DOX)-induced toxicity against tumor cell lines. Procyanidins were extracted from grape seeds by ethylacetate and water. Semiquinone radical of DOX was determined by electron spin resonance (ESR) spectrometer and NADPH: cytochrome P450 reductase activity was measured by the method based on cytochrome c reduction in the presence of NADPH. Cytotoxicity of PROs, DOX or DOX and PROs against tumor cell lines was estimated by the MTS/PMS assay	PROs decreased the ESR signal. PROs and DOX competitively inhibited the activity of NADPH:cytochrome P450 reductase. PROs did not significantly influence K-562, MCF7 and L929 cell growth. The strongest inhibition of DOX cytotoxicity was obtained when PROs were added to culture simultaneously with DOX. PROs were the most active when they were simultaneously present with DOX in culture or reaction mixtures. It was suggested that PROs reduce oxidative metabolism of DOX and toxic effects of DOX mainly by inhibition of cytochrome P450
89	Anthocyanin	This study investigated the preference in mice for maize with or without anthocyanin (specifically three colors of anthocyanins: blue, yellow and mixture of the two)	Mouse intake per 3 days for blue was 1.83 ± 0.85 g, yellow 1.78 ± 0.73 g and mixture blue 0.89 ± 0.32 and yellow 0.89 ± 0.33 . It was concluded that anthocyanin does not affect the preference for maize in mice
90	Punicalagin	We have evaluated the radical-scavenging activity of punicalagin metabolites against the stable free radicals DPPFT (hydrogen and electron transfer) and HNTTM (electron transfer exclusively). Their antiproliferative activity (IC_{50}), apoptosis and pro-oxidant activity was measured in the normal colon cell line NCM460 and the colon cancer cell line HT-29. Also, the reactivity of dimethyl-4,4',5,5',6,6'-hexahydroxy-2,2'-diphenolate (DMHD), a synthetic fragment of ellagic acid, was evaluated as the potentially responsible moiety for the activity of punicalagin	DMHD and urolithin A inhibit cell growth with lower IC_{50} values than ellagic acid
91	Hesperetin	This study investigated the anticancer effects of hesperetin in 7,12-dimethylbenz[a]anthracene (DMBA)-treated animals	In rats with DMBA-induced mammary gland tumors, hesperetin pretreatment significantly reduced the tumor burden and PCNA overexpression. The administration of hesperetin significantly inhibited mammary gland carcinoma from developing by restoring the decreased Bcl-2 and increased BAX expression. By contrast, in the livers of mice treated with DMBA, obvious DNA fragmentation was observed. Moreover, apoptosis-related gene expression in the livers of the mice differed from that in mammary gland carcinomas in rats. These changes were restored in mice treated with hesperetin, indicating inhibition of apoptosis. Based on these results, hesperetin may act not only as a proapoptotic agent, but also as an anti-apoptotic agent, depending on the circumstance

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92	Apigenin	The effects of combined treatment with 5-fluorouracil and apigenin on proliferation and apoptosis, as well as the underlying mechanism, were investigated in human breast cancer MDA-MB-453 cells	MDA-MB-453 cells, which have been shown to overexpress erbB-2, were resistant to 5-fluorouracil; 5-fluorouracil exhibited a small concentration-dependent antiproliferative effect, with an IC ₅₀ of 90 µM. Interestingly, combined treatment with apigenin significantly decreased resistance. Our results suggest that 5-fluorouracil acts synergistically with apigenin to inhibit cell growth and to induce apoptosis via downregulation of erbB-2 expression and Akt signaling
93	Quercetin	Using a randomized, crossover design, the effect of a high-quercetin diet on the interpretation of homovanillic acid (HVA) assay findings was investigated in both healthy volunteers and false-positive patients. Urine samples were analyzed by GC-MS, screening for phenolic acids	Results showed that a quercetin-rich diet significantly influenced the overall urinary phenolic profile and HVA levels in particular
94	Phenolic acids	This study aimed to determine whether a range of water-soluble antioxidants other than vitamin C could inhibit nitrosation in both the absence and the presence of lipid. Phenolics (caffeic, ferulic, gallic or chlorogenic acid) were added individually to simulated gastric juice containing sodium thiocyanate and secondary amines (markers of nitrosation), with or without lipid. Addition of nitrite triggered the reaction. NO and O ₂ levels were monitored by electrochemical detection. NOC was measured in both aqueous and lipid phases by gas chromatography/tandem mass spectrometry	Nitrite conversion to NO was highest with ascorbic acid (62.7 ± 1.2 µM) and varied with the phenolics from 0.9 ± 0.1 µM with ferulic acid to 21.9 ± 2.2 µM with chlorogenic acid. In the absence of lipids, inhibition of nitrosation ranged from 35.9 ± 7.4% with gallic acid to 93 ± 0.6% with ferulic acid. In the presence of lipids, the impact of each antioxidant on nitrosation was inversely correlated to the levels of NO they generated ($r^2 = 0.95$). Compared to the negative control (100% nitrosation), the presence of lipid, gallic, chlorogenic and ascorbic acid promoted nitrosation (111.5 ± 5.9, 184 ± 5.9 and 321.5 ± 40.8%, respectively), while ferulic and caffeic acids markedly inhibited nitrosation (13.3 ± 1.9 and 17.2 ± 2%, respectively)
95	Procyanidins	This study aimed to explore the pathways involved in the anticarcinogenic properties of procyanidins	Procyanidin specifically induced the activation of mitogen-activated protein (MAP) kinases JNK1/2 and p38α and δ, leading to increased expression of the transcription factor AP-1 and the phosphatases DUSP1 and 10. Gene-specific knockdown of the expression of JNK1, JNK2, p38α, p38-δ or AP-1 diminished procyanidin-induced effects on apoptosis and cell proliferation
96	Olive oil phenolics	The inhibition of MAP kinase signaling in human adenocarcinoma cells underlying the antiproliferative effect of olive oil phenolics was studied	Olive oil extract containing free tyrosol and hydroxytyrosol and their secoiridoid derivatives exerted a significant antiproliferative effect against adenocarcinoma cell growth, which was linked to the induction of a G ₂ /M-phase cell cycle block. Following treatment with the extract (50 pg/mL), the number of cells in the G ₂ /M phase increased markedly relative to vehicle treatment. This G ₂ /M block was mediated by the ability of olive oil polyphenols to exert rapid inhibition of p38 and CREB phosphorylation, which led to a downstream reduction in COX-2 expression

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97	Grape seed extract	This study focused on assessing the antimetastatic efficacy of grape seed extract (GSE) in prostate cancer PC-3 cells and analyzed the antioxidant properties, cell migration, expression of extracellular matrix (ECM) proteins and activity of the MAP kinase signal pathway.	A ROS assay confirmed the antioxidant property of GSE. It significantly inhibited migration of PC-3 cells in a concentration-dependent manner. Cell migration was reduced by 21, 39 and 64%, respectively, in the presence of 5, 10 and 20 µg/mL GSE, respectively. GSE differentially regulated the expression of several ECM proteins. Expression of ECM molecules was screened by a real-time reverse transcription (RT) PCR array. GSE increased the phosphorylation of p38 and JNK/MAPK proteins
98	Cola nut extract	This study was conducted to determine the mechanism of action of cola nut through the apoptotic cell approach. The effect of cola nut extract on the apoptosis of MCF7 cells was determined by flow cytometric analysis. MCF7 cells were treated with 60 and 80 µg/mL of cola nut extract for 24 h and subjected to FACS analysis	MCF7 cells treated with 60 and 80 µg/mL cola nut extract showed an increase of 6.55 and 8.29%, respectively, in the population of apoptotic cells, with a concomitant decrease in the percentage of cells in the S and G ₂ /M phase of the cell cycle compared to DMSO-treated control cells
99	Red wine polyphenols	The aim of the present study was to determine whether red wine polyphenols (RWPs) prevent tumor growth. The tumor macrovessel density was assessed by high-definition microCT and the microvessel density by immunohistochemistry. Proliferation index (Ki67), apoptosis (TUNEL, activated caspase-3) and the expression of proangiogenic factors (VEGF, MMP-5) and tumor suppressor genes (p21, p16, p53 and p73) were determined in tumors. In addition, the effect of RWPs on aberrant crypt foci (ACF) formation was determined in a model of azoxymethane-induced colon cancer in rats	Tumor size was significantly reduced by 30% compared to control. The vessel density assessed by microCT and immunohistochemistry was reduced by 40 and 47%, respectively, in the RWP-treated group. This effect was associated with decreased expression of VEGF, MMP-2 and MMP-9 in tumor cells. Moreover, RWPs reduced by 61% the proliferating index and increased by 81% the apoptotic index associated with high caspase-3 activity in tumor cells. RWPs also induced the expression of tumor suppressor genes such as p16, p21, p53 and p73 in tumor cells
100	Coffee	The impact of coffee consumption on DNA damage induced by different representatives of dietary carcinogens in comet assays in peripheral lymphocytes was studied. In the first trial (n = 15; 800 mL/day coffee; 5-day intervention, metal-filtered), the effects of simple alkylating agents on DNA migration were studied and significant protection against damage induced by <i>N</i> -nitrosodimethylamine and <i>N</i> -methyl- <i>N</i> -nitrosourea was observed, while no protection against methyl methanesulfonate was found. In a second trial (n = 8; 800 mL/day coffee; 10-day intervention) we investigated the impact of aflatoxin B1, benzo[<i>a</i>]pyrene diol epoxide (BPDE, the ultimate metabolite of benzo[<i>a</i>]pyrene) and glycidamide (GA, the active metabolite of acrylamide)	Taken together, the results of the studies suggest that coffee consumption protects humans against DNA damage caused by carcinogens contained in the diet
101	Hyperforin	A study investigated the role of hyperforin (Hyp) in the survival of multiple myeloma (MM) plasma cells and their secretion of MMP-9	Flow cytometry analysis of six MM cell lines and highly purified malignant PC from eight patients with MM and two with plasma cell leukemia (FL) showed that Hyp induced apoptosis through concentration-dependent stimulation of phosphatidylserine externalization, disruption of the mitochondrial transmembrane potential and cleavage of the caspase substrate PARF-1. Treatment of MM cells with Hyp also resulted in inhibition of their ability to secrete MMP-9. This qualifies Hyp as a lead structure for the development of new approaches for the treatment of malignant hematological tumors such as MM

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102	Apple extracts	In this study, the effect of apple extracts on the growth of the human colon cancer cell lines Caco-2, HCT 116 and HT-29 was evaluated. The extracts were analyzed for polyphenol concentration, vitamin C content and antioxidant capacity (ORAC and FRAP assays). The cancer cells were tested for cell proliferation (MTT assay) and apoptosis (cell death detection ELISA)	The results showed that apple extracts have strong inhibitory effects on the growth of human colon cancer cells. Apple skin has a stronger inhibitory effect on cell growth than apple flesh. The effect is greatly influenced by the light conditions during ripening, with the strongest effect found for sun-exposed apples
103	Fucoxanthin	In this study the colon cancer cell line WiDr was employed to study the anticancer activity of the xanthophyll fucoxanthin	Results showed that fucoxanthin inhibited the phosphorylation of retinoblastoma a protein through downregulation of the cyclin/CDK complex and upregulation of p21, and then induced cell cycle arrest at the G ₀ /G ₁ phase. Fucoxanthin exhibited apoptosis-inducing activity through stimulation of caspase-8 activity in human leukemia HL-60 cells, and also induced apoptosis specifically in osteoclasts. Thus, dietary fucoxanthin seems to possess interesting bioactivity without producing side effects
104	Curcumin, rutin and quercetin	This study was conducted to elucidate the effects of dietary polyphenols on cecal organic acids, fermentation products of microflora, in rats fed a high-fat diet (HFD) containing 30% beef tallow with or without polyphenols, including curcumin, rutin, D-(+)-catechin, ellagic acid, caffeic acid and quercetin at a level of 0.5% for 3 weeks	Succinate treatment suppressed the growth of colon cancer HT-29 cells and ex vivo angiogenesis in a rat aortic ring assay system. The migration of human umbilical vein endothelial cells (HUVEC) was suppressed by succinate treatment, but the growth of HUVEC and tube formation of HUVEC were unaffected by succinate
105	<i>Rubia cardifolia</i> L.	The precipitates from the ethyl acetate fraction of roots of <i>R. cardifolia</i> L., termed the radish calmodulin antagonist (RCA) fraction, were studied for antigenotoxic activity against oxidative mutagens, i.e., hydrogen peroxide and 4-nitroquinolin-1-oxide in <i>Escherichia coli</i> PQ37 tester strain using SOS chromotest assay and in human blood lymphocytes using the comet assay	In the single-cell gel electrophoresis assay (COMET/SCGE), the RCA fraction reduced the tail moment (a parameter for measurement of genotoxicity) induced by H ₂ O ₂ and 4-nitroquinolin-1-oxide by 58.02 and 55.51%, respectively, at the same concentration. The spectroscopic data of the RCA fraction revealed it to be anthraquinone in nature, which points to its potential as a chemopreventive agent
106	Soybean germ	The anticarcinogenic effect of soybean germ extract in human colorectal cancer HT-29 cells was studied. Cell viability was assayed by the MTT assay and apoptosis through Hoechst 33342 chromatin staining by fluorescent microscopy observation	Apoptosis of HT-29 cells by soybean germ extract may be due to p53 and caspase-3 activation. The extract shows high anticarcinogenic activity in HT-29 cells
107	Eupatilin and jaceodin	The potential chemopreventive effects of some methoxyflavonoids derived from <i>Artemisia</i> plants were investigated using Ras-transformed human breast epithelial cells. Eupatilin is one of the pharmacologically active ingredients derived from <i>Artemisia asiatica</i> and jaceodin is an eupatilin derivative from <i>Artemisia argyi</i>	An antiproliferative effect for eupatilin (5,7-dihydroxy-3,4,6-trimethoxyflavone) was observed. Eupatilin inhibited TNF- α -induced nuclear localization of β -catenin and TCF-4 DNA binding activity, as well as μ PA expression in MCF10A cells. Moreover, eupatilin significantly inhibited the TNF- α -induced invasiveness of MCF10A cells, as evidenced by reduced migration and wound healing. The proapoptotic activity of jaceosidin is associated with ROS accumulation and inhibition of ERK-1/2 activation in MCF10A/ras cells. In conclusion, methoxyflavonoids derived from <i>Artemisia</i> plants have chemo-preventive and chemotherapeutic potential

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108	(-)-Epigallocatechin-3-gallate	In the present study, human colon cancer HCT 116 and HT-29 cells were used to examine the relationships between Met activation, (-)-epigallocatechin-3-gallate (EGCG) treatment and H ₂ O ₂ generation	At concentrations of 0.5, 1 and 5 μ M EGCG suppressed the activation of Met induced by hepatocyte growth factor (HGF). Concentrations of 10 μ M EGCG and below generated low amounts of H ₂ O ₂ . Molecular docking and enzyme kinetic analyses suggested that EGCG is a competitive inhibitor, binding to the kinase domain of Met, and hence concluded that EGCG might be a beneficial therapeutic agent for inhibiting Met signaling and helping to attenuate tumor spread/metastasis in the colon
109	Resveratrol, quercetin and catechin	The combined effect of three polyphenols present in wine (resveratrol, quercetin and catechin) on cell cultures and the effect of wine extract on human tumor cell origin were studied	Results revealed that resveratrol and quercetin are inhibitors of colorectal cancer cell proliferation, resveratrol and quercetin exhibit synergetic antiproliferative effect against SW480 colorectal cell lines, and the red wine extract contains cell proliferation-inhibitory compounds
110	5-Deoxykaempferol	This study investigated the chemopreventive effect of 5-deoxykaempferol using mouse skin epidermal JB6 P+ cells	Results revealed that 5-deoxykaempferol exerts its chemopreventive effect on UVB-induced skin carcinogenesis by targeting multiple signaling molecules and suppressing COX-2 and vascular endothelial growth factor (VEGF). It was suggested that the compound docks at the ATP binding site of Src, PI3K and RSK2
111	Daidzein	7,3',4'-Trihydroxyisoflavanone, a metabolite of the soy isoflavone daidzein, was investigated for its chemopreventive effect	7,3',4'-Trihydroxyisoflavanone, effectively inhibits UVB-induced COX-2 expression through the inhibition of nuclear factor NF- κ B transcription activity in mouse skin epidermal JB6 P+ cells
112	Propolin G	To investigate the antitumor effect of propolin G (PPG) and NBM-TP-007-GS-002 (GS-002), a semisynthetic derivative of PPG, in human hepatoma Hep 3B and Hep G2 cells in vitro and in vivo	PPG- and GS-002-treated cells show indications of apoptosis such as cleavage of caspase-3 and -9 and poly [ADP-ribose] polymerase (PARP). Both PPG and GS-002 also concentration-dependently induced mRNA and protein expression of activating transcription factor 3 (ATF-3). This suggests that the induction of apoptosis by GS-002 in human hepatoma cells is partially mediated through the ATF-3-dependent pathway, and GS-002 may therefore be a potential candidate antitumor agent
113	Oligonol®	This study presented an approach to metabolic syndrome-related cancer that combines tissue engineering and adipose science and utilizes isolated metabolic stem cells (MSCs) from each patient's own fat tissue to individually treat obesity-associated disorders accompanied by dysregulated adipokine	It was shown that oligonol (lychee-derived low-molecular-weight polyphenol), lychee polyphenol and GCP (genistein-combined polysaccharide) are possible adiponectin enhancers in some individuals. It was concluded that by culturing MSCs in a 96-well plate the metabolic function of fat tissue in energy balance can be investigated

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114	Anthocyanin and vinylpyroanthocyanin catechins (porticins)	Anthocyanin and vinylpyroanthocyanin catechins (porticins) were studied to evaluate their effect on the growth of ER ⁺ MCF7 cell proliferation by measuring cellular protein content and quantifying 5-bromo-2'-deoxyuridine incorporation into newly synthesized DNA of actively proliferating cells. Changes in protein synthesis induced by Cy-3-gluc and Dp-3-glucon on MCF7 cells were investigated using two-dimensional electrophoresis of total protein cellular extract. The implication of the two anthocyanins in ER α and ER β expression was evaluated by reverse transcriptase and real-time PCR	The antiproliferative effect was greater when cells were treated with Dp-gluc and its respective porticin. The <i>ortho</i> -trihydroxylated moiety in the phenolic ring is an important structural feature for more potent inhibitory effect on MCF7 cell proliferation compared to the effect observed with the similar dihydroxylated compounds. Two-dimensional gel electrophoresis of the whole MCF7 cellular protein extract pointed to alteration in the expression of some proteins. The greater antiproliferative effect observed after treatment with Dp-3-gluc was not followed by modification of ER expression. The anthocyanin Cy-3-gluc was able to induce downregulation of ER levels although with no effect on MCF7 cell proliferation at the range of concentrations tested
115	Proanthocyanins from Rosaceae, Grossulariaceae and Ericaceae	Comparison of various proanthocyanin-rich nutritional resources for the prevention of colorectal cancer was performed on human metastatic colon carcinoma SW620 cells using a microcapillary cytometer screening assay to monitor apoptosis	Bioactivity screening highlighted the chemopreventive potential of proanthocyanin-rich fruits in colorectal cancer
116	Catechins	Comparative effects of (+)/(-)-catechins and (+)/(-)-epi-methylated catechins, (+)-catechin gallates, EGCG and its O-methyl derivatives on the cytotoxicity and tumor promotion induced by 12-O-tetradecanoylphorbol-13-acetate (TPA) were estimated. JB6 Cl 22 and Cl 41 cell lines were used for determination of cytotoxicity and neoplastic transformation	Results showed that D-ring O-alkylation of catechin gallates weakens cytotoxicity but not the inhibitory effect on tumorigenic transformation
117	Curcumin	The effect of dietary polyphenols on intestinal immunoglobulin A (IgA) and mucin levels in rats fed a high-fat diet (HFD) containing 30% beef tallow including curcumin, rutin, D-(+)-catechin, ellagic acid and quercetin at a level of 0.5% for 3 weeks was studied	Among the polyphenols examined, consumption of curcumin markedly elevates the levels of IgA in feces and colon contents. Fecal amounts of mucin were not affected. Serum levels of IgA, IgE and IgG were not affected by dietary curcumin
118	Quercetin	The time-dependent regulation of quercetin on the two main transcription factors (NF- κ B and AP-1) related to survival/proliferation pathways in human hepatoma Hep G2 cells over 0-180 min was studied	Quercetin induced significant, time-dependent activation of the NF- κ B and AP-1 pathways. NF- κ B binding activity was also downregulated. This suggests that NF- κ B and AP-1 play a major role in the tight regulation of survival/proliferation pathways exerted by quercetin
119	Tomatoes	The effect of varieties of tomatoes with different levels of quercetin, naringin and total phenolic on the proliferation of human colon adenocarcinoma cells was evaluated	All three varieties investigated were able to significantly inhibit adenocarcinoma cell growth. The mechanism involved is linked to their ability to inhibit cell cycle progression, as cell cycle analysis of the treated cells indicated reduction in the percentage of cells actively synthesizing DNA
120	Resveratrol	Chronicles the mechanism proposed for the chemopreventive effect of resveratrol in colorectal cancer considering the animal models and human cell lines involving resveratrol either individually or as a component of wine on biomarkers for colorectal cancer	It was concluded that this potentially effective dietary strategy for colorectal cancer would have significant implications for the management of this major clinical and public health problem

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121	Kakadu plum extract	The extract was assayed for antioxidant, anti-inflammatory, and proapoptotic anticancer properties. The antioxidant property was determined by ORAC and FRAP assays, anti-inflammatory activity was determined by expression of COX and inhaled nitric oxide (INO) (Western blot analysis). The antiproliferative properties were determined using HT-29 and AGS cancer cell lines. Apoptosis of cancer cells was determined by agarose gel electrophoresis and caspase-3 induction	Antioxidant activity was demonstrated in the FRAP (4538.35 $\mu\text{mol Fe}^{2+}/\text{g DW}$) and ORAC assays (1816.56 $\mu\text{mol/Trolox}^{\circ}/\text{g DW}$). Anti-inflammatory activity was demonstrated by a decrease in the expression of COX-2 and INO, while there was no effect on COX-1 levels. The extract exhibited antiproliferative activity on HT-29 and AGS cancer cell lines. Apoptosis was identified as the major mechanism for the observed antiproliferative effect. The kakadu plum extract displayed a modulatory effect on a number of vital enzyme pathways involved in carcinogenesis and chemoprevention
122	Apigenin glucoside	This study investigated the differentiation-inducing activity and mechanism of apigenin glucoside in chronic leukemia K-562 cells. Flow cytometry and MTT assays were used for cytotoxicity. Cell cycle analyses and detection of differentiation marker proteins were performed by flow cytometry. The difference in protein expression in control and treated cells was investigated by proteomics	The MTT assay showed that apigenin glucoside was cytotoxic against K-562 cells, suppressing cell growth by 20-45% at 25-100 μM compared to control after 72 h. Cell viability was 84-89% at these concentration ranges by flow cytometry. Cell cycle kinetics revealed that 51.5-87.5% of K-562 cells were arrested in the G_2/M phase at 25-100 μM apigenin glucoside after 72 h. Flow cytometry analyses showed that the megakaryocyte-specific marker CD41 was expressed in 42% of treated cells, while the erythroid marker glycophorin A was detected in almost 60% of the cells after 21-day incubation with 75 μM apigenin glucoside
123	Anthocyanins	3-O-Methylgallic acid, syringic acid, gallic acid, protocatechuic acid, vanillic acid and 2,4,6-trihydroxybenzaldehyde, along with the cabernet sauvignon whole extract containing anthocyanins, were incubated with Caco-2 cells to determine the effect on cell proliferation, cytotoxicity and apoptosis using the colorimetric method	The anthocyanin microflora metabolites gallic acid, 3-O-methylgallic acid and 2,4,6-trihydroxybenzaldehyde were able to reduce cell proliferation in Caco-2 cells, with low cytotoxicity, and thus may offer protection against colon cancer
124	Quercetin and kaempferol	This study aimed to examine the mechanism responsible for the polyphenol (quercetin and kaempferol)-derived cancer chemopreventive effect. Transiently transfected RL34 cells with a luciferase reporter construct based on the mouse NAD(P)H:quinine oxidoreductase 1 (NQO1) gene promoter were used	Western blotting showed that both quercetin and kaempferol induced endogenous NQO1 and increased the amount of Nrf2 protein, a transcription factor recruited to antioxidant response elements (AREs) in inducible genes. TaqMan analysis showed that the increase in Nrf2 protein was mainly due to stabilization of Nrf2 protein, reduced degradation and cycling
125	Flavanoids	The role of six flavanoids (apigenin, kaempferol, quercetin, hesperedin, naringenin, eriodictyol) in prostate cancer was investigated using prostate cancer LNCaP cells. The cytotoxicity of the flavanoids towards LNCaP cells was analyzed by the MTT and trypan blue exclusion assays. The metabolism of flavanoids was also studied using HPLC-DAD and LC-MS	The order of antiproliferative effect was apigenin > kaempferol > quercetin > hesperedin > naringenin > eriodictyol. They inhibited the growth of LNCaP cells within the range of 0.9-72.9 μM , while the antiproliferative effect was different. The different cytotoxicities of flavanoids towards LNCaP might be closely related to the cellular uptake by LNCaP, as well as their hydrophobicity

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Table I. Cont. Summary of studies on polyphenols presented at the 4th International Conference on Polyphenols and Health.

Ref.	Polyphenols/plants/natural interventions	Study design	Outcome
126	Asphalathin	The effect of asphalathin (ASP) on the proliferation and invasion of AH109A hepatoma cells. The proliferation of AH109A cells was assessed by [³ H]-thymidine incorporation and AH109A invasion was assessed by co-culturing the cells with the mesentery derived from mesothelial cells. The levels of ROS were analyzed by flow cytometry	ASP may suppress AH109A proliferation through cell cycle arrest and the antioxidant effect of ASP may be involved in its anti-invasive activity. This suggested that ASP is absorbed from the gastrointestinal tract and appears in blood as the active form(s)
127	Korean red ginseng	The non-organ-specific cancer preventive effect of long-term administration of Korean red ginseng extract on the incidence of malignant neoplasms was studied in a randomized, double-blind study; 325 patients with chronic atrophic gastritis received 4 capsules containing 250 mg/week of red ginseng extract powder for 3 years and 318 patients were assigned to receive placebo	The Korean red ginseng group, including both genders, had a relative cancer risk of 0.54 compared with the placebo group. The male Korean red ginseng group had a relative cancer risk of 0.35 compared with the placebo group. In conclusion, 3 years of administration of Korean red ginseng extract powder showed a non-organ-specific cancer preventive effect in terms of the incidence of malignant neoplasms in males
128	Cyandin-3-glucoside	The effect of cyandin-3-glucoside (C3G) on benzo[a]-pyrene-7-8-diol 10-epoxide (B[a]PDE)-induced COX-2 expression in JB6 P+ mouse skin epidermal cells was evaluated	C3G strongly attenuated B[a]PDE-induced phosphorylation of MEK and Akt and their downstream kinases ERK, p38 and JNK. C3G also blocked activation of AP-1 and NF-κB and suppressed B[a]PDE-induced COX-2 expression in JB6 P+ cells. C3G may prevent cancer by binding to Fyn and inhibiting its activity
129	Tomato	Randomized, crossover study in 5 volunteers and 3 interventions designed to assess the changes in plasma kinetics and urinary excretion of phenolic metabolites after administration of oil-free and oil-enriched tomato sauces. Interventions were: A) tomato sauce; B) tomato sauce with virgin olive oil; and C) tomato sauce with refined oil. The polyphenol composition of the tomato sauces and the metabolic forms in plasma and urine were identified and quantified by LC-MS/MS analysis, and product ion scan (PIS) and multiple reaction monitoring (MRM) data were used to confirm their identity	Six phenolic compounds, 3 aglycones and 3 glucuronides, appeared in urine, reaching the maximum excretion within 4 h from ingestion. Two phenolic metabolites, ferulic and naringenin glucuronides, were also confirmed in plasma by PIS and MRM analysis, reaching the maximum absorption within 30 min and 1 h, respectively, after intervention
130	Flavonoid	In this study the biotransformation of several flavonoid classes by probiotic microorganisms present in probiotic drinks and yogurts was examined. Various probiotic drinks and yogurts in their commercial concentrations were incubated with several flavonoid classes. The change in the content of the flavonoids and the β-glucosidase activity in the probiotic drinks and yogurts during incubation was investigated	Probiotic microorganisms that contain β-glucosidase enzyme can have a significant effect in improving the biological activity of these compounds
131	Quercetin glycosides and its aglycone	In this study the effect of dietary fat 8.3% (w/w) on the absorption of dietary quercetin glycosides and its aglycone from a novel onion-based matrix was investigated. Glycoside and aglycone meals were fed to 6 human volunteers (4 male, 2 female) and 5 human volunteers (4 male, 1 female) on separate occasions, respectively. Urine samples were taken hourly for 12 h and analyzed by HPLC	The coadministration of dietary fat enhanced the relative bioavailability of quercetin from both meals and a significant difference was observed between the forms of quercetin consumed
132	Almond (<i>Prunus dulcis</i> [Mill.] D.A. Webb)	This study investigated almond skin polyphenol intake on the profile of human urinary metabolomics in a placebo-controlled, randomized study. Urinary samples were analyzed by HPLC-q-ToF	Results showed a total of 52 polyphenol metabolites of polyphenol monomers, as well as colonic microbiota polyphenols such as glucuronide and sulfate derivatives of phenolic acids and hydroxyphenylvalerolactones

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Table I. Cont. Summary of studies on polyphenols presented at the 4th International Conference on Polyphenols and Health.

Ref.	Polyphenols/plants/natural interventions	Study design	Outcome
133	Almond (<i>P. dulcis</i> [Mill.] D.A. Webb)	This study investigated the metabolic profile of almond extract in humans. Two healthy volunteers receiving no medication were recruited in the study. Urinary samples were analyzed by LC-MS/MS	Results showed the detection of microbial-derived metabolites of flavanols: 5-(3,4-dihydroxyphenyl)- γ -valerolactone and 5-(hydroxylmethoxyphenyl)- γ -valerolactone in their glucuronide and sulfate forms
134	Cocoa powder	This study investigated the phenolic metabolites after regular intake of cocoa powder in humans. Forty-two volunteers presenting a high risk of cardiovascular disease were included. The subjects received two sachets of cocoa powder with 250 mL skim milk for 2 weeks. Urinary samples were analyzed by LC-MS/MS	Results revealed the presence of glucuronide and sulfate conjugates of (–)-epicatechin and O-methyl-(–)-epicatechin and microbial-derived products such as 5-(3,4-dihydroxyphenyl)- γ -valerolactone and 5-(3-methoxy-4-hydroxyphenyl)- γ -valerolactone
135	Resveratrol	This study aimed to show the potential intra- and interindividual variability of resveratrol metabolism in 14 healthy male volunteers. Volunteers followed a 3-day washout period with a diet very low in phenolic compounds. Volunteers were fed the same standardized meal supplemented with 250 mL of resveratrol. This protocol was repeated three times with at least 1 week between each. Urine samples were analyzed by LC-MS/MS after solid-phase extraction	The presence of dihydroresveratrol demonstrated the initial formation of microbial metabolites of resveratrol. Preliminary results showed marked differences in the profile of all metabolites between baseline and after moderate resveratrol consumption
136	Procyanidins from Syrah grape (de-alcoholized red wine)	Fermentation experiments were performed in an in vitro colon model using human fecal microbiota as an inoculum and analyzed either with targeted GC-MS to elucidate the impact of fruit product matrix on microbial conversion parameters or with GCxGC-TOF coupled with a compound	The maximal extent of conversion was observed with the de-alcoholized wine having short-chain procyanidins dominating the sample. Isolated fraction of long-chain procyanidins was able to inhibit the microbial metabolism of Pas by the fecal microbiota in vitro. The inhibition was also observed as suppression of SCFA formation from carbohydrates. The inhibition was not apparent in the presence of fruit matrix or suppression of SCFA formation from carbohydrates. The inhibition was not apparent in the presence of fruit matrix or wine
137	Polyphenols	Intestinal transport and metabolism of polyphenols have been investigated in vitro in different colon carcinoma cell models. Monolayers of the colon carcinoma cell line T84, as well as pig small intestinal mucosa, were mounted in a Ussing chamber. Polyphenols were applied to the apical compartment in physiological concentrations. The concentrations in the apical and basolateral compartments were determined by HPLC-DAD and HPLC-MS/MS	Results indicate differences in the intestinal transport between the in vitro colonic carcinoma cell line T84 and the ex vivo pig small intestinal model. However, since there are functional similarities, the analogical nutrition, similarities in microbiota and easy accessibility of the pig mucosa suggest it is a good model to study human intestinal transport
138	Polyflavonoids	In a randomized, crossover study the microbial potential to activate various proestrogens within an individual was evaluated. Subjects were given soy, hop and/or flax-based food supplements, dosed either separately or simultaneously 3 times/day during 5 days	The microbial bioactivation of daidzein, isoxanthohumol and secoisolariciresinol generally decreased upon coinubation in vitro (equol: 4.4%, $P = 0.164$; 8-prenylnaringenin: 20.5%, $P < 0.001$; enterolactone: 44.3%, $P < 0.001$) and cosupplementation in vivo (equol: 28.3%, $P = 0.009$; 8-prenylnaringenin: 35.4%, $P = 0.107$; enterolactone: 35.9%, $P = 0.003$). Although the bioavailabilities of total isoflavones, prenylflavonoids and lignans were not significantly affected by coadministration, the participants were exposed to lower phytoestrogen-derived 17 β -estradiol equivalents

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Table I. Cont. Summary of studies on polyphenols presented at the 4th International Conference on Polyphenols and Health.

Ref.	Polyphenols/plants/natural interventions	Study design	Outcome
139	Quercetin	In this study quercetin glucuronidation in hepatic and intestinal mucosa microsomes from male F344 rats was measured. Pooled microsomal fractions from liver and 3 equidistant small intestine (SI) segments of 4- to 28-month-old rats were employed to determine the kinetics of UDP-glucuronosyltransferase (UGT) activity quercetin. Glucuronidation rates at 30 and 300 mM quercetin were determined using individually prepared microsomal fractions	The mean rate of hepatic quercetin-4'-O-glucuronide formation peaked at 18 months at 0.9 nmol/min/mg. Intrinsic clearance ($C_{int}, V_{max}/K_m$) in the upper, middle and lower SI increased with age. At 18 and 28 months, C_{int} was > 2-fold greater than at 4 months. In upper SI at 30 mM quercetin UGT activity increased 2- and 3-fold at 18 and 28 months, respectively, from 0.348 nmol/min/mg at 4 months. Lower SI UGT activity increased 70% from 1.44 nmol/min/mg at 4 months. The lower SI preferentially catalyzed glucuronidation at the 7-OH position with 51% of total metabolites. The upper SI produced the greatest proportion of 4'-OH and 3'-OH conjugates at 26% and 33%, respectively. SI UGT quercetin regioselectivity did not change with age. Thus, the age-related increase in quercetin glucuronidation depends upon tissue type and intestinal segment and is more pronounced in the upper and lower SI
140	Polyphenol-rich juices	The bioavailability of the different phenolic compounds in the drink was investigated in an acute trial in which 10 healthy volunteers consumed 350 mL of the drink. Plasma and urine were analyzed by HPLC-MS	The plasma pharmacokinetics and recoveries of urinary metabolites, both in terms of their identity and quantity, are in keeping with data observed in similar feeding studies with green tea products, cocoa, orange juice and apple cider, as well as coffee. Therefore, there is no significant inhibition or competition for the sites and/or molecules involved in the metabolism and transport of the different phenolics into the bloodstream from the gastrointestinal tract
141	Flavanoids	This study investigated the extent to which flavonoids modulate the intestinal metabolism and transport of hesperetin in vitro by characterizing the effect of coadministering a series of flavonoids using Caco-2 cell monolayers in a 2-compartment transwell system as a model for the intestinal barrier	The amount of hesperetin metabolites transported to the basolateral side was significantly increased up to 2-fold when coadministered with quercetin. Therefore, coadministering specific flavonoids could be a strategy to improve the limited bioavailability of hesperetin in vivo
142	Furanocoumarin	This study aimed to study the variations in furanocoumarin (FC) composition and drug interaction of pomelos and grapefruits	It was reported that significant qualitative differences exist in the FC content of grapefruit and pomelos. Crosses made between selected pomelos and grapefruit yielded segregating offspring with distinctive FC profiles. Some hybrids contained the highly physiologically active 6',7'-dihydroxybergamottin (DHB) and paradisin C, similar to the parent grapefruit. However, other hybrids were much more like the lot-FC pomelo parent and contained only a set of weak inhibitors, mainly isoisomeratorin and a small amount of cnidicin

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Table I. Cont. Summary of studies on polyphenols presented at the 4th International Conference on Polyphenols and Health.

Ref.	Polyphenols/plants/natural interventions	Study design	Outcome
143	Green tea	A feeding study was carried out in 20 healthy human volunteers who ingested 400 mL of a ready-to-drink green tea containing approximately 400 mmol of flavan-3-ols	Thirty-nine relevant catabolites were identified in biological fluids by means of HPLC-tandem MS. In plasma EGCG is the only unmetabolized compound and the highest in absolute concentration; (–)-epigallocatechin (EGC) catabolites reach peak plasma concentrations at 2 h after ingestion, where as (–)-epicatechin (EC) catabolites generally reach maximum concentrations at 1 h. Colonic microflora-derived polyhydroxy-phenyl-γ-valerolactones were by far the main urinary catabolites. The sulfated conjugate of (–)-5-(3',5'-dihydroxyphenyl)-γ-valerolactone was the main colonic catabolite in the vast majority of the study group, but sulfated (–)-5-(3',4'-dihydroxyphenyl)-γ-valerolactone and sulfated and methyl-sulfated 5-(3',4',5'-trihydroxyphenyl)-γ-valerolactone were seen in high amounts in some volunteers
144	Flavanoids (hesperidin)	The study focused on the effects of flavonoids and ascorbic acid (AA) on intestinal carotenoid uptake, and was conducted using differentiated Caco-2 cells as the in vitro model. Interactions of defilament flavanones such as hesperidin (HES-G) and hesperetin (HES) with carotenoid uptake were examined. The effect of AA added to HES-G was also investigated	Data showed an enhancing effect of HES-G and HES with β-carotenoid (β-C) and β-cryptoxanthin (β-CX) uptake. Incubation in the presence of a mixture of β-C;β-CX with HES-G and HES significantly increased total carotenoid uptake by 1.7- and 1.6-fold, respectively. Moreover, AA was able to cancel the enhancing effect of HES-G by significantly decreasing the cellular uptake of carotenoids from 48.2% to 39.8% ($P < 0.05$). The results indicate that citrus flavanones enhance carotenoid uptake by intestinal cells and that iron inhibits this process
145	Caffeoylquinic acids	The aim of the study was to observe a possible effect of food matrices on polyphenol bioavailability. The intestinal availabilities of caffeoylquinic acids (CQAs) from two food sources (cloudy apple juice and coffee) were determined using ileostomy volunteers. Identification and quantification of CQAs were performed using HPLC-DAD and HPLC-ESI-MS/MS methods	Interesterification of CQAs from apple juice, 4-CQA and 5-CQA to 1-CQA, 3-CQA, 4-CQA and 5-CQA was observed during gastrointestinal passage. The extent of absorption was 74.3% and 22.2%, respectively, for CQAs (1-CQA, 3-CQA, 4-CQA and 5-CQA) from apple juice and coffee
146	Polyphenols	In this study a method was developed to analyze various polyphenols in human plasma and urine by GC-MS and HPLC and human intervention trials were also conducted with polyphenol-rich food sources to investigate their health effects and the bioavailability of polyphenols	Bioavailability data showed that the number of chlorogenic acid and caffeine metabolites increased in plasma after coffee consumption and their plasma concentrations increased with increasing dose
147	Chlorogenic acid	The objective of this study was to evaluate the effect of the addition of milk on the urinary excretion of chlorogenic acid (CGA) and metabolites in 5 healthy adults after consumption of a regular coffee brew containing 561 μmol of CGA. CGA and metabolites were determined in urine using HPLC	The total urinary excretion after coffee-milk (2.2 mmol) consumption was significantly lower ($P < 0.05$) than after coffee-water (3.3 mmol) consumption
148	Chlorogenic acid (green <i>Ilex paraguariensis</i>)	The objective of the study was to evaluate the urinary excretion of CGA (green <i>I. paraguariensis</i>) and its metabolites after CGA consumption. Urine samples were analyzed by HPLC	Results showed the 6 CGA (3-, 4- and 5-caffeoylquinic acid and 3,4-, 3,5- and 4,5-dicaffeoylquinic acid) and 16 phenolic compounds were identified in all urine samples

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Table I. Cont. Summary of studies on polyphenols presented at the 4th International Conference on Polyphenols and Health.

Ref.	Polyphenols/plants/natural interventions	Study design	Outcome
149	Chlorogenic acid	The objective of this study was to evaluate the urinary excretion of CGA and metabolites in humans after green and roasted coffee consumption. Each volunteer (N = 7) consumed on different days capsules of green coffee or roasted coffee (both containing 8.4 mmol/kg CGA) or placebo	The total urinary excretion of phenolic compounds after consumption of green coffee (2.4 mmol) and roasted coffee (2.3 mmol) was significantly higher than placebo (1.3 mmol) No significant difference was observed in the excretion of phenolic compounds after consumption of green and roasted coffee. On average, after the consumption of green and roasted coffee 34.1% and 33.7%, respectively, of total hydroxycinnamic and quinic acid moieties were recovered in urine
150	Coffee (hydroxycinnamic acid)	This study aimed to investigate the uptake and metabolism of coffee-derived hydroxycinnamic acids using Caco-2 cell cultures as a model for the gastrointestinal epithelial barrier	Results showed that reduced transport of dichlorogenic esters was attributed to size exclusion and potential efflux diffusion. Ferulic acid and monochlorogenic esters were transported in the free form by passive resistance and associated with hydrophobicity, indicating transcellular transport. Results indicate that physiological pH has a critical role in the transport of hydroxycinnamic acid
151	Cyanidin 3-O-glucoside	The aim of this study was to evaluate the fate of anthocyanins in mice after oral administration of a radiolabeled substrate, [¹⁴ C]-cyanidin 3-O-glucoside ([¹⁴ C]-CY3G). Labeled CY3G was obtained from grape cells cultured in the presence of U-[¹⁴ C]-phenylalanine	After administration of 22.2 kBq [¹⁴ C]-CY3G, radioactivity was detected in most organs tested over the following 24 h, with a peak observed in inner tissues at 3 h. The major fraction of radioactivity (44.5%) was found in feces collected 24 h after ingestion. At 3 h after oral administration of 141 kBq [¹⁴ C]-CY3G, most of the radioactivity (87.9% of intake) was recovered in the gastrointestinal tract, especially the small intestine (50.7%) and the cecum (23%). At this time, 3.3% of the radioactivity was detected in urine. There was minimal accumulation (0.76%) of radioactivity in tissues outside the gastrointestinal tract
152	Catechin-derived compounds	In this study catechin-derived compounds, i.e., absorbed homodimers (THSNs A/D and C/E, P-2 and the EGC P-2 analogue) and heterodimers (THSNs F/G and the GCG-EGC P-2 analogue), were generated by autooxidation of EGC and EGCG in vitro. Highly differentiated monolayers of Caco-2 cells were then incubated with test media containing catechin monomers and/or dimers for up to 3 h. LC-MS analysis detected both monomers and selected dimer isomers in Caco-2 cells	The presence of an O-methylated derivative of the EGC P-2 analogue and a sulfated conjugate of THSN C/E in Caco-2 cell monolayers suggested that catechin dimers may be metabolized. Net accumulation of EGC, EGC P-2 analogue and THSNs C/E after 3 h was 0.55 ± 0.07%, 0.79 ± 0.20% and 1.10 ± 0.40%, respectively. Accumulation of EGCG, P-2 and THSNs A/D was 1.35 ± 0.16%, 6.74 ± 2.17% and 9.49 ± 3.3%, respectively. Accumulation of EGCG, EGC, the heterodimer P-2 analogue and THSNs F/G was 1.24 ± 0.099%, 0.19 ± 0.02%, 4.60 ± 2.1% and 4.37 ± 2.7%, respectively. Retention (1 h) of EGCG, P-2 and THSNs A/D by Caco-2 monolayers was 56.8 ± 0.81%, 171 ± 22% and 29.6 ± 9.3%, respectively, suggesting potential conversion of THSNs to P-2 following absorption by Caco-2 cells

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Ref.	Polyphenols/plants/natural interventions	Study design	Outcome
153	Flavonoid	This study was designed to determine the kinetics of flavonoid catabolites in order to describe gut microbial phenotypes. Twenty male subjects on a low polyphenol diet received in the fasted state a single oral dose of 800 mg polyphenols in the form of grape juice/red wine extract or black tea extract, or placebo in a capsule. Kinetic profiles of phenolic acids using GC-MS were determined	Urinary excretion patterns of phenolic acid differ substantially among flavonoid sources and among individuals. Kinetics indicate that the activity of metabolic networks strongly differs among individuals. In particular, metabolites derived from gut microbial catabolism largely contributed to the variations
154	Tea catechins	The aim of this study was to investigate whether milk reduces the bioaccessibility of tea catechins and to determine the stability of polyphenol–protein complexes in black tea	Results showed that the addition of milk to tea leads to the formation of protein–polyphenol complexes, which are not protease-stable and are broken down to a major extent during small intestinal digestion
155	Tea catechins	The aim of the study was to investigate whether milk reduces the bioaccessibility of tea catechins and to determine the stability of polyphenol–protein complexes during simulated digestion in vitro	Results showed that the addition of milk to tea leads to the formation of protein–polyphenol complexes, which are not protease-stable and are broken down to a major extent during small intestinal digestion
156	<i>P. dulcis</i> (Mill.) D.A. Webb	This placebo-controlled study was carried out in 16 healthy volunteers in order to perform a targeted analysis of phase II and microbial-derived urinary phenolic metabolites after the intake of almond skin polyphenols	Maximum urinary excretion of conjugated metabolites of flavan-3-ols (glucuronide, O-methylglucuronide sulfate and O-methyl sulfate) and naringenin (glucuronide) derived from phase II metabolism was attained at 2-6 h after consumption of the almond skin extract. Hydroxyphenylvalerolactones, which are formed at the beginning of the microbial biotransformation pathway, reached maximum urinary levels at 6-10 h after the intake of almond polyphenols. The principal component analysis revealed that changes in the urinary metabolites during the first 6 h after the intake of almond polyphenols were attributed to conjugated metabolites of (epi)catechin, whereas changes observed at 6-24 h were mainly due to conjugated forms of hydroxyphenylvalerolactones and other microbial-derived phenolic metabolites
157	Diosmin	This study summarized the data on plasma pharmacokinetics and metabolism of diosmin administered orally at a dose of 500 mg to 8 healthy human volunteers. HPLC-MS/MS and GC/MS were used and samples were analyzed without enzymatic digestion or after hydrolysis with glucuronidase, sulfatase or a combination of both. In order to investigate the metabolite structure, oxidative metabolites, as well glucuronide, were also obtained in vitro by diosmin incubation with liver microsomes	Following enzymatic degradation, diosmin levels on the order of 10 ng/mL were observed in plasma; based on the enzymatic procedure, glucuronide and mixed conjugate (glucurono–sulfo conjugate) were the main metabolites in plasma, in addition to pure sulfated conjugate and monoglucuronide
158	Tangeretin	This study examined the intestinal metabolism of tangeretin using human intestinal Caco-2 cells, human intestinal microsomes and recombinant cytochrome P450 (CYP) isoforms. The metabolites were identified by LC-MS/MS	Most of the metabolites in Caco-2 cells were increased by pretreating the cells with a CYP1A1 inducer, TCDD, and were decreased by treatment with a CYP1A1 inhibitor, α -naphthoflavone. In addition, directional transport of some of the metabolites at Caco-2 cell monolayers cultured in the Transwell insert was observed

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Table I. Cont. Summary of studies on polyphenols presented at the 4th International Conference on Polyphenols and Health.

Ref.	Polyphenols/plants/natural interventions	Study design	Outcome
159	Chlorogenic acid	The inhibitory effects of 5-CQA and its components caffeic acid (CA) and quinic acid (QA) on porcine pancreatic α -amylase (PPA) isozymes PPA 1 and PPA 2 were investigated using <i>p</i> -nitrophenyl- α -D-maltoside as substrate at pH 6.9 and 30 °C	The inhibitory potencies of 5-CQA against these two isozymes were similar, and those of CA and QA were also similar. These inhibitors do not discriminate between the isozymes. The IC ₅₀ values of 5-CQA, CA and QA against both isozymes were 0.08, 0.4 and 30 mM, respectively. Their inhibitory potencies were on the order of 5-CQA > CA >> QA. The inhibition models of 5-CQA and CA were investigated by kinetic analysis and the inhibitor constants K_i and K_i' were determined. 5-CQA and CA showed mixed-type inhibition against both isozymes with $K_i > K_i'$, indicating that the inhibitors bind to ES more tightly than to E. The results obtained suggest that 5-CQA and its hydrolysis products might be useful for inhibiting α -amylase in the digestive tract, and may suppress diabetes and obesity
160	Polyphenols	To determine the influence of nonionic surfactants as solubilizing agents on the absorption of lipophilic polyphenols using Caco-2 cell cultures. Polyphenol partition coefficients were analyzed by the shake-flask method. Polyphenols were incorporated in micellar solution and dissolved in HBSS under stirring at room temperature. Their absorption was determined in Caco-2 cell cultures on Transwell inserts using pure polyphenols in HBSS as a reference. Cell integrity was monitored before and after the experiment by measuring the TEER value and lucifer yellow transport (indicating the paracellular route) at the end of the permeability study. Polyphenol concentrations in both apical and basal solutions were determined by reversed-phase HPLC with photodiode array detector	The results demonstrate the influence of nonionic surfactants on polyphenol transport
161	Dihydroresveratrol	The plasma concentration of dihydroresveratrol after oral administration of 60 mg/kg was studied in Sprague-Dawley rats. Dihydroresveratrol was analyzed by HPLC with diode array detection at 276 nm	Compound was detected in plasma at concentrations of 1.06 ± 0.20 and 0.88 ± 0.22 mM, respectively, at 10 and 30 min. Moreover, glucuronide and sulfate conjugates were found in higher amounts than the parent compound. The identity of the metabolites was confirmed by HPLC-MS. At 10 min the glucuronide and sulfate concentrations were 12.6 ± 1.1 and 4.41 ± 1.30 mM, respectively, increasing to 33.5 ± 0.9 and 6.40 ± 1.26 mM at 30 min
162	<i>trans</i> -Resveratrol	The oral availability of <i>trans</i> -resveratrol was studied using P-glycoprotein (P-gp)-deficient (<i>mdr1</i> ^{-/-}) mice. Male wild-type FVB and <i>mdr1</i> ^{-/-} mice with a body weight of 16-29 g were administered 60 mg/kg of <i>trans</i> -resveratrol by gavage dissolved in 20% cyclodextrin. The samples were analyzed by HPLC with diode array/UV detection	Results indicate that the plasma levels of <i>trans</i> -resveratrol in P-gp-deficient mice were not different from those of wild-type animals. Concentrations of <i>trans</i> -resveratrol were 1.84 ± 0.30 , 3.91 ± 1.69 and 0.75 ± 0.25 mM, respectively, in wild-type and 1.65 ± 0.10 , 3.29 ± 0.56 and 1.37 ± 0.49 mM, respectively, in <i>mdr1</i> ^{-/-} mice at 10, 15 and 30 min. The most abundant metabolite was the glucuronide, with values of 51.7 ± 14.7 , 53.9 ± 11.2 and 57.9 ± 5.8 mM, respectively, in wild-type and 31.8 ± 8.3 , 45.6 ± 5.7 and 60.8 ± 4.4 mM, respectively, in <i>mdr1</i> ^{-/-} mice. The sulfate conjugate concentrations were 6.88 ± 1.86 , 8.17 ± 1.03 and 5.12 ± 0.30 mM, respectively, in wild-type and 5.20 ± 1.15 , 7.11 ± 1.60 and 3.64 ± 0.73 mM, respectively, in P-gp-deficient mice

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Table I. Cont. Summary of studies on polyphenols presented at the 4th International Conference on Polyphenols and Health.

Ref.	Polyphenols/plants/natural interventions	Study design	Outcome
163	<i>trans</i> -Resveratrol	This study aimed to assess the bioavailability of <i>trans</i> -resveratrol, considering the intestinal metabolism, via a population pharmacokinetic model after i.v. and p.o. administration of 2, 10 and 20 mg/kg to male Sprague-Dawley rats. Plasma was analyzed by HPLC. Concentrations of <i>trans</i> -resveratrol and its metabolites were sequentially evaluated using the nonlinear mixed-effects approach implemented in NONMEN VI	Results showed that the metabolic conversion rate constant of resveratrol to sulfate was > 10 times lower than that of glucuronide. Glucuronide formation was dose-dependent, being slower at 2-10 mg/kg (3.82 h) compared to 20 mg/kg (4.5 h). Glucuronide and sulfate showed linear elimination. An integrated model was developed to simultaneously describe the pharmacokinetics of <i>trans</i> -resveratrol and its metabolites and the relative contribution of intestinal metabolism
164	Curcumin	A study was planned with a view to improve the bioavailability of curcumin (Cmn). Solid lipid nanoparticles (SLNs) were prepared by microemulsion technique and their efficacy in the treatment of menopause-associated memory loss and anxiety using ovariectomized rats and in depression using the forced swim test (FST) model in rats was investigated	The Cmn-SLNs were able to withstand the ICH accelerated stability test conditions of 3 months and long-term stability testing for 12 months. In vitro release was predominantly by diffusion and release was prolonged up to 7 days. The in vivo pharmacokinetics using LC/MS/MS method revealed that Cmn-SLNs demonstrate at least a 44-fold increase (C_{max} : 12,000 ng/mL) in plasma levels of drug, indicating an enhancement in oral bioavailability in comparison to free Cmn (274 ng/mL). Treatment with Cmn-SLNs at 30 and 45 mg/kg significantly attenuated memory deficits in comparison to free Cmn at corresponding doses at the end of 7 weeks. FST results confirmed the effectiveness of Cmn-SLNs in depression at very low doses of 2.5 and 1 mg/kg. These results clearly indicate the promise of Cmn-SLNs for oral delivery
165	Hydroxytyrosol and hydroxytyrosyl acetate	The absorption of hydroxytyrosol and hydroxytyrosyl acetate and the extent to which they are conjugated and metabolized during transfer across Caco-2 cell monolayers was investigated	The results indicated that both compounds were transferred across human Caco-2 cell monolayers; hydroxytyrosyl acetate exhibited a P_{app} ratio 1.6-fold higher than free hydroxytyrosol, indicating that it was better absorbed. Homovanillyl alcohol was the only conjugate detected as a result of hydroxytyrosol metabolism, representing 20% of the total metabolites detected in the basolateral compartment after 2 h of incubation. Hydroxytyrosyl acetate was largely converted to free hydroxytyrosol (38.4%) and subsequently metabolized to homovanillyl alcohol (6.7%). Moreover, small amounts of hydroxytyrosyl acetate glucuronide (17.4%) together with nonmetabolized hydroxytyrosyl acetate (37.5%) were also detected

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Ref.	Polyphenols/plants/natural interventions	Study design	Outcome
166	Quercetin	In this study, integrated assessment of the behavior of quercetin delivered in aqueous oil-in-water emulsions and oil-in-water emulsions containing surfactants (Labrasol, Span 80), using models of gastric/duodenal digestion and the differentiated Caco-2 cell monolayer small intestinal transport model was done, and the rate of quercetin uptake by Caco-2 cells and the rate of apical and basolateral efflux of quercetin and the glucuronide and sulfate conjugates that are produced by these cells were also evaluated	The presence of oil or surfactants considerably increased the stability and aqueous solubility of quercetin. When subjected to duodenal digestion, the oil-in-water emulsion systems were digested to release fatty acids and there was an increase in the concentration of quercetin in the bulk aqueous phase. It was observed that the delivery system containing micelles derived from duodenal digestion of the oil-in-water emulsion with surfactants inhibited apical efflux and enhanced basolateral efflux of quercetin conjugates such that it enhanced absorption by 7-fold compared to the aqueous delivery system
167	Flavonoid glycosides	The different pH values representative of the gastrointestinal (GI) tract, along with reasonable incubation times, have been investigated for a wide range of flavonoid glycosides	Studies have shown that glycosidases are also present in human saliva. Interindividual variability and effect of oral hygiene were discussed
168	Procyanidins (<i>Vitis vinifera</i>)	The present work aimed to study the effect of procyanidins on the activity of the digestive protease trypsin and the effect that different carbohydrates have on the trypsin–procyanidin system. Procyanidins were extracted from <i>V. vinifera</i> grape seeds and then fractionated through a TSK Toyopearl HW-40(s) gel column, yielding several fractions with different degrees of polymerization. The inhibition of trypsin was assessed using the substrate <i>N</i> -benzoyl-D,L-arginine- <i>p</i> -nitroanilide in the presence of different carbohydrates	The interaction phenomena and the ensuing aggregate formation were achieved using nephelometry, fluorescence quenching and dynamic light scattering (DLS). This work may be relevant in understanding the influence of tannin-rich foods as antinutritional factors through inhibition of digestive enzymes, and in the development of pharmaceutical approaches to treat obesity
169	Xanthones	The study aimed to test whether the cardiovascular impact of naturally occurring xanthones is modulated either by taste or body posture. Two plants were tested: BX, which contains both bitter principles and xanthones, and BC, which contains bitter substances but not xanthones. Continuous recordings of the finger pulse contour of the experimental participants were obtained with the Finometer	BX capsules decreased diastolic pressure ($P = 0.032$), total peripheral resistance ($P = 0.017$) and arterial compliance ($P = 0.049$) in the supine position. There were no changes for the capsules in the upright position or for the fluid extract in either position
170	<i>B. oleracea</i> var. <i>sabellica</i> L.	The flavonoids and hydroxycinnamic acids of curly kale (<i>B. oleracea</i> var. <i>sabellica</i> L.) were characterized and quantified primarily based on HPLC-DAD-ESI-MSn analysis	Thirty-two phenolic compounds, including glycosides of quercetin and kaempferol and derivatives of coumaric, ferulic, sinapic and caffeic acid, were identified. Two flavonol aglycones were identified, quercetin and kaempferol, with a total content of 44 and 58 mg/100 g of fresh weight (f.w.), respectively. This study shows that curly kale is a valuable dietary source of polyphenols, especially flavonoids, with a total content of 0.6 rutin eq/100 g f.w.

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Ref.	Polyphenols/plants/natural interventions	Study design	Outcome
171	Delphinidin and cyanidin	This study aimed at testing whether the anthocyanidins delphinidin and cyanidin could exert cytotoxic effects on different colorectal cancer cell lines and whether their cytotoxicity corresponded to their potency to induce redox alterations in these cells	Results showed that metastatic cell lines were sensitive to anthocyanidins, whereas no cytotoxic effect was detected in primary tumor cells. The strength of the cytotoxic effect of delphinidin and cyanidin in metastatic cells was inversely proportional to cellular drug sensitivity; the more the cell line was resistant to the antineoplastic agent camptothecin, the more it was sensitive to anthocyanidins. The cytotoxic properties of delphinidin and cyanidin correlated with their ability to induce glutathione reductase inhibition, glutathione depletion and ROS accumulation in these cells
172	Genistein and daidzein	The purpose of this study was to determine the inhibition by isoflavones (genistein [Gen] and daidzein [Daid]) of NTF disposition mediated by the BCRP/ABCG2 protein in wild-type mice compared with <i>Bcrp1</i> knockout mice	The in vivo interaction of flavonoids with several ABC transporters, including BCRP/ABCG2, was demonstrated. Gen and Daid have been identified as the main isoflavones accumulated in soy cotyledons. Plasma concentrations of NTF were significantly higher in wild-type mice after isoflavone administration ($21.1 \pm 7.1 \mu\text{g/mL}$ vs. $14.2 \pm 6.5 \mu\text{g/mL}$; $P < 0.05$), indicating inhibition of BCRP. In addition, milk secretion was inhibited since milk/plasma ratios were significantly higher in wild-type lactating females without isoflavones: 7.1 ± 4.2 (NTF, control) vs. 4.2 ± 1.6 (NTF+Gen-Daid) ($P < 0.05$). Moreover, inhibition by isoflavones of bile excretion of NTF was shown since the bile NTF levels were significantly decreased by isoflavone administration: $8.8 \pm 3.4 \mu\text{g/mL}$ in wild-type (NTF, control) vs. $3.7 \pm 3.3 \mu\text{g/mL}$ in wild-type mice (NTF+ Gen-Daid) ($P < 0.05$). Plasma, milk and bile concentrations of NTF were unmodified in <i>Bcrp1</i> knockout mice in all experimental conditions. These results accurately support the in vivo modulation of BCRP/ABCG2 by isoflavones such as genistein and daidzein when the drug is a good substrate of this transporter
173	Chlorogenic acids	A study investigated the plasma appearance of coffee phenolic acids derived from CGAs after ingestion of a single dose of instant coffee	Two groups of metabolites appeared over 12 h after coffee ingestion when plasma phenolic acids were measured. Caffeic, ferulic and isoferulic acids appeared rapidly, with mean C_{max} of < 2 h after ingestion. Dihydrocaffeic and dihydroferulic acids peaked much later (between 10 and 12 h)
174	Cocoa flavanols	A randomized, triple-blind, crossover study to investigate the absorption and metabolism of cocoa flavanols from a high-flavanol chocolate made with added sugar and a high-flavanol chocolate containing the sugar substitute maltitol; a nutrient-matched low-flavanol control product was also fed. High-flavanol products contained 259 mg cocoa flavanols, while the low-flavanol chocolate contained 48 mg of cocoa flavanols. Plasma levels of flavanols were assessed using HPLC with fluorescence detection	Consumption of the maltitol-containing product led to a 23% decrease in the overall plasma levels of flavanols compared with the sugar-containing product ($P = 0.002$). Despite this reduction in the plasma pool, t_{max} was unaffected

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Ref.	Polyphenols/plants/natural interventions	Study design	Outc
175	Apple juice	The purpose of this study was to distinguish the effect a whole-apple phytonutrient composition of metabolic syndrome markers towards fruit sugars in clarified apple juice. The effects of apple components in a smoothie liquefied form, completed by Pomelite dried soluble fiber and Pomactive apple polyphenolic extract (verum), towards a clarified apple juice containing no more dietary fiber and flavonoids (placebo) were studied in a randomized, double-blind postprandial study including 50 volunteers	Pomelite and Pomactive may have a positive effect on metabolic syndrome by lowering fructose assimilation
176	Genistein, quercetin and chrysin	In this study the interaction between flavonoids and intestinal CYP activities was investigated using Caco-2 cells	Genistein, quercetin and chrysin induced a strong concentration-dependent inducing effect on CYP1A1 activity. Quercetin was shown to inhibit the constitutive CYP3A4 activity of Caco-2 cells and to impair its induction by 1,25-vitamin D ₃ . Quercetin, genistein and mainly chrysin were also detected as direct inhibitors of 1,25-vitamin D ₃ -induced CYP3A4 activity
177	Fruits and vegetables	In this study 59 subjects, selected on the basis of an increased risk of developing CVD and low fruit and vegetable consumption, were randomly assigned to either a control group (habitual diet, n = 20) or one of two intervention groups, increasing their intake of flavonoid-rich (HF, n = 19) or flavonoid-poor (LF, n = 20) fruits and vegetables over a 6-month period. Fecal bacteria were enumerated using fluorescent in situ hybridization (FISH) and species diversity monitored using PCR-DGGE	Increased fruit and vegetable intake, either flavonoid-rich or flavonoid-poor, stimulated the growth of <i>Bifidobacterium</i> , <i>Eubacterium rectal Clostridium</i> , <i>Coccidioides</i> and <i>Faecalibacterium prausnitzii</i> . These bacteria, particularly eubacteria which contain flavonoid-degrading bacterial species, are important members of the saccharolytic intestinal microbiota and have been implicated in protection from disease both locally within the gut and systemically
178	Isoflavones	By using selected enzyme sources and isoflavone sources, a novel natural style soy-based food was developed in which isoflavones existed mainly as some aglycones. A human interventional study was then carried out to investigate the different efficiency of absorption of isoflavones from the ingested designed food, which contained isoflavones either as the aglycone or the glycoside form	It was found that the aglycone form of isoflavone was absorbed and excreted faster and more efficiently than the ingested glycoside form, although the amount excreted was similar, with significantly greater bioavailability for daidzein than for genistein
179	Epigallocatechin gallate (EGCG), epigallocatechin (EGC) and epicatechin gallate (ECG)	The study investigated the influence of dietary proteins (milk protein, casein, soy protein) on the pharmacokinetics of EGCG, EGC and ECG in humans. In a crossover design with 1-week intervals, 24 healthy adult women (fasted overnight) consumed a single oral dose of 300 mL. Plasma concentrations of catechins were analyzed by HPLC with electrochemical detection	Compared to controls the addition of milk (M), casein (C) and soy (S) protein significantly decreased the bioavailability of total catechins (mean \pm SEM: AUC = M 68 \pm 5%, C 67 \pm 6% and S 77 \pm 6%; C _{max} = M 62 \pm 5%, C 62 \pm 7% and S 69 \pm 5%) but not of EGC (mean \pm SEM: AUC = M 134 \pm 10%, C 122 \pm 8% and S 121 \pm 9%; C _{max} = M 117 \pm 8%, C 125 \pm 12% and S 119 \pm 9%)
180	Grape antioxidant dietary fiber	The aim of this study was to identify the main phenolic metabolites present in rat feces after grape antioxidant dietary fiber (GADF) ingestion using a combination of different MS/MS modalities on a triple quadrupole instrument	In most studies the metabolic fate of pure products (e.g., EC) or simple plant extracts (e.g., purified procyanidins) is examined

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Ref.	Polyphenols/plants/natural interventions	Study design	Outcome
181	Quercetin	An anesthetized, mesenteric lymphatic/duodenum-cannulated rat model was used to investigate the role of lymphatic absorption with intraduodenally administered drugs. Quercetin dissolved in PEG400: ethanol (4:1 v/v) solution was administered intraduodenally. Lymph fluid and plasma samples were prepared by protein precipitation, and then analyzed by HPLC with a UV detector	The AUC of quercetin in lymph fluid was higher than that in plasma. However, the elimination half-life ($t_{1/2}$) of quercetin in plasma was longer than that in lymph fluid. The time to reach the peak plasma concentration of quercetin (t_{max}) in lymph fluid after intraduodenal administration was longer than in plasma
182	Anthocyanins and hydroxycinnamates	In this study the fate of two types of grape polyphenols in the rat, i.e., anthocyanins and hydroxycinnamates, was investigated	Results showed that both classes of compounds rapidly accumulated in the kidney. There, the main phase II metabolism was methylation at the level of their catechol moieties. These findings point to the fact that the urinary elimination of grape polyphenols does not result in only glomerular filtration (i.e., a passive event), but is also based on carrier-mediated uptake from the blood into the kidney tubular cell, methylation and carrier-mediated excretion into the tubular lumen
183	Hydroxycinnamic acids	Activities of the phase II enzymes UDP-glucuronosyl-transferases (UGTs) and sulfotransferases (SULTs) towards five dietary hydroxycinnamic acids were evaluated	Analysis of kinetics of hydroxycinnamic acid conjugation in the human liver and intestinal S9 homogenates revealed that sulfation is the major pathway of metabolism. Assessment of activity using SULTs showed that SULT1A1 was active in conjugation towards all five phenolic acids. Only isoferulic acid was significantly glucuronidated by human liver S9 homogenates, explained by the high activity of liver-specific UGT1A9
184	Quercetin	The objective of this study was to investigate the effects of various components (lipids, surfactants, micelles) on the intestinal uptake and transport of a lipophilic flavonoid (quercetin) using a small intestinal epithelial cell transport model (Caco-2/TC7 cell monolayers). Quercetin was incorporated into the various delivery solutions which were applied to the apical compartment of the Caco-2 cell monolayers	As a result of the influence of the surfactants on the rates of apical and basolateral efflux, the apical:basolateral ratio was changed from 3.2:1 for quercetin in water to 0.13:1 for quercetin in the mixed micelle system containing surfactants
185	Resveratrol	The prodrugs resveratrol triacetate (RTA) and resveratrol-trimPEG ₁₉₀₀ (RPEG) were formed by linking the hydroxyls to methyl groups or polyethylene glycol chains via carboxy ester bonds. Glucosyl groups were joined to the resveratrol kernel via a succinic acid moiety to give 3,4,5-tri-(D-glucose-3-O-succinyl)resveratrol (RGS) and then permeation experiments were performed	In permeation experiments with explanted rat intestinal segments, the mesylate was transported without modification, while resveratrol and RTA were rapidly hydrolyzed at the intestinal surface or inside enterocytes, and were then processed as resveratrol. When the PEGylated derivative was provided on the apical side, unconjugated resveratrol accounted for about 50% of the material in the basolateral side chamber. Pharmacokinetic determinations showed that administration of RGS resulted in concentration–time curves shifting to longer times from administration in comparison to those obtained with an equimolar dose of resveratrol, a useful modulation of pharmacokinetics

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Ref.	Polyphenols/plants/natural interventions	Study design	Outcome
186	Oleuropein aglycones	A study investigated the absorption and metabolism of two oleuropein aglycones, 3,4-dihydroxyphenylethanol elenolic acid (3,4-DHPEA-EA) and 3,4-dihydroxyphenylethanol elenolic acid dialdehyde (3,4-DHPEA-EDA), using two models of the small intestine	Data from both the isolated rat small intestine model and human Caco-2 cell monolayers indicated that 3,4-DHPEA-EA and 3,4-DHPEA-EDA may be transferred across the small intestine. In the small intestinal model the secoiridoids were found to transfer across both the jejunum and ileum, and were both extensively metabolized to glucuronides. Apparent permeability coefficients (P_{app}) in Caco-2 monolayers were significantly higher than 1×10^{-6} ($P = 0.001$) for both compounds. However, in isolated jejunum and ileum, only 3,4-DHPEA-EA had a P_{app} higher than 1×10^{-6} ($P = 0.001$), with 3,4-DHPEA-EDA not being detected in serosal fluid due to its extensive metabolism
187	Irilone	An experiment was planned with two objectives: 1) to test the human gut microbiota for its ability to transform irilone; and 2) to investigate the bioavailability of irilone in a pilot intervention study in 7 volunteers who ingested a single dose of a commercially available red clover dietary supplement	Irilone was largely resistant to transformation by fecal slurries in the human subjects. Only one metabolite, dihydroirilone, was formed in minor amounts. A single intake of an amount as low as 3.8 mg of irilone (of 38.8 mg irilone in total) by the 7 volunteers resulted in a mean total irilone plasma concentration of 351 ± 156 nM 6.5 h post-ingestion, compared to the mean plasma concentrations found for formononetin (111 nM), daidzein (385 nM), biochanin A (14 nM) and genistein (63 nM), which were expected to be the main irilone metabolites in plasma
188	Resveratrol	The purpose of this study was to demonstrate that a 99% pure synthetic, nature-identical form of <i>trans</i> -resveratrol (resVida®) is absorbed and effectively distributed into the plasma. A secondary objective was to compare the absorption of synthetic and a natural resveratrol supplement (40% <i>trans</i> -resveratrol) derived from <i>Polygonum cuspidatum</i> . Twelve healthy adult volunteers consumed 30 mg synthetic and 32 mg natural resveratrol in a crossover design. Plasma free and total <i>trans</i> -resveratrol and dihydroresveratrol were measured by HPLC/MS	Resveratrol from both forms appeared in the plasma within 30 min of ingestion and returned to baseline within 6 h. The synthetic form reached an earlier t_{max} (0-480 min) (71.3 ± 16.8 min vs. 132.5 ± 15.0 min; $P = 0.03$) and greater C_{max} (0-480 min) (273.4 ± 16.7 ng/mL vs. 212.4 ± 22.6 ng/mL; $P = 0.04$) compared to natural resveratrol
189	Flavanoids	This study aimed to test the impact of selected polyphenols on the modulation of P-gp activity in human Caco-2 cells. Polyphenols used here could be classified into several groups: coumarin, phenolic acid and flavonoids (flavanone, flavanonols, flavanoid aglycone, flavonones, flavonol) and isoflavones. Capillary flow cytometry was used to evaluate the intrinsic load of rhodamine 123 in the presence of the different polyphenols as compared to the activity of PSC-833, a selective P-gp inhibitor	Results showed that certain polyphenols can increase (coumarin +14%; flavanones +14%; isoflavones +20%) or at least reestablish (flavanone) the initial activity of P-gp, which is decreased in the inflammatory phenotype. Polyphenols can also inhibit P-gp activity in Caco-2 cells (flavanonol 20%; flavonoid aglycone 12%) in a manner that could decrease the doses of chemotherapeutics while increasing the concentration of intracellular xenobiotics

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190	Caffeoyl and feruloyl quinic acid esters and free caffeic acid	This study estimated usual dietary intakes of the 10 phenolic acids known in coffee (caffeoyl and feruloyl quinic acid esters and free caffeic acid) and total polyphenols (Folin assay) among 67,703 French women from the E3N-EPIC cohort study and prospectively examined associations between these dietary intakes and the risk of invasive breast cancer	Coffee provided a median of 476 mg/day phenolic acids, which contributed between 86% and 100% of the various caffeoyl and feruloyl esters and 3% of the free caffeic acid. Other foods contained the same phenolic acids as found in coffee, but their contribution was relatively low. Coffee also contributed 32% of the total polyphenol intake, the median of which was 2122 mg/day (interquartile range: 1583-2785 mg/day). No associations were found between breast cancer risk and dietary intakes of total polyphenols or coffee phenolic acids
191	Resveratrol	This study aimed to assess urinary resveratrol as a biomarker of wine consumption. Analyses of urinary resveratrol metabolites were carried out by LC-MS/MS	The results of this study showed that most of the dietary sources of resveratrol were wines (98.4%). Urinary resveratrol metabolites can be correlated directly with the daily amount of wine consumed
192	Flavonoids and resveratrol	The aim of this study was to estimate flavonoid and resveratrol dietary intake and to assess the main food sources in an adult Spanish population. The study included 40,683 subjects aged 35-64 years from northern and southern regions of Spain who were included in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Spanish cohort	The main sources of total flavonoid intake were apples (23%), red wine (21%), unspecified fruit (12.8%) and oranges (9.3%). The most important sources of resveratrol and piceid were wines (98.4%) and grapes and grape juices (1.6%), whereas other sources were minimal (< 0.01%)
193	Resveratrol	In a randomized, crossover, controlled trial, 50 volunteers with a high rate of cardiovascular risk factors were included to study the association between wine consumption and cardiovascular health. Subjects were given 300 mL of red wine, 300 mL of dealcoholized red wine (polyphenols control) or 94 mL of gin (alcohol control) every day during 28 days. Samples of 24-h urine were collected on the last day of each period. To evaluate red wine consumption, resveratrol and its metabolites were measured in urine samples by HPLC-MS/MS	In this study several phase II metabolites (glucuronide, sulfate and sulfoglucuronides) of resveratrol and piceid were identified. In addition, dihydroresveratrol derivatives (glucuronides, sulfates and sulfoglucuronides) were identified as microbial resveratrol metabolites. Resveratrol metabolites were reported to be nutritional biomarkers to evaluate red wine consumption
194	Anthocyanidin	This study assessed the age and time trends for anthocyanidin intake in infants and toddlers in Germany and analyzed 3-day weighed dietary records of subjects aged 3 months to 3 years in the period of 1990 to 2008	For the study period (1990-2008) 4,364 3-day weighed dietary records of 907 subjects (457 girls, 450 boys) aged 3 months to 3 years were available. Subjects consumed 5,664 food items consisting of 858 different ingredients including 245 fruits, vegetables and juices
195	Cocoa and chocolate products	This study was designed for the dietary assessment of cocoa and chocolate products in epidemiological studies	It was concluded that with only high-quality food frequency questionnaires (FFQ) providing valid estimates of catechin and procyanidin intake would it be possible to examine the association of cocoa products with disease risk and to distinguish them from effects due to other PC

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Ref.	Polyphenols/plants/natural interventions	Study design	Outcome
196	Polyphenols	This study investigated the polyphenol composition of foods and dietary intake in Finland. Contents of anthocyanins, proanthocyanidins, phenolic acids, ellagitannins, flavonols, flavones and flavanones were analyzed from 143 food items of plant origin including berries, fruits, vegetables, grain products and beverages	The highest contents of anthocyanins, proanthocyanidins, other flavonoids, phenolic acids and ellagitannins were found in bilberry, chokeberry, grapefruit, rye and wheat bran, and cloudberry, respectively. The mean daily absolute intakes of phenolic acids, proanthocyanidins, anthocyanidins, other flavonoids and ellagitannins were 641 ± 363 , 128 ± 120 , 47 ± 79 , 33 ± 43 and 12 ± 37 mg, respectively, resulting in a total daily intake of these polyphenols of 861 ± 415 mg. The main polyphenol group was phenolic acids (74% of total intake). Coffee, cereals, tea and fruits were the main sources of the total intake of polyphenols. Coffee was the primary food item contributing to phenolic acid intake, berries to anthocyanidin intake, fruits (especially apple and citrus fruit) and tea for flavonol, flavanone and flavone intake, and berries, fruits and chocolate for proanthocyanidin intake
197	Flavanoids	The aim of this study was to form a network to fulfill the need for assembling knowledge and holistic information on the fate of 3 phytochemical groups (isothiocyanates, polyacetylenes and flavanoids)	In order to understand the fate of phytochemicals from farm to fork in an Irish population, probabilistic exposure assessment models for dietary intake and bioavailability of phytochemicals will be developed
198	Flavonoids	This study was designed to identify patterns and sources of dietary intake of individual flavonoids in an Australian population, data from the 24-hour diet recall questionnaire of the national nutrition survey ($n = 10,851$) were combined with USDA data on flavonoid content of foods to identify consumption patterns and key sources	Results showed that black and green teas were the dominant sources of flavonols and flavon-3-ols. English spinach (luteolin) was the major flavone sources. Wine was the major anthocyanadin source (delphinidin, malvidin, peonidin and petunidin), with smaller amounts from cherry (pelargonidin and peonidin) and blueberry (delphinidin, malvidin, peonidin and petunidin)
199	Polyphenol	This study assessed the polyphenol intake for 498 phenolic compounds using the new Phenol-Explorer database on polyphenol content in foods. Dietary intake was assessed using at least six 24-h dietary records collected during a 2-year period from 3,078 men and 2,375 women aged 45-60 years who participated in the SU.VI.MAX cohort study during 1995-1997	Analyses were stratified by gender, age, education level and occupational category. These data were suggested to be useful for further prospective analyses of the relationship between polyphenol intake and incidence of several pathologies in the SU.VI.MAX cohort
200	Coffee and coffee compounds	The antioxidant potential of selected coffee constituents (polyphenols, hydroxybenzenes, <i>N</i> -methylpyridinium compounds) and extracts in a cell-free system was investigated in the colon cancer cell lines HT-29 and Caco-2. DNA damage (Comet assay) and <i>tert</i> -butylhydroperoxide-induced ROS levels were monitored. Modulation of DNA damage was also studied in a human intervention study with coffee, either rich in chlorogenic acids or in <i>N</i> -methylpyridinium ion	The highest cell-free antioxidant capacity ($1.3\text{--}0.9$ mM Trolox®) was observed with the coffee compounds chlorogenic acid, caffeic acid and phenolic degradation products (catechol, 1,2,4-trihydroxybenzene); alkylpyridines (trigonellin, <i>N</i> -methylpyridinium) were clearly less effective. The cellular ROS level was reduced in HT-29 cells by chlorogenic acid (by 3 mM or more), phenolic degradation products (> 20 mM), trigonellin (> 30 mM) and coffee extracts (> 10 mg/mL), but not by <i>N</i> -methylpyridinium. Oxidative DNA damage was only decreased by caffeic acid (> 1 mM, Caco-2 cells) and oxidative DNA damage in blood was significantly reduced by both coffee brews

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201	Flavonoid	In this study the antioxidant activity of different phenolic acids from flavonoid degradation was evaluated by FRAP and TEAC in vitro assays. Different combinations were also evaluated for their antioxidant activity so as to conclude about possible interactions	All compounds showed lower antioxidant activity than flavonoid aglycones. Antagonist effects were observed in combinations of phenolic acids and flavonoid and phenolic acids
202	Gallic acid	This study investigated the antioxidant profile of gallic acid (0.2 mg/kg/day corresponding to the average intake of 12.8 mg/person/day) consumption in a 3-day, placebo-controlled intervention trial	Results showed a significant reduction in endogenous formation of oxidized purines and pyrimidines (55% and 67%, respectively) in peripheral lymphocytes with lesion-specific endonucleases (FPG and EndoIII). Gallic acid increased activities of CuZn-SOD, GST-pi and GPX enzymes by 61%, 22% and 60%, respectively
203	Polyphenols	The antioxidant properties of 26 molecules representative of the main groups of dietary polyphenols, namely phenolic acids, flavonoids and stilbenes, were compared. All compounds were evaluated using in vitro approaches including the Folin-Ciocalteu reducing test, the DPPH scavenging activity assay and the hemolysis inhibition test on human blood cells treated with MPH free radical	Results demonstrated that the most bioactive compounds were quercetin, myricetin, dimer B ₂ , epicatechins and catechin followed by 3,4-diOH benzaldehyde, caffeic, chlorogenic and ferulic acids. These compounds significantly inhibited (2-4-fold) MPH free radical-induced hemolysis and were more efficient than vitamin C
204	Red propolis	Ethanol extracts of various red propolis (EEP) were compared with those of Brazilian Baccharis origin and Chinese poplar origin propolis. The qualitative and quantitative analysis of polyphenols in EEP from Shandong China was carried out by HPLC with photo-diode array (PDA) detection	EEP from Shandong China had the most potent antioxidant activity followed by Brazilian Baccharis origin > Brazilian red > Chinese poplar origin > Cuban red propolis. Seventeen compounds, comprising 9 flavonoids, 5 aromatic carboxylic acids and 3 phenolic acid esters were identified. EEP from Shandong contained large amounts of antioxidant compounds such as galangin and phenethyl caffeate
205	<i>Malaxis acuminata</i> D. don	This study characterized stilbenoids of <i>M. acuminata</i> using UV, IR, MS, ¹ H-NMR and ¹³ C-NMR. Antioxidant activity in in vitro models of DPPH and ABTS assay was also evaluated	Five stilbenoids, 3 of which were bibenzyls (3,4-dihydroxy-3,5'-dimethoxybibenzyl, 3-hydroxy-3,5'-dimethoxybibenzyl, 3,3'-dihydroxy-5-methoxybibenzyl) and 2 of which were 9,10-dihydrophenanthrenes (4-methoxy-9,10-dihydrophenanthrene-2,7-diol and 7-methoxy-9, 10-dihydrophenanthrene-2,5-diol) were identified. Only gigantol (3,4'-dihydroxy-3,5'-dimethoxybibenzyl) showed significant activity in the DPPH assay that was better than standard drug Trolox® in the ABTS assay. The dihydrophenanthrenes also exhibited good activity in the ABTS assay. The significant antioxidant activity shown by these stilbenoids validates the traditional claim of the <i>M. acuminata</i> plant as a tonic and rejuvenator

Continued

Table I. Cont. Summary of studies on polyphenols presented at the 4th International Conference on Polyphenols and Health.

Ref.	Polyphenols/plants/natural interventions	Study design	Outcome
206	Australian fruits and herbs	The antioxidant properties and phenolic composition in commercially grown endemic Australian fruits and herbs were investigated	Kakadu plum (<i>Terminalla ferdinandiana</i>) contained an exceptionally high level of total phenolic compounds (TP), 932.1 μmol GAE/gDW, which was 4.7-fold of that of a blueberry (<i>Vaccinum</i> spp., cv. Biloxi) control (199.0 μmol GAE/gDW). Quandong (<i>Santalum acuminatum</i>) contained 193.2 μmol GAE/gDW TP and was comparable to blueberry. The total reducing capacity (TRC; FRAP assay) of Kakadu plum exceeded 10-fold the TRC of blueberry. Tasmania pepper leaf (<i>Tasmannia lanceolata</i>), anise myrtle (<i>Syzygium anisatum</i>) and lemon myrtle (<i>Backhousia citriodora</i>) contained the highest TP (599.9; 328.8 and 184.8 μmol GAE/gDW, respectively). Tasmania pepper leaf exhibited superior antioxidant activity to all other herbs in the ORAC assay. Anise myrtle exhibited the highest TRC. Australian bush tomato (<i>Solanum centrale</i>), with TP content of 72.9 μmol GAE/gDW and TRC of 206.2 μmol Fe ⁺² /gDW, resembled the Chinese Barbary Wolfberry fruit (<i>Lycium barbarum</i>) from the same Solanaceae family. Tasmania pepper berry had similar TP to black pepper (92.9 μmol GAE/gDW) but 25% lower TRC
207	Korean onion (<i>Allium cepa</i> L.)	This study evaluated the total soluble phenolics and antioxidant activity using the ORAC assay of selected Korean onion (<i>A. cepa</i> L.). The inhibitory activity of onion extracts against α -amylase and α -glucosidases was also investigated	Quercetin, a major phenolic compound in onion, had the highest α -glucosidase-inhibitory activity, which correlated with the phenolic content and antioxidant activity of the extracts
208	Olive oil polyphenolic extract	The effect of olive oil polyphenolic extract (PFE) on serum antioxidant levels and hepatic lipid peroxidation (LP) following 1/3 partial hepatectomy (pHx) was studied in mice, along with implications of these effects on liver regeneration. The radical scavenging ability was also assessed in C57/BL6 mice	In vitro data showed that PFE was a 1.5-fold more effective radical scavenger than α -tocopherol. pHx induced a marked increase in liver MDA levels, as well as active consumption of serum antioxidants. Although the level of MDA in the PFE+pHx group was higher than in the control group, treatment with PFE prior to pHx reinforced TAC depletion and significantly reduced liver MDA level when compared to pHx animals
209	<i>Elaeis guineensis</i>	This study investigated the antioxidant, antihypertensive and cardioprotective effects of oil palm (<i>E. guineensis</i>) leaf methanolic extract in models of hypertensive rats. The extract was administered orally (500 mg/kg/day) to normotensive Wistar rats, spontaneously hypertensive rats (SHR) and L-NAME-induced nitric oxide (NO)-deficient hypertensive rats	The oil palm significantly ($P < 0.05$) attenuated BP increases in NO-deficient rats and prevented cardiac hypertrophy in SHR. It also decreased coronary arteriole wall-lumen ratio to normal values under NO deficiency and reduced myocyte damage by 39% in SHR. Administration of the extract significantly prevented this neurodegeneration by retaining the viable neurons to between 72-76% of the normal control rats. The extract significantly upregulated brain SOD and catalase activities (38% and 24%, respectively) while maintaining the MDA levels to near normal levels under NO deficiency

Continued

Table I. Cont. Summary of studies on polyphenols presented at the 4th International Conference on Polyphenols and Health.

Ref.	Polyphenols/plants/natural interventions	Study design	Outcome
210	Epicatechin gallate (ECG), epigallocatechin (EGCG), rutin, catechin and vitamin C	This study compared the total antioxidant activities (TEAC) of flavonoids of tea with ECG, EGCG, rutin, catechin and vitamin C. The concentration chosen was 1 mmol/L	The flavonoids were significantly more potent than vitamin C ($P < 0.001$), with TEAC ranging between 0.9–6.49 mmol/L Trolox [®] equivalents. The highest TEAC was EGCG (6.49 mmol/L) and the lowest was rutin (3.18 ± 0.1 mmol/L), whereas vitamin C was only 0.91 ± 0.22 mmol/L
211	<i>Grewia asiatica</i> , <i>Eugenia jamboiana</i> and <i>Carissa carandas</i>	The small tropical fruits of Pakistan (<i>Grewia asiatica</i> , <i>Eugenia jamboiana</i> and <i>Carissa carandas</i>) are rich in polyphenolics and are known for their medicinal value. The methanolic extracts of these fruits were separated into four distinct fractions including phenolic acids, monomer flavanols, oligomer procyanidins and anthocyanins using solid-phase extraction (SPE). Each fraction was further analyzed and verified by TLC, PC and other spectroscopic methods. The effect of the interaction of these flavonoids with different proteins were examined using the TEAC assay	Results showed that the antioxidant effects of the individual fractions were masked by the mixture. This masking was dependent upon both protein and flavonoid fractions
212	<i>Cytisus multiflorus</i>	To determine the phenolic composition and evaluate the antioxidant effects of <i>C. multiflorus</i> . Also, the extract was fractionated by reverse-phase HPLC and the major phenolic compounds of each fraction were identified by ESI-MS analysis	The total amount of phenolic compounds and flavones accounted for 140 mg/g and 47 mg/g of the ethanolic extract from <i>C. multiflorus</i> , respectively. The extract exhibited potent antioxidant effects, with an EC ₅₀ value of 29.7 mg/mL. The main phenolic compounds in the plant included chrysin and some glycoside derivatives of luteonine and quercetin
213	Curcuminoids	Structure-activity relationship studies of 3 curcuminoids (curcumin, demethoxycurcumin and bisdemethoxycurcumin) were performed in in vitro and ex vivo assays to determine their antioxidant effects. Hep G2 cell line was used in an MTT assay to compare their cytotoxicity	The ORAC _{ROO} against peroxy radical showed that the 3 curcuminoids were potent antioxidants in the following order: curcumin > demethoxycurcumin > bisdemethoxycurcumin. The cytotoxicity of demethoxycurcumin (IC ₅₀ = 38 mM) was somewhat lower than curcumin (IC ₅₀ = 29 mM) but higher than bisdemethoxycurcumin (IC ₅₀ = 66 mM)
214	<i>Corylus comuta</i>	The biological activities of <i>C. comuta</i> extracts rich in polyphenols were evaluated to determine their antiradical, antioxidant and antifungal properties	Phenolic composition of the most active extracts was determined by chromatographic methods. Structures of the main compounds were defined by nuclear magnetic resonance
215	Quercetin, isorhamnetin and catechins	Various quercetin, isorhamnetin and catechin metabolites were synthesized and characterized by ESI-MS and NMR. The evaluation of antioxidant activity was assessed in 3 different in vitro assays	The antioxidant activity of the compounds was shown to be dependent on the pH of the medium, showing higher activity at pH values closer to neutrality than at acidic pH values. Among the metabolites, methylated derivatives in the B-ring were the most active compounds compared to sulfates and glucuronides, particularly 3'-O-methylcatechin, which is able to scavenge free radicals similar to catechin
216	Genistein	The antioxidant and anticarcinogenic effects of genistein on Hep G2 and HT-29 cells were investigated. Cellular antioxidant activity was estimated using Hep G2 cells, a well-differentiated transformed cell line. Anticarcinogenic activity was measured by MTT assay in human colorectal cancer HT-29 cells. Apoptosis of HT-29 cells was observed by chromatin staining and fluorescent microscopy	The antioxidant effect of genistein was dose dependently increased in ORAC and was active against oxidative stress induced by AAPH and Cu ²⁺ in Hep G2 cells. The anticarcinogenic effects were also concentration- and time-dependently increased in HT-29 cells

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Table I. Cont. Summary of studies on polyphenols presented at the 4th International Conference on Polyphenols and Health.

Ref.	Polyphenols/plants/natural interventions	Study design	Outcome
217	<i>Amaranthus cruentus</i> , <i>Corchorus olitorius</i> , <i>Cucurbita maxima</i> , <i>Vigna unguiculata</i> , <i>B. oleracea</i> var. <i>capitata</i> and <i>Spinacea oleracea</i>	The total polyphenol and flavonoid content of aqueous extracts from <i>A. cruentus</i> , <i>C. olitorius</i> , <i>C. maxima</i> and <i>V. unguiculata</i> derived from fresh and boiled plant material was determined. For comparative purposes, cabbage (<i>B. var. capitata</i>) and spinach (<i>S. oleracea</i>) also cultivated in this region were included. The effects of cooking on antioxidant levels and activity were determined	The polyphenol and flavonoid content of fresh African green leafy vegetables was significantly greater than that of <i>B. oleracea</i> var. <i>capitata</i> and <i>S. oleracea</i> . Increased content was associated with increased antioxidant activity and was observed for the green leafy vegetables except <i>C. olitorius</i> , where levels remained constantly high
218	Green tea	This study was performed to test if the ingestion of green teas (GT) with different solid content (1.4 g/L, 1.6 g/L, 1.8 g/L and 2.0 g/L) could induce a dose-response effect on reducing potency (FRAP), antioxidant potential (TRAP) and triglyceride (TG) levels in healthy people	Results showed that the ingestion of GT 2.0 g/L significantly increased plasma FRAP at 1 h (+2.9%), 2 h (+2.5%) and 4 h (+3.6%). TG plasma levels were significantly reduced after 30 min (−9.2% and −8.5% for GT 1.8 g/L and GT 1.4 g/L, respectively), at 1 h (−17.1%, −14.2%, −8.5% and −11.8% for 2.0, 1.8, 1.6 and 1.4 g/L, respectively) and at 2 h (−16.7%, −14.3%, −10.8% and −21.3% for 2.0, 1.8, 1.6 and 1.4 g/L, respectively)
219	<i>Vernonia amygdalina</i> , <i>Manihot utilissima</i> , <i>Corchorus olitorius</i> and <i>Occimum gratissimum</i>	The antioxidant effects of 4 Nigerian tropical green leafy vegetable extracts (<i>V. amygdalina</i> , <i>M. utilissima</i> , <i>C. olitorius</i> and <i>O. gratissimum</i>) were investigated for their cellular antioxidant activity against peroxyl radical-induced oxidation in Hep G2 cells. Cytotoxicity was also evaluated in drug-sensitive and -resistant Lovo and Lovo-Adr cancer cell lines	Results showed that at a concentration of 1.00 mg/mL all of the extracts inhibited peroxyl radical-induced oxidation, <i>O. gratissimum</i> by 68%, <i>V. amygdalina</i> by 51.6%, <i>C. olitorius</i> by 32.4% and <i>M. utilissima</i> by 25%. Cytotoxicity studies in Lovo and Lovo-Adr cancer cell lines revealed that the extracts were active against both cell lines with IC ₅₀ s (µg/mL) ranging from 1.3 to 2.6 for Lovo and 1.5 to 2.7 for Lovo-Adr. Overall, <i>O. gratissimum</i> had the best antioxidant activity in Hep G2 cells and <i>V. amygdalina</i> was the most active in the Lovo and Lovo-Adr cancer cell lines
220	Wine pomace and juice pomace extract	To evaluate the hypolipidemic and antioxidant properties of wine and grape byproducts. In vitro testing was performed with the DPPH method and in vivo testing in hamsters	Wine pomace and juice pomace extracts showed very good in vitro antioxidant effects. In the animal model, both the wine- and juice-treated groups showed significant improvement in the lipid profile and CAT enzyme antioxidant activity in comparison with the hypercholesterolemic and control groups ($P < 0.05$). The values for SOD and GPx were better in the treated groups than in the hypercholesterolemic group
221	<i>Psidium guajava</i>	This study investigated the effects of dried ground leaves and seeds of <i>P. guajava</i> L. (guava; pink variety). Antioxidant and antimicrobial activity of the leaves and seeds were evaluated and the flavanoid compounds for both samples were detected using HPLC	Results showed that the leaves had higher phenolic content (356.98 mg GAE/100 g of dried weight material) compared to the seeds (87.23 mg GAE/100 g of dried weight material). The leaves exhibited 93% scavenging effect as determined by DPPH while the seeds showed 30% scavenging effect. For antimicrobial activity, both the leaves and seeds inhibited the growth of <i>Bacillus subtilis</i> and <i>Staphylococcus aureus</i> bacteria at 100, 150 and 200 mg/mL of the extracts. The chromatogram data indicated that the extracts contained flavanoids such as quercetin, myricetin and catechin which might be responsible for their antioxidant and antimicrobial activity

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Table I. Cont. Summary of studies on polyphenols presented at the 4th International Conference on Polyphenols and Health.

Ref.	Polyphenols/plants/natural interventions	Study design	Outcome
222	Red wine	The aim of the study was to compare the effects of a moderate intake of an alcoholic beverage with high polyphenol content (red wine) and another without polyphenol content (gin) on antioxidant status, serum lipid and lipoprotein levels, and oxidation of low-density lipoprotein (LDL) particles. Forty healthy men were included in a randomized, crossover trial. After a 15-day washout period, subjects received 30 g/ethanol/day as either wine or gin for 28 days	The observed reduction in SOD activity may indicate that the body saves energy and lowers enzyme activities when they are not needed. Lag phase time of LDL oxidation analysis increased by 11.0 mm after wine, compared to gin, whereas no differences were observed between the two drinks in oxidation rate of LDL particles. Peroxide concentration in LDL particles also decreased after wine, as did plasma oxidized LDL concentrations
223	Grape polyphenols	The influence of grape polyphenols on the growth of probiotic <i>Lactobacillus acidophilus</i> CECT 903 was investigated. In addition, a stimulatory trend in bacterial growth was observed in the presence of tannic acid and grape phenolic extracts	Results showed that <i>L. acidophilus</i> CECT 903 was resistant to grape extractable polyphenols at a maximum concentration of 5000 µg/disk in agar diffusion assays. A remarkable finding was that grape pomace phenolic extract (1 mg/mL) induced a significant biomass increase of <i>L. acidophilus</i> grown in liquid culture media
224	Red wine	This study evaluated the effects of red wine intake on kidney oxidative stress	Red wine intake decreased carbonyl groups and malondialdehyde and increased the reduced glutathione levels in rats treated with tamoxifen
225	Flavanoids	This study determined the transport inhibition of danofloxacin by BCRP/ABCG2 protein mediated by a cocktail of isoflavone, considering the additive effects of multiple flavonoids on BCRP inhibition	Results showed that the transport in BCRP-MDCKII cells was completely abolished by the cocktail of isoflavones, but the main inhibition was due to the isoflavone genistein as well as daidzein. These results suggest the potential use of these isoflavones as BCRP/ABCG2 inhibitors since drug interaction with flavonoids occurs in vivo
226	Phenolic acids	The antimicrobial activity of 13 phenolic acids against three strains of <i>E. coli</i> and other nine probiotics and pathogens was studied	The growth of <i>E. coli</i> ATCC 25922 was only inhibited by 4 of the phenolic acids tested at concentrations up to 1000 pg/mL, whereas the pathogen O157:H7 CECT 5947 was sensitive to 10 of them. The genetically manipulated <i>E. coli</i> lpxC/tolC strain exhibited high sensitivity to the presence of phenolic acids. The growth of lactic acid bacteria (<i>L. paraplantarum</i> LCH7, <i>L. plantarum</i> LCH17, <i>L. fermentum</i> LPH1, <i>L. fermentum</i> CECT 5716, <i>L. brevis</i> LCH23, and <i>L. coryniformis</i> CECT 5711) and pathogens (<i>S. aureus</i> and <i>C. albicans</i>) was also inhibited by phenolic acids, but to a different extent. Only <i>P. aeruginosa</i> was found not to be affected by any of the phenolic compounds tested
227	<i>Chrysanthemum indicum</i> L.	The volatile chemical constituents of <i>C. indicum</i> L. were separated by hydrodistillation extraction using a Clevenger-type apparatus and were analyzed by gas chromatography-mass spectrometry (GC/MS). Bioactivities of the essential oil on the function of osteoblastic MC3T3-E1 cells were tested	Results showed that α-pinene, 1,8-cineol and chrysanthenone were the predominant aroma components. It increased the collagen, ALP activity and mineralization of osteoblasts significantly, indicating that <i>C. indicum</i> L. may help prevent osteoporosis

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Ref.	Polyphenols/plants/natural interventions	Study design	Outcome
228	Dehydrocostus lactone	To elucidate the protective effects of dehydrocostus lactone on the response of osteoblasts to oxidative stress, osteoblastic MC3T3-E1 cells were incubated with 0.3 mM hydrogen peroxide (H ₂ O ₂) and/or dehydrocostus lactone (0.1-10 µg/ml), and markers of osteoblast function and oxidative damage were examined	Dehydrocostus lactone (0.1-10 µg/mL) significantly increased osteoblast growth. H ₂ O ₂ -induced reduction of differentiation markers such as alkaline phosphatase (ALP), collagen content and calcium deposition were recovered in the presence of dehydrocostus lactone (0.4-2 µg/mL). Treatment with dehydrocostus lactone (10 µg/mL) decreased the production of osteoclast differentiation-inducing factors such as interleukin (IL)-6 and receptor activator of nuclear factor-κB ligand (RANKL) in the presence of H ₂ O ₂
229	Hydroxytyrosol (HT) and homovanillic acid (HVA)	To investigate the capacity of hydroxytyrosol (HT) and homovanillic acid (HVA) to inhibit <i>tert</i> -butyl hydroperoxide (TBH)-induced oxidative damage in Caco-2 cells	Exposure to the organic hydroperoxide TBH (2.5 mM) increased the levels of MDA together with disruption of the membrane structure, with the loss of unsaturated fatty acids and cholesterol, and the formation of fatty acid hydroperoxides and 7-ketocholesterol. Pretreatment with HT protected Caco-2 cells from oxidative damage. Both HT and HVA may represent potential therapeutic agents against these disorders in the intestinal tract, where the lipid peroxidation process plays a central role
230	Urolithin B, urolithin A and pyrogallol	This study evaluated the ex vivo protective effect of low-molecular-weight colonic catabolites of dietary PC in human neuron cells subjected to mild and intense oxidative stress. Human neuroblastoma SK-N-MC cells were cultured for 36 h before treatment. The tested compounds were pyrogallol(1,2,3-trihydroxybenzene), feruloylglycine, urolithin A, urolithin B, dihydrocaffeic acid, dihydroferulic acid, 3,4-dihydroxyphenylacetic acid, 3-hydroxyphenylacetic acid and 4-hydroxy-3-methoxyphenylacetic acid. Cell viability was measured using a quantitative colorimetric assay with MTT	The most effective compounds were urolithin B, followed by urolithin A and pyrogallol. Preliminary results indicated that low-molecular-weight catabolites of dietary flavonoids and polyphenols are protective against mild oxidative stress in neuronal cells, whereas their benefits are significantly reduced when the induced stress increases above physiological levels
231	Oregonin	Effect of 2 ethyl acetate extracts with 60% and 90% oregonin content on human blood biochemical parameters (plasma total antioxidant capacity, superoxide dismutase, catalase, glutathione peroxidase, reducing glutathione, malondialdehyde, glucose content) was investigated	The experiments confirmed potent antioxidant effects of the extracts and revealed their ability to normalize lipid metabolism and to increase the glutathione level in blood. The inhibition of pancreatic lipase observed is important for correction of obesity, metabolic syndrome and atherosclerosis. The extract with 90% oregonin increased the hemoglobin content in blood erythrocytes, decreased sugar content and lipase activity and increased glutathione levels in blood
232	Polyphenols	This study examined the effect of flax lignans on intestinal inflammation by using Caco-2 cells stimulated with IL-1β. Polyphenols tested were secoisolariciresinol diglycoside (SDG) and its glycone (SECO), pinoresinol (PINO), lariciresinol (LARI), matairesinol (MAT), hydroxyl-MAT (hMAT) and its colonic metabolites enterolactone (ENL) and enterodiol (END), ferulate and <i>p</i> -coumarate (<i>p</i> -COU)	Data showed that IL-1β enhanced the production of the three proinflammatory markers IL-8, IL-6 and PGE ₂ . None of the polyphenols tested had a significant inhibitory effect on the induced IL-8 secretion, although QUER tended to reduce it. Polyphenols reduced IL-6 and PGE ₂ levels with the following importance: QUER PINO > LARI <i>p</i> -COU > FERU for IL-6 and QUER > PINO > FERU > SDG > MAT > <i>p</i> -COU for PGE ₂ . PINO effect on IL-6 secretion was concentration-dependent (IC ₅₀ = 12.5 µM)

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Ref.	Polyphenols/plants/natural interventions	Study design	Outcome
233	Ethanol	This study compared the effects of the consumption of 30 g/day (during 1 month) of ethanol in the form of gin, red wine and the equivalent quantity of dealcoholized red wine on the cardiovascular system in 25 high-risk subjects. The effects of the three interventions were analyzed on the expression of intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), E-selectin, P-selectin, monocyte chemoattractant protein 1 (MCP-1), TNF- α , matrix metalloproteinase-9 (MMP-9), oxidized LDL (LDLOx), tissue inhibitor of metalloproteinase 1 (TIMP-1), IL-1a, IL-6, IL-10, IL-18 and TNF- α by ELISA. We also analyzed the expression of adhesion molecules (CD49d, CD11a, CD11b, CD40, CD15, CD36 and CCR2) on lymphocyte and monocyte surface via double direct immunofluorescence using commercial monoclonal antibodies	CD11a, CD11b, CD49d, CD40 and CD36 monocyte expression and IL-10 and E-selectin levels decreased significantly after the dealcoholized red wine intervention compared to gin. CCR2 monocyte expression and ICAM-1 also decreased significantly after red wine compared to gin. In addition, ICAM-1 and CCR2 decreased significantly after red wine compared to dealcoholized red wine, whereas CD49d, CD11a and CD40 decreased significantly after dealcoholized red wine compared to red wine
234	Olive tree	The phenolic fraction extracted from the leaves of the olive tree, which contains significant amounts of oleuropein, prevents lipoprotein oxidation	The results provide a molecular basis for some of the potential benefits from oleuropein consumption
235	Flavanoids	Effects of polyphenols on immunobiological responses triggered by LPS and interferon- γ were tested under in vitro conditions using murine resident peritoneal macrophages. Namely, production of NO and secretion of cytokines and chemokines were investigated	Test agents comprised samples in each group differing by number and/or position of hydroxyls, methoxyls and glucosyls). Relationship between the molecular structure and immunobiological activity was investigated, and implication of structural changes was assessed. Comparable high activity was achieved by apigenin and luteolin (flavones), glycitein (isoflavone) and all stilbene aglycones
236	Hesperetin-7-O-glucuronide	The effect of hesperetin-7-O-glucuronide (Hp7G) on osteoblast function was examined. Primary osteoblasts were isolated from calvaria of newborn Wistar rats. Stability and cellular uptake of 40 μ M of hesperetin 7-O-glucuronide (Hp7G) were determined by LC-MS/MS after 24 h of culture. Proliferation and enzymatic activity of alkaline phosphatase (ALP) were measured kinetically. Messenger levels of genes were measured using real-time PCR and phosphorylation of Smad1/5/8 and ERK1/2 using Western blot	A transient presence of Hp7G inside primary rat osteoblasts after either Hp or Hp7G exposure was observed. The glucuronide at either concentration did not affect proliferation but enhanced differentiation by significantly increasing ALP activity from day 14 of exposure (day 19: Hp7G: +18%, Hp7G10: +14% vs. control, $P < 0.05$). Hp7G significantly induced mRNA expression of ALP (1.4-fold vs. control), Runx2 (2.6-fold vs. control) and Osterix (1.4-fold vs. control) after 48 h of exposure. Moreover, phosphorylation of Smad1/5/8 was enhanced by Hp7G, while ERK1/2 remained unchanged after 48 h. Finally, Hp7G induced a downregulation of RANKL expression (2-fold vs. control)

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Table I. Cont. Summary of studies on polyphenols presented at the 4th International Conference on Polyphenols and Health.

Ref.	Polyphenols/plants/natural interventions	Study design	Outcome
137	Resveratrol, daidzein and genistein	The effects of SIRT1 overexpression and treatment with polyphenols on methylation of the LINE-1 retrotransposon in human intestinal Caco-2 cells were examined	SIRT1 mRNA and protein expression in Caco-2 cells was increased substantially 96 h after transfection with a SIRT1 expression construct. SIRT1 overexpression+resveratrol (10 μ M for 72 h) or SIRT1 overexpression+daidzein (50 μ M for 72 h) alone had no effect on LINE-1 methylation. Genistein (50 μ M for 72 h) cells was increased substantially 96 h after reduced LINE-1 methylation (1.00 ± 0.01 ; 0.79 ± 0.01 ; $P < 0.05$). Together, SIRT1 overexpression+resveratrol or SIRT1 overexpression+daidzein increased LINE-1 methylation (0.95 ± 0.02 , 1.23 ± 0.08 [$P < 0.01$]; 1.0 ± 0.01 , 1.15 ± 0.07 [$P < 0.05$], respectively) and SIRT1 overexpression reversed the effect of genistein to reduce LINE-1 methylation. These observations indicate that polyphenols may interact with SIRT1 to affect DNA methylation and thus suggest a possible mechanism by which these dietary components may promote longevity
238	Epicatechin	This study focused on the uptake and accumulation of epicatechin metabolites in lymphoid organs, including the thymus, spleen and mesenteric lymphoid nodes, as well as liver and testes, after a regular diet rich in coca. Tissues were subjected to solid-phase extraction and analyzed by liquid chromatography tandem mass spectrometry	The glucuronide derivatives of epicatechin and methylepicatechin were recovered as major compounds. The highest concentrations were found in thymus and testicles, followed by liver, lymph nodes and spleen
239	<i>Urtica dioica</i> seed	This study was designed to investigate a possible prophylactic effect of <i>U. dioica</i> seed extract pretreatment on prevention of oxidative stress generated by CCl_4 in rats. A dose of 25 mg/kg of <i>U. dioica</i> extracts was administered i.p. Lipid peroxidation and serum liver enzyme activities were measured. Histopathological examinations were also studied	The CCl_4 treatment of rats increased lipid peroxidation and liver enzymes, and also decreased antioxidant enzyme levels (superoxide dismutase, catalase, glutathione peroxidase and the levels of glutathione)
240	Caffeoylquinic acid	This study examined the effect of caffeoylquinic acid derivatives on osteoclast and osteoblast cells	Caffeic acid (CA), chlorogenic acid (ChA), 3,4-di-O-caffeoylquinic acid (3,4-di-CQA) and 3,4,5-tri-O-caffeoylquinic acid (3,4,5-tri-CQA) concentration-dependently inhibited the osteoclast differentiation and its inhibitory level was on the order of $\text{ChA} \ll \text{CA} \ll 3,4\text{-di-CQA} = 3,5\text{-di-CQA} = 4,5\text{-di-CQA} \ll 3,4,5\text{-tri-CQA}$. 3,4,5-tri-CQA showed the most pronounced inhibitory effect, CA and di-CQAs were obstructions of the almost same degree. It seems that uptake to the cell is related to CA having shown inhibition that is higher than ChA

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Table I. Cont. Summary of studies on polyphenols presented at the 4th International Conference on Polyphenols and Health.

Ref.	Polyphenols/plants/natural interventions	Study design	Outcome
241	(-)-Epicatechin	The aim of this study was to determine if the stereochemical configuration of a flavanol monomer was a factor influencing flavanol-mediated vasodilatation in vivo	Results showed that bolus injections of (-)-epicatechin at 1-1000 nM into the femoral artery (FA) of rats induced vasodilatation in a dose-dependent manner with maximal dilatory effects at 10 nM. This effect was nitric oxide synthase-dependent, as coinfusion of L-NMMA abolished the effect. In contrast, dose-equivalent infusions of the stereoisomers (+)-epicatechin, (-)-catechin, and (+)-catechin did not induce vasodilatation. While the 4 isomers have been reported to exhibit very similar antioxidant properties in vitro, in this study they only exhibited antioxidant properties at 100 µM to 1 mM concentrations spiked in plasma (measured by FRAP and ORAC assays), which are improbable concentrations to reach in vivo from a dietary source
242	Epigallocatechin gallate	This study investigated the effect of EGCG on IL-13 gene expression in human basophilic KU812 cells	The IL-13 mRNA expression level was concentration-dependently increased by treatment with EGCG (5-20 µM) for 1 h and additional incubation in medium for 23 h. EGCG significantly increased the intracellular peroxide level using the peroxide-sensitive H ₂ DCFDA probe. The data provide biological evidence that EGCG induces IL-13 mRNA expression via the JNK-dependent NFATc1 pathway in KU812 cells
243	Extra virgin olive oil and 2,2',-azobis-(2-amidinopropane) dihydrochloride	This study investigated the morphological and chemical and physical changes in Caco-2 cells at various concentrations of phenolic extract from extra virgin olive oil and 2',2'-azobis(2-amidinopropane) dihydrochloride (AAPH)	Results showed that the monolayer of Caco-2 cells treated with different concentrations of polyphenol extract from extra virgin olive showed a decrease of the electric potential <i>trans</i> -epithelial electric resistance, and when tested with the AAPH it was shown that it induces a significant morphological change in Caco-2 cells
244		This study evaluated the use of electrochemical assisted ionization technique for the measurement of different model compounds (4-hydroxyestradiol, butylated hydroxytoluene and eugenol) by LC-MS	
245	Galangin, kaempferol, quercetin and myricetin	The antiangiogenic activities of various flavonoids in foods, including galangin, kaempferol, quercetin and myricetin, were examined. The effects of these flavonoids were tested in an in vivo model of angiogenesis, the chorioallantoic membrane (CAM) assay. Compounds to be tested were administered on the CAM of fertilized hen's eggs at 10 µg	The antiangiogenic activity was determined after incubation for 3 days. The activities of 4 flavonoids (galangin, kaempferol, quercetin and myricetin) at 11,150 nmol/egg were evaluated by observation of blood vessel-free areas. These flavonoids showed significant antiangiogenic activities in a concentration-dependent manner
246	Beer	This study evaluated the effects of prolonged beer consumption on hepatic redox status and metabolic markers in rats	Results do not support the existence of deterioration in hepatic redox status or plasma metabolic markers following chronic consumption of beer or 5.4% ethanol solution

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Table I. Cont. Summary of studies on polyphenols presented at the 4th International Conference on Polyphenols and Health.

Ref.	Polyphenols/plants/natural interventions	Study design	Outcome
247	Polyphenols	This study compared the effects of 2 polyphenols produced by cultivated plant cells (<i>Syringa vulgaris</i> cells, verbascoside [VB] and chlorogenic acid [CA]) and the polyphenols resveratrol and quercetin on keratinocyte response to sublethal solar irradiation doses of UV (A or A+B). Sublethal UV-irradiation caused upregulation of inflammation-associated genes assessed by QRT-PCR in HaCaT cells and primary human keratinocytes at 1 h postirradiation and accumulation of proinflammatory cytokines (TNF- α , IL-6, IL-8, IL-1 β , MCP-1, MIP-1 α , MIP-1 β , PDGF-BB and VEGF) in culture medium	Results showed that plant polyphenols alone induced an inflammatory response similar to that of UV irradiation. Quercetin and resveratrol but not VB and CA acted synergistically with UV light on the upregulation of the cytokines and COX-2 mRNA and production of proinflammatory cytokines. ELISA revealed significant early phosphorylation of c-Akt (prosurvival pathway) but not ERK1/2. Both quercetin and resveratrol possessed UV-like effects on c-Akt phosphorylation
248	Grape seed proanthocyanidins	The aim of this study was to determine the effects of grape seed proanthocyanidins (GSPE) on plasma triglycerides and elucidate the contribution of chylomicrons (QM) and VLDL to this phenomenon during lipid absorption. To this end, male Wistar rats were deprived of food for 14 h before the experiment. A lard oil (2.5 mL/kg) with GSPE (250 mg/kg) was administered orally	Results indicated that a single oral administration of GSPE significantly blocked the increase of plasma total TG, TG-VLDL and free fatty acid. GSPE did not affect the level of plasma TG-QM and β -hydroxybutyrate. The secretion of VLDL by the liver indicated a significant repression
249	Yellow birch and black spruce bark	In this study, cultures of normal human keratinocytes were exposed to polyphenolic extracts (concentration range of 250-1000 μ g/mL) from the bark of yellow birch (<i>Betula alleghaniensis</i>) and black spruce (<i>Picea mariana</i>) over a period of 24 and 48 h. The toxicological effects were quantified using the dye exclusion method and the MTT assay. The antiproliferative activity of the extracts was determined on normal and psoriatic keratinocytes and compared to Oligopin [®] as a control	Results revealed that black spruce extract had the lowest toxicity as assessed by the determination of the minimal toxic doses (C10) using both methods. Black spruce extract showed the lowest toxicity with the MTT method (C10 = 400.22 mg/mL) but no significant differences were observed between extracts of Canadian species and Oligopin [®] using the dye exclusion method. Antiproliferative activity of Oligopin [®] and the yellow birch extract was higher than that of black spruce on normal keratinocytes, while on psoriatic keratinocytes Oligopin [®] and the black spruce extract showed higher antiproliferative activity. The low cytotoxicity and the antiproliferative effects of the polyphenolic extracts suggest that Canadian species may be potential candidates for psoriasis treatment
250	Polyphenols	In a crossover design (4 weeks each; all food provided), a diet rich in plant-based phenolics and a diet in which the phenolic content was minimized was given to healthy volunteers for 4 weeks. Fecal samples were collected during the maintenance period and at the end of each dietary intervention. The exogenous metabolites in the aqueous fecal extracts were quantitatively analyzed by LC-MS	A diet low in plant phenolics revealed a significant decrease in the major fiber cross-linking compounds and their metabolites, having anti-inflammatory properties. There were also significant increases in protein-derived metabolites and higher levels of potentially carcinogenic and toxic gut metabolites in this low-phenolic dietary regimen
251	Quercetin	In this work the effect of quercetin on the lifespan of <i>Caenorhabditis elegans</i> and preliminary studies on the bioavailability of the flavonol were performed. Bioavailability of quercetin was assessed using wild-type N2 <i>C. elegans</i> worms incubated after synchronization for 4 days on NGM plates using <i>E. coli</i> OP50 as a food source	The direct uptake of quercetin by <i>C. elegans</i> was confirmed, as well as the formation of some metabolites that did not result from bacterial biotransformation. In addition, it was observed that quercetin prolonged the lifespan of adult <i>C. elegans</i> worms by 13% and 16% in the presence of 100 and 200 mM quercetin, respectively

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Ref.	Polyphenols/plants/natural interventions	Study design	Outcome
252	Phenolic compounds	The anti-inflammatory effects of phenolic compounds in an in vitro model of inflamed human intestinal epithelium using Caco-2 cells were studied. Differentiated cells cultivated in bicameral inserts were treated with a cocktail of proinflammatory substances (IL-1 β , TNF- α , interferon- γ and LPS) in the presence or absence of PC. The gene expression level was measured using a TaqMan low-density array configured with 46 genes. Proinflammatory cytokines were determined by ELISA	Results showed that in cells treated with the proinflammatory cocktail, 18 genes were upregulated, mainly those related to inflammation such as IL-1, IL-8, IL-6, NF- κ B, NOS2A, CCL2, CCL5, ICAM-1 and ICAM-2. Moreover, the secretion of IL-8 and IL-6 was significantly stimulated, while transepithelial resistance was slightly decreased
253	Flavonoid analogues	The biological evaluation of 18 flavonoid analogues with B-ring substitution of hydroxyl and methoxy groups was investigated in order to find potent and selective CYP1B1 inhibitors by EROD assay using recombinant human CYP1	The flavones and flavonols were more potent inhibitors than the flavanones. The methoxy-flavonoids such as tamarixetin and chrysoeriol preferentially inhibited CYP1B1. The IC ₅₀ values of tamarixetin for CYP1B1 and 1A2 were 17.0 \pm 2.7 and 1261 \pm 65 nM, respectively. The 3D structures of CYPs demonstrated that substrate binding specificity may be based on the amino acid reduction, i.e., Thr-124 of CYP1A2, Ser-122 of CYP1A1 and Ala-133 of CYP1B1. Docking studies of tamarixetin with CYP1B1 and 1A2 showed that it fit well into the pocket of CYP1B1 but not 1A2 because of collision between a methoxy substituent of tamarixetin and a methyl group of Thr-124
254	Phenolic compounds	This paper reviewed the data generated to date on the amount of phenolic compounds necessary to elicit certain cardioprotective effects and chemopreventive activity, and whether isolated individual phenolic compounds are as effective as those administered in wine medium	The data suggests that although phenolic compounds are absorbed in the blood stream in measurable amounts, their metabolites are more likely to be biologically active compounds in vivo
255	Tomato	This study used genetically modified tomatoes engineered to have increased levels of polyphenols, anthocyanins and flavonols, and its extract was used in an in vitro primary cell inflammation model	The addition of extracts from these tomato lines to an in vitro primary cell inflammation model resulted in reduced chemokine production by intestinal epithelial cells, effectively disrupting their ability to communicate with and to promote the migration of DCs. The inhibition of chemokine production by dietary flavonoids identifies a mechanism by which these compounds can inhibit chronic inflammation in the gastrointestinal tract
256	Pomegranate juice	The effect of pomegranate juice consumption on blood pressure, body composition, antioxidant status and 11-HSD activity was evaluated in 19 healthy volunteers who consumed 500 mL/day of a commercially available fruit juice (Pomegreat Pure 100% natural juice, 1685 mg/L polyphenols) over a 2-week period	Results demonstrate that after fruit juice consumption there was an increase in the concentration of total phenolics (59.2 \pm 31.9 mM/day to 94.6 \pm 54.9 mM/day; P = 0.003) and antioxidant capacity (2.1 \pm 1.5 mM Fe[II] to 3.6 \pm 1.9 mM Fe[II]; P = 0.001). There were reductions in systolic blood pressure (P = 0.007), waist circumference (P = 0.001), urinary cortisol:cortisone ratio (P = 0.031) and salivary cortisol:cortisone ratio (P = 0.024). No changes were detected in diastolic blood pressure

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Ref.	Polyphenols/plants/natural interventions	Study design	Outcome
157	Nonalcoholic beer	The effect of supplementation of nonalcoholic beer (500 mL/day for 25 days) on oxidative metabolism and its relation to lipid metabolism and inflammation processes was evaluated in a group of elderly nuns in a closed order	A significant decrease ($P < 0.05$) in total cholesterol levels was observed in subjects who had a total cholesterol level of 240 mg/dL or more, as well as a significant decrease ($P < 0.05$) in oxidized LDL antibodies. After nonalcoholic beer supplementation, a significant decrease in damage to macromolecules was observed as determined by TBARS ($P < 0.005$) and in CGC ($P < 0.005$) assays. At the end of the study GSH and α -tocopherol levels had significantly increased ($P < 0.005$), while there were no significant changes in inflammation parameters
258	Apple polyphenols	The mechanisms and hepatoprotective effects of apple polyphenols (AP) against CCl ₄ -induced acute liver were investigated in mice	AP significantly prevented the increase of serum ALT and AST in acute liver injury induced by CCl ₄ and ameliorated the histopathological hepatic lesions. MDA formation was decreased, SOD activity was enhanced and GSH content was increased in hepatic homogenates in AP-treated mice compared to CCl ₄ -intoxicated mice. AP also exhibited antioxidant effects on FeSO ₄ -L-Cys-induced lipid peroxidation in rat liver homogenates and DPPH free radical scavenging activity in vitro
259	Olive oil polyphenolic extract	The effect of olive oil polyphenolic extract on serum olive oil polyphenolic extract antioxidant levels and hepatic lipid peroxidation following 1/3 partial hepatectomy (pHx) was studied in mice, along with implications of these effects on liver regeneration	In vitro data showed that olive oil polyphenolic extract was 1.5-fold more effective as a radical scavenger than α -tocopherol. pHx induced a marked increase in liver MDA levels, as well as active consumption of serum antioxidants. The relative liver weight in the olive oil polyphenolic extract +pHx group was significantly higher than in the pHx group
260	Ferulic acid	This study described the isolation and characterization of a monoclonal antibody, designated LM12, raised in rat against feruloylated sugar beet pectin (0.8% ferulic acid w/w)	ELISA results revealed that the most effective inhibitor was free ferulic acid. There was no inhibition by unferuloylated lime pectins, propionic or synameic acids. Immunofluorescence microscopy indicated that LM12 binds to cell walls of spinach (<i>Spinacia oleracea</i> L.) stem, which supports the presence of feruloylated pectins in this plant species. Alkali treatment, which causes removal of methyl and acetyl esters of pectin, did not affect LM12 binding. LM12 is therefore a useful antibody probe for the analysis of the phenolic content in biological material
261	Flavanoids	The synthesis of systematically available flavanoid conjugates was described. LC-MS was used both for the quantitative measurement of the aglycone and for the quantitative determination of forms in which these compounds are available in vivo	The glucuronidated and sulfated conjugates of the main flavanoids were successfully synthesized using enzyme preparations from rat liver

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Ref.	Polyphenols/plants/natural interventions	Study design	Outcome
262	Flavanoids	The use of electrochemistry for the measurement of polyphenols in plants and animals was studied using HPLC with coulometric electrode array detection	Polyphenols are electrochemically active and easily oxidized. Compounds that are low potential sensors can be selectively detected upstream, while high potential sensors respond downstream. Consequently, this approach is both extremely sensitive and provides qualitative information (voltammetric behavior) for analyte identification
263	4-Hydroxyestradiol butylated-hydroxytoluene and eugenol	The use of this EC-assisted ionization technique for the measurement of several different compounds (4-hydroxyestradiol butylated-hydroxytoluene; and eugenol) by LC-MS was evaluated. Oxidation and resulting positive-ion ESI-MS data were studied as a function of electrode potential and at different pH conditions	Data for 12 compounds showed that ESI-MS base peak ion abundance increased 3- to 72-fold as a result of EC oxidation when compared to ESI alone. EC reactions occurred at specific potentials, thus providing an additional means of achieving selectivity. EC oxidation for some compounds was easier to perform at lower pH, a condition in which many polyphenols are more stable. These data suggest that EC-assisted ionization can provide a simple means of improving sensitivity and selectivity of LC-MS analysis of polyphenols
264	<i>Anastatica hiererchuntica</i>	In this study, HPLC-PDA-MS was used to identify the phenolic compounds found in aqueous extracts of dry seeds of <i>A. hiererchuntica</i> . Their structures were determined by co-chromatography and mass fragmentation of the molecular ions	Luteolin was found to be the major flavonoid
265	Resveratrol	The quantification of resveratrol metabolites with the LC-ESI-MS/MS system was investigated in order to obtain correction factors that could be applied in clinical and epidemiological studies to evaluate the real concentration in biological fluids and tissues. Ionization was performed for commercial resveratrol glucuronides and sulfates and synthesized dihydroresveratrol (microbial metabolite) was optimized in LC-MS/MS by flow-injection analysis and infusion experiments	Correction factors were obtained for each resveratrol metabolite, allowing the quantification of the real amount of metabolites present in tissues and biological fluids The correction factors will improve results of a large number of clinical and epidemiological studies
266	Polyphenols in cereals	The purpose of this study was to determine the total content of polyphenols in cereals, including HPLC-MS analysis in methanol-acetone-water extracts and in acidic and alkali hydrolysates of the corresponding residues	The amount of polyphenols found in extracts of wheat flour and wheat bran were 109 and 161 mg/100 g weight, respectively. Hydroxybenzoic acid, ellagic acid, epicatechin and hydroxycinnamic acids were the main compounds identified. The amount of polyphenols found in acidic hydrolysates of wheat flour and bran (240 and 1600 mg/100 g, respectively) were higher than in alkali hydrolysates (0.2 and 372 mg/100 g, respectively). Hydroxybenzoic, caffeic, cinnamic, ferulic and protocatechuic acids were the main constituents of the hydrolysates.
267	Catechins	The purpose of this study was to develop a validated LC-MS-MS method for quantification of tea catechins and their metabolites in human skin biopsy samples, skin fluid and urine	A new method for quantification of tea catechins was developed and validated achieving analysis via HPLC coupled with Triple quadrupole MS/MS detection

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Ref.	Polyphenols/plants/natural interventions	Study design	Outcome
268	Flavanoids	This study was done to optimize the solvent-free microwave extraction of antioxidant flavanoids from onions	Microwave extraction offers important advantages such as shorter extraction time (23 min). Microwave extraction resulted in a significant yield (81.5%) with 41.9% of flavanol contents, while retaining the remaining flavanoid (55.9%) in residues of onions. Quercetin-3,4'-diglucoside, quercetin-4'-monoglucoside (239.7 mg/100 g DW) and quercetin-4'-monoglucoside (82.55 mg/100g DW) were reported to be the main flavanols in this study
269	Epicatechin	A method for the determination of catechin and epicatechin from serum after eating cocoa was described. Samples were analyzed with LC-MS-MS (Ion Trap Time-of-Flight) mass spectrometer by monitoring the transition of m/z 465 to 289	(-)-Epicatechin monoglucuronide was detected eluting at the retention time of 16.1 min, with a serum concentration of 200 nm. The limit of quantification in serum was determined to be 125 nm/mL with a limit of detection of 75 nm/mL. The assay was determined to be linear from 125 ng to 1 µg/mL
270	Procyanidins	This study describes the characterization of a series of available procyanidin standards from dimers DP=2 to decamers DP=10 for the determination of procyanidins from cocoa and chocolate using a combination of HPLC with fluorescence detection and MALDI-TOF. The purity of each standard was determined and these data were used to determine relative response factors. These response factors were compared with other response factors obtained from published methods for cocoa and chocolate	Data comparing the procyanidin analysis of a commonly available dark chocolate calculated using each of the calibration methods indicated divergent results and demonstrated that previous methods significantly underreport the procyanidins in cocoa-containing products
271	Tomato polyphenols	The aim of this study was to develop a new LC-MS/MS method for the determination of tomato polyphenols in biological fluids	For separation and quantification, LC-MS/MS was confirmed to be a more powerful analytical tool, due to its high universality, sensitivity and specific information, than LC with UV detection or electrochemical methods. Lower detection limits and adequate selectivity versus interfering substances of the matrix were obtained
272	Total polyphenol in tomato	The aim of this study was to improve the determination of total polyphenols in tomato samples using solid-phase extraction (SPE) with an Oasis MAX 96-well plate in order to eliminate these substances before the Folin assay. Seven samples were analyzed and total polyphenols were expressed as mg of GAE/100 g dry material	The results of the Folin assay were linear over the working range of 1-75 mg/L. Assay precision and accuracy were between the accepted values according to AOAC International standards. The recoveries for nine polyphenol standards after SPE were between 79.12% and 108.75%. The concentrations of total polyphenols for tomato samples after SPE were between 149.99 and 247.12 mg of GAE/100 g dry material

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273	Flavonol	This study examined the subcellular localization of flavonol in mouse hepatoma Hepa-Ic1c7 cells and mouse myotube C2C12 cells using a confocal laser scanning fluorescence microscope	In Hepa-Ic1c7 cells, the intensity of green autofluorescence from kaempferol aglycone increased in a concentration- and time-dependent manner. Other flavonol aglycones, namely quercetin, isorhamnetin, morin and galangin, also showed green fluorescence in Hepa-Ic1c7 cells. The green fluorescence from flavonol aglycone overlapped with red fluorescence from propidium iodide, indicating that flavonol aglycone can accumulate in the nucleus. In C2C12 cells, the green autofluorescence from quercetin was observed in the cells, and the intensity of autofluorescence in nucleus was stronger than that in cytoplasm
274	<i>Ficus deltoidea</i>	In this study HPLC-PDA-ESI-MS with negative ionization was used to analyze proanthocyanidins in the water extract of <i>F. deltoidea</i> leaves	The MS analysis revealed the presence of a number of prodelphinidins (m/z 305), procyanidins (m/z 289) and propylarganidin (m/z 273), as well as afzelechin and epiafzelechin, which were reported for the first time in this plant
275	Quercetin and hesperidin	In the present study two polyphenols (quercetin and hesperidin), chosen according to their structural characteristics, were used to evaluate the localization by their natural fluorescence properties in human intestinal Caco-2 cell lines	The results showed that the passage of quercetin occurred rapidly via a transcellular mechanism, while the passage of hesperidin occurred via a transcellular mechanism the first time and then via a paracellular mechanism after an incubation time of 90 min
276	Flavan-3-ols	The objective of this study was to develop and validate a comprehensive LC-MS method for the detection and quantification of flavan-3-ols and phenolic acids in milk-based food products. Five different flavan-3-ols (including epicatechin), 2 proanthocyanidins and 16 phenolic acids (including <i>trans</i> -resveratrol) were used as standards for optimization purposes	Separation of 23 analytes was achieved by reverse-phase chromatography. Detection was performed by negative-ion ESI in a multiple-ion monitoring (MRM) mode for maximized selectivity and sensitivity. The quantitative performance of the method was validated based on signal intensity ratio between analytes and isotope-labeled internal standards
277	Epicatechin gallate	This study investigated the dynamics and orientation of epicatechin gallate (ECg) in DMPC liposomes by solid-state ¹³ C and ³¹ P NMR spectroscopy using ¹³ C-labeled ECg ([¹³ C]-ECg)	In solid-state ³¹ P NMR experiments under the static condition, the ³¹ P chemical shift anisotropy of DMPC in the presence of ¹³ C-ECg changed compared to that in the absence of the catechin, demonstrating that ¹³ C-ECg causes the change in the dynamics around the phosphate groups of the phospholipids in the lipid membranes. The results of solid-state ¹³ C NMR measurements indicate that ¹³ C-ECg molecules rotate normally around the bilayers with a constant angle of tilt to the axis because they provide an axially symmetric powder pattern. Furthermore, we obtained the accurate ¹³ C- ³¹ P interatomic distance between the carbonyl carbon of ¹³ C-ECg and the phosphate group of DMPC by using the ¹³ C- ³¹ P REDOR method. These results may provide insight into the location of ECg in the lipid membranes

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278	Ferulic acid and caffeic acid	This study was designed to synthesize and characterize glucuronides and dimethyl esters of ferulic acid and caffeic acid for metabolomic studies	After chromatographic separation and purification by crystallization, all the synthesized compounds were identified by NMR analysis
279	Resveratrol, naringenin and quercetin	This study was designed for the microbial preparation of glucuronide conjugates of polyphenols using bacterial strain MS2104. All glucuronides were characterized by MS and NMR	Bacterial strain MS2104 transformed <i>trans</i> -resveratrol to a mixture of 3-O- β -D-glucuronide and 4'-O- β -D-glucuronide. Naringenin-7-O-glucoside was converted to a mixture of two major O- β -D-glucuronides and a minor O- β -D-glucuronide. Quercetin was converted to a mixture of major O- β -D-glucuronides
280	Phytoestrogens	The aim of this study was to develop a high-throughput LC-APCI-MS method for the determination of 13 phytoestrogens (including gut microbial metabolites) in human urine and serum	A PC-UV-APCI-MS method was developed for the simultaneous determination of 13 phytoestrogens (genistein, daidzein, equol, dihydradaidzein, O-desmethylan golenin, coumestrol, secoisolariciresinol, matairesinol, enterodiol, enterolactone, isoxanthohumol, xanthohumol and 8-prenyl-naringenin) in human urine and serum. The assay consists of a simple sample preparation procedure, using enzymatic deconjugation followed by liquid-liquid extraction (urine) or solid-phase extraction (serum) and reversed-phase HPLC coupled to a photodiode array detector and Multimode Source Detector operating in APCI mode, using both positive and negative mode ionization. This method is suitable for the estimation of urinary and serum levels of the major phytoestrogens and their microbial metabolites in the low parts per billion range
281	Prenyl flavonoids (<i>Humulus lupulus</i> L.)	This study reports the production of monoclonal antibodies against hop-derived prenylflavonoids (<i>H. lupulus</i> L.) and the development of immunological assays	Generation of monoclonal antibodies raised against XN/IX/8-PN-4'-O (carboxymethyl) ether-bovine serum albumin (BSA) conjugates showed highly specific binding to their haptens and negligible crossreactivity with other chemically related hop-derived compounds
282	Hesperitin and naringenin	In this study the glucuronides of hesperitin and naringenin, the major flavanone aglycones in orange juice and grapefruit, respectively, were chemically synthesized and investigated for their affinity for HSA	The most reactive hydroxyl group at position C7 was protected by selective benzoylation to allow subsequent glucuronidation at C3' or C4' (B-ring). On the other hand, selective debenzoylation at C7 of the perbenzoylated flavanone aglycone allowed glucuronidation at the same position (A-ring). After careful deprotection, the target compounds were purified and characterized by NMR and MS
283	α -Tocopherol and γ -tocopherol	The objective of this study was to optimize an <i>in vivo</i> oxidative stress model for the evaluation of antioxidants. A diabetic rat model was investigated as a potential oxidative stress animal model. Diabetes was induced by a single <i>i.p.</i> injection of streptozotocin (60 mg/kg). Markers of oxidative stress (malondialdehyde, nitrotyrosine) and antioxidative defense (coenzyme Q9, α - and γ -tocopherol) were specifically analyzed in plasma using HPLC-fluorescence and HPLC-coulometric detection assays	Within 3 weeks after diabetes induction, various parameters of oxidative stress, including plasma malondialdehyde, nitrotyrosine coenzyme Q9, α - and γ -tocopherol, were significantly changed in diabetic rats. Compared to the initial 7-week induction period, this 3-week induction time will result in important reductions in duration and cost of the antioxidant supplementation studies

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Ref.	Polyphenols/plants/natural interventions	Study design	Outcome
284	<i>Prunus armeniaca</i> L	A study was carried out to identify and characterize the compound that may be responsible for the antioxidant effect of apricot (<i>P. armeniaca</i> L.). 20 selected samples from cultivars and hybrids were studied. Seven different derivatives of quercetin, kaempferol and naringenin glycoside were identified. Total antioxidant capacity (FRAP values), total phenolic content (TPC) and antiradical activities of the samples were also determined	There was considerable variation in antioxidant effects among the compounds, as well as radical scavenging capacities and total phenolic, vitamin C and flavanoid contents
285	Polyphenols	Polyphenol composition is increasingly seen as a target for enhancement in crops, especially soft fruit. This study analyzed the progeny of 200 lines from a well-established segregating cross derived from the black currant parental lines S36/1/100 and S10-2-27/28	Metabolomic screening was undertaken for all progeny. Screening was done using LTQ orbitrap mass spectrometer, coupled to LC, and diode array provided high mass accuracy to analyze juice and pomace extracts
286	Olive cake	This study investigated the isolation, optimization, quantification and characterization of phenolic extracts of olive cake. Reverse-phase HPLC and MS were used for the identification of individual phenolic components. Antioxidant activity was measured using a linoleic acid/ β -carotene assay	Results revealed that the high phenolic content and antioxidant activity of olive cake can be attributed to the extraction process (time [12 h], temperature [70 °C] and solvents). The RP-HPLC for the full fat and the defatted olive cake showed syringic acid (20-21%), sinapic acid (14.5-16%) and caffeic acid (9-13%) total peak area concentrations as the major predominant bound phenolic acids
287	<i>V. vinifera</i> L.	The aim of this study was to characterize grape seeds and skin polymeric polyphenols obtained from 6 different cultivars of <i>V. vinifera</i> L. during the ripening stages of the berries. Their quantification was determined using the colorimetric electrode array. The evaluation of the degree of polymerization was performed using spectrophotometric-based techniques	For all cultivars the mean degree of polymerization in berry skin increased during ripening, with values ranging from 7.1 (cv. Malvasia Bianca) to 80.5 (cv. Nascetta). There were no significant changes in the mean degree of polymerization in seeds; values ranged from 3.9 (cv. Cabernet Sauvignon) to 16.3 (cv. Pinot Bianco)
288	<i>trans</i> -Resveratrol	This study investigated <i>trans</i> -resveratrol content in 75 samples of traditional wines from Piedmont and evaluated their radical scavenging capacity. The <i>trans</i> -form prevailed over the <i>cis</i> -form in all samples that were analyzed	The total <i>trans</i> -resveratrol content in the Piedmont wine ranged from 0.10 to 3.55 mg/L. Among all the samples, the highest median value of radical scavenging capacity was shown by Barbaresco wine, with 56.6% inhibition of DPPH radicals
289	Tomato fruit	This study investigated the paste-making process of tomato fruit in a Turkish factory. Genes from the flavanoid biosynthesis pathway were tested for changes in their expression during fruit-breaking	Results demonstrated that glucosyltransferase regulation corresponded to an increase in rutin. The activity of this enzyme was characterized both in the tomato fruit and after expression in <i>E. coli</i>
290	Almond	This study evaluated the effects of roasting, pasteurization and storage conditions on the polyphenol content and antioxidant capacity of California almond skins	Results showed that roasting did not affect the polyphenol content of the skin. Storage of almonds at 4 °C and 23 °C for 15 months resulted in a gradual increase in polyphenol content up to 177% and 200%, respectively. Antioxidant capacity also increased with storage duration, with FRAP values increasing to 200% at 9 months
291	Virgin olive oils	This study analyzed the phenolic compounds in Portuguese and Spanish virgin olive oils using RP-HPLC coupled to DAD and MS as detector	Phenolic components such as tyrosol and hydroxytyrosol were identified. Several secoiridoids were also identified, including oleocanthal

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Ref.	Polyphenols/plants/natural interventions	Study design	Outcome
292	Almonds	LC-MS was used in this study to determine the polyphenolic content and antioxidant activity of nonpareil, Carmel, Butte, Sonora, Fritz, Mission and Monterey almond cultivars harvested over 3 years in 3 regions of California	The 3-year mean polyphenol content of the cultivars ranged from 4.0 to 10.7 mg/100 g almond, with Sonora and Fritz being the highest and the lowest, respectively. Isorhamnetin-3-O-rutinoside was the most abundant flavanoid present at 28-49% of total polyphenols among almond cultivars. Sonora almonds had the highest total phenol (159 mg GAE/100 g) and FRAP value (891 µmol/100 g). Epicatechin and procatechin contents were the major contributing factors for distinguishing among almonds harvested over 3 seasons. Procatechin and rutin were the best constituents for discriminating among regions. The flavanoid content and antioxidant capacity of almond skins appear to be more dependent on cultivars than region or seasonal differences
293	Coffee beans	The effects of extraction time, temperature and solvents on the phenolic content and antioxidant activity of coffee beans were studied. Total phenolic content was determined using the Folin-Ciocalteu method and antioxidant activity was measured using a methyl linoleate assay	Total phenolic content was 3.3 mg/100 g for coffee waste and 21 mg/100 g for green Guinea coffee beans. The antioxidant activities had a significant variation of 8.4% for roasted Colombia and 19.7% for green Guinea. RP-HPLC profile showed that caffeic acid was the dominant acid for coffee waste (3.9 mg/100 g) and green India coffee beans (28.1 mg/100 g). The highest total phenolic content was obtained using an extraction time of 40 min, temperature of 60 °C, particle size of 68 µm and liquid/solid ratio of 30 mL/g
294	Olives	This study describes the analysis and characterization of wastewater of two Portuguese olive mills. For the characterization of phenolic compounds, the extracts were fractionated by HPLC and analyzed by ESI-MS	The results showed that 17 uncommon secoiridoids were found in the olive mills' wastewater. The fragmentation pattern of the compounds suggested that they are glycosylated derivatives of ligstroside
295	Apples	The aim of this study was to compare the Folin-Ciocalteu method and HPLC-MS method to determine the total phenolic content in apple cultivars	The Folin-Ciocalteu method was found to be an appropriate tool for the screening of total polyphenols in apples. However, although the total polyphenol content in all desert cultivars was similar, differences in individual polyphenol patterns and contents generated by UPLC were found among cultivars
296	Polyphenols	The aim of this study was to build a total and specific polyphenol content database of more than 100 food products. The selection of specific phenolic compounds (20 aglycones and 5 glycosides) was based on their biological effects reported in the literature and expertise shared in PHENOBASE consortium. Quantification of individual phenolic compounds was performed by HPLC	Products displaying the highest total phenolic content (expressed as mg GAE/100 g of f.w.) were strawberries (252.1), red cabbage (188.8), grapefruit (160.8), artichokes (115.2) and cherries (114.7). Cocoa powder, unrefined rice, dried black grape, black tea and stewed apples were the greatest sources of procyanidin content with 178.9, 21.8, 21.1, 17.3 and 14.1 mg catechin equivalent/100 g of f.w., respectively. Anthocyanins were mostly found in cherries, red cabbage, radishes and black grapes with respective amounts of 64.1, 18.3, 17.3 and 14.2 mg/100 g of f.w.

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Ref.	Polyphenols/plants/natural interventions	Study design	Outcome
297	Quercetin	This study analyzed the flavanoid content of common vegetables consumed in China	Results showed that Mei celery sampled from Hangzhou was the highest in flavanoid content among 46 vegetables. The dietary intake of flavanoids from vegetables by Chinese people was estimated to be 13.90 mg, in which quercetin is the most common flavanoid contained in vegetables
298	Black currant	This study evaluated the changes in black currant juice anthocyanins during refrigeration and at room temperature. The major anthocyanins (cyanidin-rutinoside, delphinidin-glucoside and cyanidin-glucoside) were analyzed by HPLC at selected time points	The results showed that after 1 month of refrigeration the juice still had approximately 80% of the initial anthocyanin content while only 40% was left in the juice stored at room temperature. In the juice stored at room temperature the half-lives of anthocyanins varied from 18 to 28 days for delphinidin-3-glucoside and cyanidin-3-rutinoside, respectively. The half-lives were 102 days (delphinidin-3-glucoside) and 126 days (cyanidin-3-rutinoside) for the refrigerated juices
299	Lamiaceae species	This study investigated the changes in total phenolic content and antioxidant capacity of 6 Lamiaceae species (rosemary, oregano, marjoram, sage, basil and thyme) after 3 different drying treatments (air-dried, freeze-dried and vacuum oven-dried) and stored for a period of 60 days at -20 °C and compared them with fresh samples	Air-dried samples showed significantly higher phenolic content and antioxidant capacity than freeze-dried and vacuum oven-dried samples throughout the storage period. Fresh samples when stored at -20 °C showed a significant increase in antioxidant capacity
300	Cocoa powder	The methanol extracts of cocoa powder and beans were analyzed using positive-ion MALDI-TOF mass spectrometry. Monomer cyanidin arabinoside and cyanidin galactoside were identified in cocoa preparations using LC-MS-MS	Results showed the presence of A-type proanthocyanidins in cocoa extracts containing up to 6 epicatechin units. A second series of polyflavan-3-ol oligomers containing up to 6 epicatechin residues were detected that were different from the first series by containing an additional oxygen atom. Finally, a dimer procyanidin A ₂ was identified in cocoa and cocoa beans by comparison of HPLC retention times and tandem mass spectra with a standard
301	Onion	This study investigated the extract of dried outer scales of onion by LC-ESI-MS and achieved the isolation of a yellow low-molecular-weight compound	The structure determined by chemical modification and 2D-NMR was 9-carboxy-1,3,6,8-tetrahydroxyxanthylum and named cepaic acid
302	Green “mouthfeel” wines	The aim of this work was to determine differences between green and soft wines for specific parameters of the wine and characterize the indicators responsible for the green sensory properties. Characterization was done by HPLC-DAD	The results showed differences in total phenolic and polysaccharides among the green and the soft wines. Green wines have more color intensity and a higher grade of co-pigmentation than soft wines
303	Chocolate	This study was designed to identify and quantify flavanoids in commercially available chocolate bars. Furthermore, methylxanthines and chlorogenic acid were identified using Au-NP-based colorimetric assay and RP-HPLC	Results showed the RP-HPLC rapidly resolved monomeric (-)-epicatechin, (+)-catechin and procyanidin dimer B2. Dark chocolate contains higher levels of flavonoids than milk or white chocolate

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Ref.	Polyphenols/plants/natural interventions	Study design	Outcome
304	Coffee	The roast levels and characteristics of extracted antioxidants present in a coffee beverage were investigated in lab-scale systems. Green Robuste coffee was from Vietnam. Three roast levels (light, medium and dark) were prepared in a Neotec roaster	The green and roasted coffees were ground at –500 m. The ground coffees were sequentially extracted at 100 and 180 °C using a Dionex extractor. The extracts were further analyzed for their total phenol content (Folin-Ciocalteu) and antioxidant capacity using radical scavenging assays (ABTS). LC-MS was performed to identify neo-formed species containing the phenolic moiety
305	Almond	This study used microstructural analysis under UV light to reveal the autofluorescent components in almond skins before and after digestion. Blue autofluorescence was emitted from the phenolics within the wall of the sclerenchyma cells, the lignified cells of the xylem and from the cuticle overlying the nucellar layer	The major flavonoids identified in almond skins were (+)-catechin, (–)-epicatechin, kaempferol and isorhamnetin. Almond skins in water showed the highest release of phenols and flavonoids during simulated GI digestion, whereas bioaccessibility of the polyphenols was restricted by the presence of food matrices such as biscuits, milk and crisp bread
306	Anthocyanin	The aim of this study was to evaluate the variation in the anthocyanin content among commercial juices purchased from Finland, Poland, Germany and the U.K. Anthocyanins (cyanidin-3-rutinoside, delphinidin-3-rutinoside, cyanidin-3-glucoside and delphinidin-3-glucoside) were analyzed by HPLC using external standard method	There was 14-fold variation in the contents of anthocyanins among the 12 analyzed European commercial black currant juices (from 4.3 to 58 mg/2.5 dL) and the mean contents of anthocyanins varied widely among Finnish, British, Polish and German juices (11.9, 7.45, 32.0 and 38.6 mg/2.5 dL, respectively). In addition, there was statistically significant within-country variation ($P = 0.0202$). The variation within trademarks was also significant in many cases
307	Cocoa	This study showed the comparative analysis of cocoa products and various fruit powders and products for antioxidant capacity (ORAC, $\mu\text{M TE/g}$) total polyphenols (TP, mg/g) and total flavanoids (TF, mg/g) measured using 4-dimethylaminocinnamaldehyde	Cocoa powder and cocoa products are fruit-based products and are among the most concentrated natural sources of ORAC, TP and TF
308	<i>P. dulcis</i> (Mill.) D.A. Webb	This study characterized the almond skin polyphenols by comparing the proanthocyanidin profile with those of peanuts and hazelnuts	The flavan-3-ol composition of the skins from the three sources differed in concentration, structural composition, type of interflavan linkage and degree of polymerization (DP). Polymeric flavan-3-ols in peanuts occurred as both A- and B-type procyanidins (up to DP12), hazelnut skins were composed of partially galloylated B-type procyanidins (up to DP7) and procyanidin-prodelphinidin heteropolymers (up to DP9). Almond skins presented a higher degree of structural heterogeneity, being composed of A- and B-type procyanidins, propelargonidins and prodelphinidins. Procyanidins were found up to DP6 for A-type structures and up to DP8 for the B-type ones; prodelphinidins occurred as heteropolymers (up to DP6) containing up to two epigallocatechin units; and propelargonidins were detected up to DP7 as heteropolymers containing only one epiafzelechin unit

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Ref.	Polyphenols/plants/natural interventions	Study design	Outcome
309	<i>B. oleracea</i> var. <i>italica</i>	This study compared the phytochemical profile of Marathon and Nubia Broccoli (<i>B. oleracea</i> var. <i>italica</i>) by analyzing both leaves and stalks from plants grown in hydroponics and treated with abiotic stressing factor (0 and 80 mM NaCl) as experimental model. This model allows testing the effects of adverse conditions of low-quality irrigation water in Mediterranean agroecosystems of Spain	The results showed that phenolic compounds and vitamin C contents did not change significantly as a result of the saline treatments, with the most significant effect being on the phytochemical content attributed to the cultivar factor. In vitro antioxidant capacity assays revealed much higher levels of activity in leaves than in stalks
310	Anthocyanins (broccoli sprouts)	This study characterized and identified acylated anthocyanins in broccoli sprouts using HPLC-ESI-MS/MS	The main peaks were cyanidin-3-O-diglucoside-5-O-glucoside acylated and double acylated with <i>p</i> -coumaric, sinapic, caffeic, ferulic or subaouic acids. At least three predominant anthocyanins (cyanidin-3-O-(<i>p</i> -coumaroyl)(sinapoyl) diglucoside-5-O-glucoside, Cy-3-O-(sinapoyl)(feruloyl)-diglucoside-5-O-glucoside and Cy-3-O-(sinapoyl)(diglucoside-5-O-glucoside) in the cultivar studied
311	Pomegranate juices	This study investigated the polyphenolic content and antioxidant activity of a variety of pomegranate juices	A variety of pomegranate juices, some containing additional fruit extracts, were analyzed for their antioxidant activity by FRAP and in an HPLC online antioxidant detection system and their polyphenolic content was identified by HPLC-MS-MS
312	Quercetin	The antioxidant activities and total phenolic contents of 11 plants from Polygonaceae were investigated using diphenyl picrylhydrazyl radical (DPPH), ORAC and Folin-Ciocalteu assays. Additionally, total quercetin contents were determined by HPLC	These plant extracts showed high antioxidant activities by both DPPH (111.9-950.5 μ mol of TE/g.dw) and ORAC assays (770.7-2307.9 μ mol of TE/g.dw) and high total phenolic contents (20.84-113.86 mg of GAE/g.dw). These antioxidant activities were positively correlated with total phenolic content (DPPH: $r = 0.98$; ORAC: $r = 0.83$). Moderate correlations were observed between antioxidant activities and total quercetin contents (DPPH: $r = 0.58$; ORAC: $r = 0.51$). These results suggest that quercetin glycosides may be the main contributors to the antioxidant effects of Mongolian Polygonaceae plants
313	Oat	This study profiled levels of free and bound polyphenols in 6 different oat fractions generated using a pilot scale mill and three Endecott test sieves. Total phenolic levels were measured using the Folin-Ciocalteu method and levels of important polyphenol groups (flavanols, flavanones, hydroxycinnamic acids and dihydrochalcones) were measured using RP-HPLC	All oat fractions contained levels of bound phenols. For example, in the oat flour fraction, total phenolic level of cell wall-bound polyphenols was 34.5-48 mg of GAE/100 g f. w. compared to 71.23 mg GAE/100 g f.w. for free polyphenols
314	Artichoke (<i>Cynara cardunculus</i> var. <i>scolymus</i> L.)	The aim of this study was to characterize the phenolic profile in botanical varieties of globe artichoke cultivated in an experimental station in the Catania Plain in Italy. The analysis was carried out by HPLC	Data showed that apigenin and apigenin derivatives represent ~50% of total phenolics measured, including caffeoylquinic acids and luteolin derivatives

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Ref.	Polyphenols/plants/natural interventions	Study design	Outcome
315	Broccoli sprouts (<i>B. oleracea</i> var. <i>italica</i>)	The objective of this study was to determine the effect of packaging with different films (low, intermediate and high permeability) on total phenolics and the phenolic compounds such as flavonoids and hydroxycinnamic acids and derivatives (sinapic, ferulic and chlorogenic acid derivatives) on broccoli sprouts. The phenolic compounds were determined by HPLC-DAD techniques	Results showed that flavonols (quercetin and kaempferol derivatives) represented over 85% of total phenolic compounds. Intermediate permeability film preserved phenolic compounds in broccoli sprouts better than low or high permeability films. The young broccoli sprouts are an excellent source of antioxidant phenolic compounds, reaching higher values than those found in other sprouting species and even richer than commercial broccoli heads
316	Polyphenols	The objective of this study was to build a comprehensive database, Phenol-Explorer, to gather content values of all flavonoids, phenolic acids, lignans and stilbenes known in foods, including their glycosides and esters. A total of 63,291 polyphenol content values were collected by a systematic search of the scientific literature in over 1,000 peer-reviewed scientific papers	Only those values filling specified minimal requirements were selected to produce representative mean values. A total of 35,837 content values originating from 608 publications were finally selected to produce mean content values for 498 phenolic compounds in 429 foods and beverages. These data are available using an open-source user-friendly web interface (http://www.phenol-explorer.eu/) to allow any user to retrieve content values obtained by a given analytical method for the different compounds in the different foods
317	<i>Apollonias barbujana</i> , <i>Ocotea foetens</i> , <i>Prunus azorica</i> , <i>Rumex maderensis</i> and <i>Piantago arborescens</i> subsp. <i>maderensis</i>	The total phenolic contents of 5 Macaronesia endemic species (<i>A. barbujana</i> , <i>O. foetens</i> , <i>P. azorica</i> , <i>R. maderensis</i> and <i>P. arborescens</i> subsp. <i>maderensis</i>) were determined in this study	<i>A. barbujana</i> has the highest contents of both phenolics and flavonoids and demonstrated the highest antioxidant activity, and <i>O. foetens</i> exhibited the lowest antioxidant activity. <i>P. azorica</i> , <i>R. maderensis</i> and <i>P. arborescens</i> had similar scavenging capacity for peroxy radicals, despite the fact that they contain widely different contents in flavonoids. <i>P. arborescens</i> demonstrated less capacity for hydroxyl scavenging
318	Olive cake	The physicochemical properties and phenolic compounds of olive cake were evaluated after 60 days of fermentation	Results showed that olive cake is rich in crude fiber (44.0-44.5%) and carbohydrates (34.9-31.3%) and contains a moderate amount of crude protein and fat. Olive cake also contains a good amount of ash. The total phenolics content decreased from 4142.7 to 2965.7 mg/100 g during fermentation and no changes in antioxidant activity or nitrogen (1.09-1.11%) and carbon (33.94-34.50) levels were observed. The pH values were between 4.4-4.6 during storage and the temperature was increased from 28.4 to 59.9 °C, which means that conditions were suitable for thermophilic bacteria growth
319	Sour cherry	The aim of this study was to determine the antioxidant capacity of a special sour cherry cultivar, which has an unusual pale color. The antioxidant capacity was determined for several compounds, including anthocyanins, flavonoids and flavonoid derivatives, phenolic acids and ascorbic acid	Anthocyanins did not contribute to the fruit's total antioxidant capacity, since this fruit is pale. The role of ascorbic acid was also not significant because the measured concentration was very similar to the control. However, the concentration of flavonoids and flavonoid-glycosides was almost 10-fold higher than the control sample. The major flavonoid compounds were genistein derivatives

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320	Irish grown vegetables	This study examined the effect of agronomic practices on accumulation of phytochemicals in Irish grown vegetables. Variety, tissue type, plant maturity and fertilizer trials were performed	Data from pilot scale field trials carried out in autumn 2008 indicate significant differences in total phenolic content in onion varieties, with highest levels detected in the Napoleon cultivar. In a variety trials of green- and purple-sprouting broccoli, the highest total phenolic contents were found in the Steel and TZ 5055 cultivars, respectively. Different tissue types (leaf, immature primary floret, mature primary floret and flower) were examined in 3 purple-sprouting broccoli varieties. Levels of total phenolics were significantly higher in leaf than in primary floret for all 3 varieties. In a trial of planting space for purple-sprouting broccoli (cultivar TZ 6002), the highest levels of total phenolics were found in plants grown at 60 cm space between rows and significantly lower levels were found for plants grown at 75 cm and 90 cm between rows
321	Red clover (<i>Trifolium pratense</i> L.)	The aim of this study was to identify and characterize phenolic compounds in red clover by HPLC-MS, and to study the effect of elevated ozone doses on changes in the concentrations of antioxidant phenolic compounds	Concentrations of formononetin, biochanin A, daidzein and genistein were determined after hydrolysis of leaves, roots, stems, petioles and flowers of red clover grown in the greenhouse and in a field. Leaves were rich in formononetin and biochanin A (max. 9.05 and 14.59 mg/g, respectively), whereas the highest amounts of daidzein and genistein were found in petioles (max. 0.28 and 0.54 mg/g, respectively). High formononetin concentrations were also found in roots (max. 5.8 mg/g), whereas the level of biochanin A was especially low in field-grown roots
322	Dicaffeoylquinic acids	The study describes the process of isolation, structure elucidation and characterization of dicaffeoylquinic acids as primary reference substances for analytical purposes	
323	Cocoa beans	This study evaluated the changes in flavanols and procyanidins after processing in cocoa beans, cocoa powder, commercial chocolate and cocoa-containing products	Unripe beans, followed by ripe cocoa beans, have the highest naturally occurring levels of flavanols with (–)-epicatechin [(–)-epi] being the dominant monomer, 30-fold greater than (+)-catechin [(+)-cat]. About 15% of the dry weight of ripe cocoa beans is procyanidins and flavanol monomers. As fresh cocoa beans are processed, there is a loss of (–)-epi during the cocoa fermentation and bean roasting steps. Roast temperatures above 70 °C are the threshold for epimerization
324	Thai foods	This study selected 9 spicy Thai foods, categorized as ready-to-cook sauce and ready-to-eat food, in order to determine their phenolic content and antioxidant effects	Antioxidant capacity and total phenolic content of methanol extracts obtained from sterilized food samples ranged from 15.5 to 6.4 mg vitamin C equivalent and from 61 to 182 mg GAE, respectively. After sterilization heat treatment at 118, 120 and 121 °C for approximately 25-30 min, 89% of the products had an improvement in antioxidant capacity (0.4-120%). Phenolic content was increased in all products by 4-54%

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325	<i>Ocimum</i> species	Blanching, boiling, steaming, sautéing and high-temperature cooking methods were evaluated in <i>Ocimum amehcanum</i> (hairy basil), <i>O. tenuiflorum</i> (holy basil), <i>O. basilicum</i> (sweet basil) and <i>O. gratissimum</i> (wild basil) in order to determine heat effects on antioxidant capacity, total phenolic content and presence of phytochemicals	The HPLC chromatograms revealed that substances were leached out from leaves into cooking water. The sautéing, steaming at atmospheric pressure and high pressure generally enhanced the antioxidant capacity, which correlated with increased phenolic content. Similar chromatograms were detected for fresh, atmospheric steamed and sautéed leaves, although with different intensity. The phenolic content and antioxidant activity of a major compound, rosmarinic acid, was increased in sautéed leaves but was substantially less than from leaves steamed under pressure
326	Bamboo species	This study characterized the secondary metabolite profiles (with a focus on polyphenols) of several bamboo species from different genera. The extracts were simultaneously examined for their antioxidant and anti-inflammatory activity in order to isolate and identify the main bioactive secondary metabolites. In a first stage, extracts of leaves and culms of 3 highly heterogeneous bamboo species, (<i>Phyllostachys nigra</i> , <i>Sasa veitchii</i> and <i>Fargesia robusta</i> Pingwu) were analyzed using HPLC-DAD	The main compounds in leave extracts of <i>P. nigra</i> were identified as homo-orientin, orientin and isovitexin. The extracts from leaves and culms had the highest antioxidant capacity (4371 µmol Trolox®/g leaf extract)
328	Ellagitannins	This study was designed to clarify and quantify the structures of each ellagitannin (ET) in its native form using 59 raspberry and 36 blackberry extracts. The UPLC Acquity and QTOF-HDMS Synapt (Waters) assays were used for the structural analysis	The presence of 14 ETs and 8 ellagic acid conjugates (EACs) in the raspberry extracts, and 17 ETs and 5 EACs for the blackberry extracts was confirmed. A significant variation among cultivars was observed
329	Red cabbage	The objective of this study was to determine the amount of anthocyanins in fresh, blanched, pasteurized, stewed, fermented and storage red cabbage using HPLC-DAD-MS screening	From among a variety of red cabbages, 21 derivatives of cyanidin were identified. The core of the identified compounds was cyanidin 3-diglucoside-5-glucoside. Results confirmed that fresh red cabbage contained large amounts of anthocyanins (0.37 mg/g f.w.). Moreover, the results showed that the pasteurization process was the treatment that decreased the amount of anthocyanins the most (by 40%), and the treatment that decreased the amount the least was blanching (by 7%)
330	Eggplant (<i>Solanum melongena</i> L.)	This study measured the contents of total polyphenols, chlorogenic acid and anthocyanins in 7 varieties of eggplants, including Senryo Nigo (long oval type), Chikuyo (long type), Shoya Naga (very long type), Kurowashi (American eggplant, big oval type), Maru-nasu (round type), Mizu-nasu (water eggplant, long oval type) and Anominori (long oval type). 1,1-Diphenyl-2-picrylhydrazyl (DPPH) radical scavenging activity was used to evaluate the antioxidant activity	Antioxidant activity was the highest in Kurowashi and the lowest in Shoya Naga. Higher activity was found in the peel in all types of eggplant and 3.1- to 5.5-fold higher than in the flesh. Total polyphenol and chlorogenic acid contents were also the highest in Kurowashi and the lowest in Shoya Naga. The contribution of chlorogenic acid to total polyphenol content ranged from 39 to 75% in the flesh and 70 to 85% in the peel. In regard to anthocyanin content, the highest content was found in Senryo Nigo and Anominori

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331	Polyphenols	Polyphenols in fruits, vegetables and minimally processed vegetable oils are antioxidants which could reduce the incidence and severity of coronary heart disease. Therefore, the effects of dietary polyphenols on several cardiovascular risk factors were studied	Results revealed that certain naturally occurring edible compounds found in plants, such as dietary polyphenols, had beneficial effects. Consumption of polyphenols had no effect on fasting concentrations of lipids, lipoproteins, insulin or glucose. However, chronic consumption reduced fasting LDL cholesterol concentrations and increased HDL cholesterol concentrations
332	Quercetin	In this study the effects of quercetin on LPS-induced changes in coronary artery nitrite/nitrate production were compared to those of two human metabolites, quercetin-3'-sulphate (QS) and quercetin-3-glucuronide (QG). Segments (5 mm) of the porcine coronary artery were incubated for 24 h in DMEM with quercetin (10 μ M), QS (10 μ M) or QG (10 μ M) in the absence or presence of 1 μ g/mL LPS. The nitrite/nitrate content of the bathing medium was determined by spectrophotometry	Results showed that following overnight storage in DMEM, control artery segments produced between 3 and 30 nmol nitrate/nitrite per mg wet weight. Exposure to LPS (1 μ g/mL) was associated with a 5-20-fold increase in nitrite/nitrate ion production, which was significantly reduced by exposure to 1 μ g of dexamethasone (70.9 \pm 4.8%) or 10 μ g 1400W (77.6 \pm 5.3%). Exposure to 10 μ M of quercetin (89.6 \pm 4.3%), 10 μ g of QS (76.9 \pm 5.9%) and 10 μ g of QG (91.6 \pm 4.7%) was also associated with a significant reduction in nitrite/nitrate production
333	Myricetin and quercetin	In this study the effect of quercetin was compared with that of its 5'-hydroxylated analogue myricetin against LPS-induced changes in NO production in the porcine isolated coronary artery	Results revealed that exposure to 1 μ g/mL of LPS was associated with a 5-20-fold increase in basal nitrite/nitrate ion production (3-30 nmol/mg wet weight), which was significantly reduced by exposure to 0.1 μ M (33.3 \pm 12.5%), 1 μ M (66.7 \pm 22.6%) and 10 μ M of quercetin (89.6 \pm 4.2%), but not by 10 μ M of myricetin (9.2 \pm 6.0%). The inhibitory effect of 1 μ M of quercetin (88.5 \pm 2.7%) on LPS-induced nitrite/nitrate production was significantly reduced when coincubated with 10 μ M of myricetin (23.5 \pm 17.0%)
334	Cocoa powder	The study was a 4-week randomized, crossover, controlled clinical trial. After a 2-week lead-in diet, subjects received two sachets of 20 g of cocoa powder (40% cocoa) per day with 250 mL of skim milk or only 500 mL/day of skim milk for 4 weeks in random order. Urinary metabolome was analyzed by HPLC-q-ToF	A total of 30 compounds related to cocoa intake (food metabolome) including <i>N</i> -phenylpropenoyl-L-amino acids and polyphenol host metabolites were identified. In addition, colonic microbial metabolites such as phenylvalerolactones, phenylvaleric acids and their conjugates were identified in urine samples from the subjects who received cocoa plus skim milk
335	Mediterranean diet (virgin olive oil)	A parallel-group, multicenter, controlled clinical trial was designed to assess the effects of Mediterranean diet on the primary prevention of cardiovascular disease	Results suggest that 1-year dietary supplementation with Mediterranean diet improves plasma antioxidant status in people with CVD risk
336	Epigallocatechin-3-O-gallate	This study examined the mechanism underlying the stimulatory effect of catechins on the endothelial formation of NO. The phosphorylation level of Akt and eNOS was assessed in cultured coronary artery endothelial cells by Western blot and ROS formation using dihydroethidine. Natural and hemisynthetic catechins were evaluated	EGCG causes endothelium-dependent NO-mediated relaxation of coronary artery rings via the redox-sensitive Akt-dependent activation of eNOS in endothelial cells. The stimulatory effect of catechins is critically dependent on the gallate moiety and on the presence of hydroxyl functions possibly leading to the intracellular auto-oxidation in endothelial cells

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337	Red wine extract	The purpose of the present study was to identify active polyphenols using a multistep bioguided fractionation of the red wine extract. The phosphorylation level of Akt and eNOS was assessed in cultured porcine coronary artery endothelial cells by Western blot analysis	Results showed that the fractionation yielded 9 fractions, 4 of which significantly increased the phosphorylation level of Akt and eNOS in endothelial cells. The active fractions contained mainly procyanidins and some anthocyanin compounds. The fractionation of one of the active fractions yielded 11 subfractions, all of which significantly increased the phosphorylation level of Akt and eNOS. Analysis of the phenolic compounds indicated that these subfractions contained mainly mixtures of procyanidin dimers and conjugated anthocyanins
338	Aronia juice	The aim of the present study was to examine whether aronia juice causes endothelium-dependent relaxation of isolated arteries and to determine the underlying mechanism	The findings indicated that aronia juice causes endothelium-dependent relaxation of coronary arteries due to the activation of eNOS via the redox-sensitive Src/PI3-kinase/Akt pathway. They also suggest that calmodulin may contribute to the signaling pathway leading to the eNOS activation response to aronia
339	Resveratrol	This study investigated whether the consumption of resveratrol can acutely enhance flow-mediated dilatation of the brachial artery	Results showed that there was a significant log-dose effect of resveratrol on flow-mediated dilatation, as demonstrated by an increase from $4.1 \pm 0.8\%$ at 0 g to $7.7 \pm 1.5\%$
340	Polyphenols	The association between dietary intake of polyphenols and the risk of acute coronary syndrome by the use of a newly developed biomarker for intake of PC was investigated in a prospective, nested, case-control study. The study was performed on urine samples from the Danish follow-up study Diet, Cancer and Health, which included diet and lifestyle questionnaires, anthropometric measurements and biological material from 57,055 volunteers. The biomarker analyses were performed on an HPLC single quadrupole mass spectrometer	Eleven dietary polyphenols were measured, including hesperetin, naringenin, quercetin, kaempferol, sorhamnetin, tamarixetin, phloretin, genistein, daidzein, apigenin and enterolactone. Statistical analysis is currently under way
341	Flavanone	This study was designed to investigate the impact of physiological concentrations of flavanone metabolites on the activity of human umbilical vein endothelial cells (HUVEC). The first step, which is described here, was to identify the flavanone metabolites occurring in human plasma after consumption of orange or grapefruit juice by LC MS/MS	Studies to characterize the impact of flavanone metabolites on HUVEC viability, proliferation, migration, production of vasoactive molecules and monocyte adhesion are currently in progress
342	Flavonoids from fruits and vegetables	In a randomized, controlled, parallel, diet intervention study, 180 subjects at risk for cardiovascular disease were included who were low fruit and vegetable consumers. Subjects were recruited and randomly assigned to either a control group or one of two treatment groups –high-flavonoid (HF) diet and low-flavonoid (LF)– diet to examine the impact of defined quantities of flavonoids from fruits and vegetables	Dietary intakes from a subgroup of subjects (N = 73) showed that the mean flavonoid intakes from fruit and vegetables in LF and T groups were close to baseline intake throughout the study (35–63 mg/day). Those in the HF group increased throughout the study period (55 mg/day at baseline; 140 mg/day at 6 weeks; 160 mg/day at 12 weeks; 199 mg/day at 18 weeks). Target portion numbers were achieved for the treatment groups (HF: +2.6, +2.8 and +5.4; LF: +2.9, +3.7 and +5.5)

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Table I. Cont. Summary of studies on polyphenols presented at the 4th International Conference on Polyphenols and Health.

Ref.	Polyphenols/plants/natural interventions	Study design	Outcome
43	Red wine polyphenols	The aim of this study was to determine whether intake of red wine polyphenols, which are known to have antioxidant properties and to stimulate the endothelial formation of NO and endothelium-derived hyperpolarizing factor (EDHF), improves endothelial function in aged rats	Results indicate that aging is associated with blunted endothelium-dependent relaxation involving increased oxidative stress. Intake of red wine polyphenols for 4 weeks by aged rats improved endothelial dysfunction and normalized vascular oxidative stress and the expression of eNOS, arginase I, NADPH oxidase and angiotensin receptors
344	Resveratrol, quercetin and catechin	This study investigated the effects of resveratrol, quercetin and catechin on colon carcinoma cell proliferation and cell distribution in the cell cycle	Results showed that resveratrol/quercetin combination showed an additive antiproliferative effect on colon carcinoma SW480 cells and metastatic colon carcinoma SW620 cells. These effects correlated with the S phase arrest of the cell cycle and an increase in apoptotic cells. The addition of catechin prevented this increase due to the resveratrol/quercetin combination
345	Procyanidins	The effects of fraction-enriched large procyanidins (LP) isolated from cocoa were investigated using a liposome model (with different lipid compositions) and Caco-2 cells as a model of intestinal epithelium	In Caco-2 cells, LP inhibited NP-B activation initiated by different prostimulatory compounds to a different extent; the highest inhibitory capacity for signals was initiated at rafts, i.e., TNF- α and deoxycholate. LP inhibited deoxycholate-induced calcium mobilization, oxidant production and the activation of mitogen activated kinases (MAPKs)
346	Flavanone-enriched orange extract	In this study a genome-wide microarray technique was used to search for molecular changes in response to exposure to a flavanone-enriched orange extract in human colon fibroblasts (CCD-18Co)	Results showed downregulation of the expression of plasminogen activator inhibitor 1 (PAI-1) and upregulation of the metalloproteinase MMP-12 (mRNA and protein levels), both critically involved in extracellular matrix (ECM) remodeling and fibroblast migration. Results were indicative of a general moderate activation of the colon fibroblast inflammation-related function in the gut after exposure to the orange extract
347	Urolithin A	The effect of urolithin A was examined in an animal model of DSS-induced colon inflammation. Oral administration of urolithin A to male Fisher rats during 25 days, at concentrations representative of those found in vivo in humans, preserved colonic architecture, markers (COX-2 and mPGES-1) and induced changes in microbiota composition	Colon fibroblasts were treated with urolithins and EA and then stimulated with IL-1 β . Urolithin A (Uro-A) and urolithin-B (Uro-B) (10 μ M) inhibited prostaglandin (PGE ₂) production (by 85% and 40%, respectively) after IL-1 β stimulation, whereas EA did not show any effect. Uro-A but not Uro-B down-regulated COX-2 and mPGES-1 mRNA expression and protein levels. Slight but significant effects were found on MAPK pathway activation
348	Barley, oat, wheat and buckwheat	This study examined the effect of different phenolic extracts from barley, oat, wheat and buckwheat on the modulation of basal and LPS-induced NF- κ B activity and elucidated the role of phenolic acids in this modulation. Three extracts were prepared: extracts of free phenolic compounds, extracts of free phenolic acids and extracts of bound phenolic acids	Extracts of free phenolic acids exhibited potent inhibition of LPS-induced NF- κ B activity and basal NF- κ B activity at low concentrations. Furthermore, extracts of bound phenolic acids also inhibited LPS-induced NF- κ B activation. Bound phenolic acids and most extracts of free phenolic compounds increased both basal and LPS-induced NF- κ B activation

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Table I. Cont. Summary of studies on polyphenols presented at the 4th International Conference on Polyphenols and Health.

Ref.	Polyphenols/plants/natural interventions	Study design	Outcome
349	Oligonol®	A double-blind, randomized, crossover study in healthy males was conducted to evaluate the effects of consuming a single dose of 0, 100 or 200 mg/kg of Oligonol® on platelet reactivity as measured by platelet function analysis. Vascular endothelial function was measured by peripheral arterial tonometry and gene expression was measured by whole genome microarrays	No significant differences in mean platelet function analysis or peripheral arterial tonometry were observed 2 h after a single dose of 100 or 200 mg of Oligonol®
350	Polyphenol juice drinks	This study investigated the effects of polyphenol juice drinks on plasma glucose and insulin levels in response to dietary stress induced by a high-fat meal (HFM). Subjects consumed a HFM of 1351 kcal with a placebo drink or with a different polyphenol juice (2.B.3; 2.4.5; 457)	The HFM induced a peak in both glucose (+15.11 mg/dL) and insulin (+40.19 mU/L) at 0.5 h. Glucose levels returned to baseline values within 1 h, and differed from insulin which began to decrease after 1 h (+20.91 mU/L) and returned to baseline levels in 2 h. None of the polyphenol juice drinks affected the glucose increase induced by the HFM. Beverage 2.B.3 significantly increased insulin production at 0.5, 1 and 2 h with respect to the placebo HFM. This effect could be due to the higher content of glucose (37 g/L vs. 6.3 g/L) and fructose (57 g/L vs. 6.4 g/L) present in beverage 2.B.3 compared to the placebo drink
351	Punicalagin and ellagic acid	In this study the human intestinal Caco-2 cell line was used after 21 days of differentiation. These cells were submitted to a proinflammatory cocktail (IL-13, TNF- α , LPS and IFN- γ) for 24 h, in the presence or absence of 50 μ m punicalagin or ellagic acid	No cytotoxicity was detected, as verified by LDH release. IL-6 and IL-8 secretion was quantified by ELISA. The proinflammatory cocktail enhanced the secretion of the two proinflammatory markers IL-6 (113.4-fold) and IL-8 (104.2-fold). IL-6 secretion was significantly (3.8-fold) reduced by punicalagin whereas the reduction by ellagic acid was less (1.9-fold) and insignificant. IL-8 secretion was not significantly reduced (1.2-fold) by ellagic acid
352	Hop bract polyphenol	This study examined the inhibitory effect of hop bract polyphenol (HBP) against cellular inflammatory responses induced by <i>P. gingivalis</i> . Gingival epithelial cells were stimulated with <i>P. gingivalis</i> membrane vesicles and the effects of HBP on cellular inflammatory mRNA expression were examined using RT-PCR method	HBP concentration-dependently inhibited the mRNA expression of COX-2, IL-6, IL-8 and MMP-1 and MMP-3, whereas epigallocatechin gallate (a control polyphenol) inhibited only COX-2 expression. 2-[(2-Methylpropanoyl)-phloro-glucino]1-O- β -D-glucopyranoside (MPPG) was finally identified to be the significant anti-inflammatory element which completely inhibited inflammatory mRNA induction. Kaempferol 3-O- β -glucopyranoside (astragalin) was also found to have anti-inflammatory activity
353	Equol	This study compared the effects of equol (Eq), the main metabolite of daidzein, to those of urolithin A (UroB) and urolithin B (UroA) on osteoblast functions. Primary osteoblasts were cultured with phenol red-free medium. Proliferation and activity of alkaline phosphatase (a marker of osteoblast differentiation) were measured	No stimulation of osteoblasts up to calcium nodule was observed. However, UroA, UroB and Eq tended to enhance osteocalcin secretion. Taken together, these findings suggest that ellagitannin metabolites are implicated in the regulation of osteoblast differentiation through estrogen receptor-dependent and -independent mechanisms of action

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Ref.	Polyphenols/plants/natural interventions	Study design	Outcome
354	<i>Pyrus communis</i> cv. La France	This experiment in active polyphenols contained in the branches of <i>P. communis</i> cv. La France investigated the relationship between their skin-lightening effects and liver injury-mitigating effects	Isolated compounds were identified as arbutin (hydroquinone glucoside), hydroquinone (6- <i>O</i> -caffeoyl)-glucoside and hydroquinone (2- <i>O</i> -caffeoyl)-glucoside by NMR and MS spectra analyses. Eluate from the Diaon column-absorbable fraction of the extracts with 50% EtOH and some fractions obtained by further fractionation inhibited tyrosinase and showed inhibitory activity on melanogenesis in cultured B16 melanoma cells. Arbutin and hydroquinone (6- <i>O</i> -caffeoyl)-glucoside inhibited release of ALT in primary cultured hepatocytes exposed to carbon tetrachloride
355	Polyphenolic compounds	This study investigated the effects of chronic administration of polyphenolic compounds (PC) on plasma lipid concentration and oxidative stress in diet-reduced hypercholesterolemic rats. In addition, the effect of PC on aortic endothelial function was also studied in male F344 rats (2-month-old) that were fed standard diet (ST), 4% cholesterol-rich diet (CH) or 4% cholesterol-rich diet plus 2% freeze-dried red wine for 3 months	The high-cholesterol diet tended to reduce the GSH level, but in PC-fed rats it was increased to the control level. In aortic vascular ring preparations, All induced vascular smooth muscle contraction. In cholesterol-fed rats, the tension was significantly greater than that of PC-fed rats. The results suggested that chronic administration of PC in dietary-induced hypercholesterolemic rats increased GSH and improved the endothelial function to produce vasorelaxing factors like NO
356	<i>Helychrisum plicatum</i>	This study examined the antioxidant and hepatoprotective activity of <i>H. plicatum</i> extracts in in vitro and in vivo conditions. Phytochemical screening was done using HPLC	Extracts exhibited radical-scavenging activity (IC ₅₀ = 6-11 mg/mL). In in vivo studies, the biochemical parameters in groups treated with <i>H. plicatum</i> extracts (25 mg/kg) had significantly different values than those in the CCl ₄ -treated group. Phytochemical screening of extracts from Macedonia revealed the presence of apigenin and naringenin as free aglycones and glycosides of apigenin, naringenin, quercetin and kaempferol in the flowers, as well as quercetin and luteolin glycosides and free luteolin in stems and leaves
357	Piceatannol	The aim of this study was to compare the mechanism of action and antiatherosclerotic effects of piceatannol with those of resveratrol	Piceatannol inhibited platelet-derived growth factor (PDGF-BB)-induced cell migration in a modified Boyden chamber assay and wound-healing assay. Western blot analysis showed that PDGF-BB-induced phosphorylation of Akt, p70(S6k) and p38 was inhibited by piceatannol, but not by resveratrol. In vitro and ex vivo assays demonstrated that piceatannol suppressed PI3K activity more effectively than resveratrol. Both in vitro and ex vivo pull-down assays revealed that piceatannol directly binds with Sepharose 4B-PI3K beads in an ATP-competitive manner

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Ref.	Polyphenols/plants/natural interventions	Study design	Outcome
358	Quercetin and resveratrol	In this work the effects of biotechnologically produced verbascoside (VB) and chlorogenic acid (CA) on HUVEC response to oxLDL were compared with those of quercetin and resveratrol. OxLDL was prepared using myeloperoxidase/nitrite system	QRT-PCR analysis of the effects of oxLDL on the expression of 14 genes associated with oxidative stress and inflammation revealed a significant upregulation of genes specifically involved in the recruitment and adhesion of leukocytes. The upregulation of <i>IL8</i> , <i>MCPI</i> , <i>ICAM1</i> , <i>VCAM1</i> and <i>IFNG</i> was significantly suppressed by the addition of VB, resveratrol or CA, while treatment with quercetin resulted in an increase in the expression of these genes and <i>COX2</i> . Quercetin was found to be the most effective inhibitor, whereas resveratrol was the least effective
359	Phorbol	This study focused on phorbol ester-induced COX-2 expression in nontumorigenic MCF-10A and breast cancer MCF7 cells	Results showed that IFN- γ downregulated PMA-induced COX-2 expression by modulating ERK1/2 signaling
360	Hydroxytyrosol	This study investigated the molecular mechanisms involved in hydroxytyrosol's (HTy) protective effect against <i>tert</i> -butyl hydroperoxide (t-BOOH)-induced damage in human Hep G2 cells	Treatment of Hep G2 cells with HTy increased the expression and activity of glutathione-related enzymes and also induced the nuclear translocation of the erythroid 2p45 (NF-E2)-related factor (Nrf2). Moreover, two important signaling proteins involved in Nrf2 translocation, protein kinase B (Akt) and extracellular regulated kinases (ERKs), were also activated by HTy
361	Cocoa powder	The aim of this work was to evaluate the effects of chronic cocoa consumption on cellular and serum biomarkers related to atherosclerosis in high-risk patients. Forty-two high-risk volunteers (19 men and 23 women, mean age 69.7 ± 11.5 years) were included in a randomized, crossover feeding trial. All received 40 g of cocoa powder with 500 mL/day skimmed milk (C+M) or only 500 mL/day skimmed milk (M) for 4 weeks	No significant changes were found in the expression of adhesion molecules on T lymphocyte surface after C+M intake compared to that observed after M intake. However, the expression of VLA-4, CD40 and CD36 in monocytes was significantly lower after C+M intake than after M intake. In addition, serum concentrations of soluble endothelial-derived adhesion molecules P-selectin and ICAM-1 were significantly reduced after C+M intake compared to those observed after M intake
362	Orange juice	The goal of this human intervention trial was to study the effect of orange juice, a flavonoid rich-source, on functional blood pressure and endothelial microvascular reactivity, as well as systemic parameters linked to CV risk. The role of hesperidin, the major flavonoid of orange juice, was also determined	The results suggest that hesperidin may contribute to the vascular health effects of orange juice
363	Tea polyphenols	The ability of flavanols and related compounds to inhibit VEGF signaling was investigated. HUVECs were stimulated with VEGF-A and treated with the polyphenols. VEGF signaling was assessed using Western blotting and an antibody that specifically binds to VEGFR2 phosphorylated at Tyr1175	The procyanidin fraction completely inhibited VEGFR-2 phosphorylation. However, epicatechin, catechin and procyanidin B2 were ineffective at 20 μ M, indicating that only epicatechin oligomers with DP > 3 are effective. The green tea catechin EGCG, which is galloylated at the 3-position and contains a trihydroxy B-ring, also completely inhibited VEGFR-2 phosphorylation. Gallic acid was a weak inhibitor, while ellagic acid (a dimer of gallic acid) completely inhibited VEGF signaling

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Ref.	Polyphenols/plants/natural interventions	Study design	Outcome
364	Cocoa powder	This study evaluated the principal active components and potential mechanism(s) for the hypocholesterolemic effect of polyphenolic substances from cocoa powder in rats. Male Wistar rats were fed a 1% high-cholesterol diet (HC) or an HC diet containing 1% polyphenol extract from cocoa powder or a mixture of 0.024% catechin and 0.058% epicatechin (CE) for 4 weeks	The cocoa powder group had significantly lower plasma cholesterol concentrations and significantly greater fecal cholesterol and total bile acids excretion than the HC group. The CE mixture did not influence plasma cholesterol concentrations, fecal cholesterol or total bile acids excretion. Micellar solubility of cholesterol in vitro was significantly lower for procyanidin B2 (dimer), 85 (dimer), C1 (trimer) and A2 (tetramer), which are the main components of polyphenol extract from cocoa powder, compared to catechin and epicatechin
365	Xanthohumol (XN), and its metabolites soxanthohumol (IXN) and 8-prenylnaringenin (8-PN)	The aim of this study was to investigate the in vivo modulation of angiogenesis and inflammation by XN, IXN and 8-PN. C57BL/6J mice were injected s.c. with Matrigel® containing VEGF with or without polyphenol	Both plug and skin wound-healing assays confirmed that treatment with XN and IXN decreased the number of vessels formed and serum NAG activity, while 8-PN increased the formation of blood vessels in both assays and enzyme activity in the wound-healing assay. A similar profile was found for serum IL-1 β determination in the wound-healing assay. Results demonstrate that while 8-PN appears to stimulate angiogenesis, XN and IXN exhibit antiangiogenic and anti-inflammatory effects
366	Cocoa procyanidins	The aim of this study was to evaluate the effects of cocoa procyanidins (CP) on plasma cholesterol levels in an experimental animal model and in subjects with hypercholesterolemia	In rats, supplementation of CP significantly decreased plasma cholesterol to levels similar to those of the normal diet group. Raised liver cholesterol and triglyceride levels were reduced in rats fed a 1.0% CP diet. In the human study, 273 subjects with hypercholesterolemia were enrolled in a double-blind, randomized, placebo-controlled comparative trial. Results showed that plasma total and LDL cholesterol concentration was reduced significantly throughout the ingestion period. HDL cholesterol plasma levels were increased significantly during the experimental period in the cocoa group
367	Dark chocolate enriched in flavan-3-ols and procyanidins	A randomized, controlled, crossover intervention trial assessed the acute effects of consumption of dark chocolate enriched in flavan-3-ols and procyanidins compared with standard dark chocolate and white chocolate on several measures of platelet function (platelet aggregation, in vitro coagulation and platelet activation) in healthy volunteers. In addition, the study examined the effects of flavan-3-ols consumption on differential regulation of the platelet proteome to elucidate pathways by which these bioactive cocoa compounds affect platelet function	
368	Grape seed proanthocyanidin extract	To evaluate the hypothesis that proanthocyanidins affect mitochondrial activity in obesity, this study measured the expression of several key genes in skeletal muscle of diet-induced obese rats. Rats were given a varied diet of 25 or 50 mg/kg of a grape seed proanthocyanidin extract (GSPE)	Only mRNA levels of MCAD were higher in rats fed a varied diet than in chow-fed rats. The expression of mRNA was also higher: 50 mg GSPE/kg > 25 mg GSPE/kg > control rats

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Ref.	Polyphenols/plants/natural interventions	Study design	Outcome
369	<i>Sasa borealis</i>	In this study <i>S. borealis</i> was screened for adipocyte differentiation in 3T3-L1 cells	Results showed that all fractions of <i>S. borealis</i> extracts inhibited intracellular accumulation in a concentration-dependent manner in 3T3-L1 cells. Among the four different fractions, the ethylacetate-soluble fraction had the highest inhibitory effect on adipocyte differentiation and proliferation. The extract also suppressed the expression of genes involved in adipogenesis, such as <i>PPARG</i> and <i>CEBPA</i> . It was concluded that the ethylacetate-soluble fraction of <i>S. borealis</i> extract has antiadipogenic effects by regulating adipogenic transcription factors
370	Grape seed proanthocyanidins	The aim of this study was to determine the effects of GSPE on plasma triglycerides and elucidate the contribution of chylomicrons (QM) and VLDL to this phenomenon during lipid absorption	Results indicated that a single oral administration of GSPE blocked the increase of plasma total TG, TG-VLDL and free fatty acids. Under the same conditions, GSPE did not affect plasma TG-QM and <i>p</i> -hydroxybutyrate levels. After 2 h of acute treatment with GSPE, there was a significant decrease in liver secretion of VLDL. Results indicated that proanthocyanidins improve the state of circulating lipoproteins in the postprandial state by reducing VLDL production
371	α G-rutin	The effects of α G-rutin, which has an antioxidant action similar to rutin but is more easily absorbed from the intestine, were investigated in a mouse model of atherosclerosis: 4-week-old male C57BL/6.KOR/Stn-Apoe(shl) mice. The aorta was excised; the atherosclerotic regions were stained by Nile red and analyzed as the area and number. Moreover, the levels of triglyceride (TG), total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol (HDL-C), lipid peroxidation and TNF- α in serum were measured.	It was suggested that the development of atherosclerosis was inhibited by administration of 0.1% α G-rutin in mice. However, the level of TG in 0.1% α G-rutin group significantly increased, while the levels of TC, LDL-C, HDL-C, lipid peroxidation and TNF- α were no different compared to the control
372	Tea polyphenols	The aim of this study was to investigate the ability of the major tea polyphenols to protect from oxidative damage based on the levels of ROS production and inflammatory CRP markers after tea consumption	Consumption of tea revealed alterations in ROS generation. There was a decrease in ROS generation after tea consumption and there was no effect on CRP markers
373	Champagne wine	The effect of acute and moderate champagne wine consumption on vascular function was investigated in healthy volunteers in a randomized, placebo-controlled, crossover trial. Peripheral microvascular function was assessed postintervention using laser Doppler imaging with iontophoresis	Consumption of champagne wine induced an acute change in endothelium-independent vasodilatation at 4 and 8 h postconsumption ($P = 0.045$ and $P = 0.037$, respectively), while the alcohol-matched control did not induce endothelium-independent changes in vascular reactivity

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Ref.	Polyphenols/plants/natural interventions	Study design	Outcome
374	Pelargonidin, quercetin, hesperetin, caffeic acid, derivatives of catechin and epicatechin	This study evaluated the effect of polyphenols on cortical neurons against endogenous neurotoxins	Results showed that the polyphenols (+)-catechin and caffeic acid inhibited tyrosinase-induced formation of 5-S-cysteinyl-dopamine via their capacity to undergo tyrosinase-induced oxidation to yield cysteinyl-polyphenol adducts. In contrast, the inhibition afforded by the flavanone hesperetin was not accompanied by the formation of cysteinyl-hesperetin adducts. Pretreatment of cortical neurons with pelargonidin, quercetin, hesperetin, caffeic acid, the 4'-O-Me derivatives of catechin and epicatechin resulted in protection against 5-S-cysteinyl-dopamine-induced neurotoxicity which was mediated by their ability to induce phosphorylation/activation of both the Akt/PKB and ERK1/2 signaling pathways
375	Quercetin	This study examined the ability of quercetin and its major human metabolites to attenuate the inflammation-induced expression of ICAM-1, VCAM-1 and MCP-1 in HUVECs and human umbilical artery smooth muscle cells (HUASMCs)	Quercetin treatment reduced the expression of VCAM-1, ICAM-1 and MCP-1 in prestimulated (TNF- α) HUVECs and HUASMCs at both the protein and transcript levels. The quercetin metabolites (quercetin-3'-sulfate, quercetin-3-glucuronide and 3'-methylquercetin 3-glucuronide) also inhibited the inflammation-induced expression of VCAM-1, ICAM-1 and MCP-1 in HUVECs, although less effectively than quercetin. In HUASMCs the quercetin metabolites were ineffective in overcoming the inflammation-induced overexpression of ICAM-1, VCAM-1 and MCP-1
376	Grape seed extract	The effects of dietary supplementation with grape seed extract (GSE) on hepatic gene expression were investigated in vivo under normal and inflammatory conditions in male Fischer rats. The absorption and metabolism of GSE-derived catechin and epicatechin were also assessed. Total RNA was extracted from liver for microarray analysis using the Affymetrix Rat Genome 230 2.0 GeneChip Array	GSE supplementation did not cause significant suppression of TNF- α -induced inflammatory gene expression. Results showed that catechin and epicatechin from GSE are highly absorbed and metabolized in rats but have very limited effects on gene expression both under normal and inflammatory conditions
377	Bilberry (<i>V. myrtillus</i> L.)	The aim of this study was to examine the possible role of bilitranslocase in the vasodilating activity of flavonoids. Bilberries were used as a source of flavonoids because they are rich in anthocyanins and have strong affinity for bilitranslocase. HPLC-DAD system was used for the qualitative and quantitative analysis of anthocyanins in the prepared bilberry extract	Bilberry extract relaxed aortic rings in a concentration-dependent manner in the control group, but not in endothelium-denuded aortic rings or in rings with inhibited NOS. Results suggest that the vasodilating activity of flavonoids in bilberry extract is dependent on the bilitranslocase-mediated transport of flavonoids into the endothelium, followed by the activation of NOS
378	Hydroxytyrosol	The potential role of HTy in the induction of heme oxygenase (HO-1), a phase 2 detoxifying enzyme, and the underlying mechanism of this expression in vascular endothelial cells were investigated	Exposure of vascular endothelial cells to HTy stimulated the phosphorylation of Akt, ERK and MAPK. HT induced the translocation of the transcription factor Nrf2 into the nucleus, which is implicated in HO-1 expression. These results suggest that HO-1 was responsible for the HTy-mediated protection of vascular endothelial cells against oxidative stress through the activation of both PI3K/Akt and ERK pathways and transcription factor Nrf2 translocation

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Table I. Cont. Summary of studies on polyphenols presented at the 4th International Conference on Polyphenols and Health.

Ref.	Polyphenols/plants/natural interventions	Study design	Outcome
379	Polyphenols	A single-blind, randomized, placebo-controlled, crossover study investigated the effect of polyphenol-rich dark chocolate on biomarkers of glucose metabolism, lipid profile, blood pressure (BP) and salivary free cortisol (F) in 21 females and a control group of 23 females. Volunteers consumed 20 g of DC containing 500 mg of dark chocolate polyphenols or placebo for 4 weeks, separated by a 2-week washout period	This study provided evidence for the metabolic benefits of consuming polyphenol-rich dark chocolate in overweight and obese subjects, while demonstrating the possibility of adverse effects occurring with a polyphenol-poor diet
380	3-O-Acyl-catechins	This study examined whether 3-O-acyl-catechins could promote GLUT4 translocation in L6 myotubes. The affinity of catechins and 3-O-acyl-catechins for the lipid bilayer membrane was also investigated using surface plasma resonance analysis	3-O-Myristoyl(-)-epicatechin (EC-C14) and 3-O-palmitoyl(-)-epicatechin (EC-C16) promoted GLUT4 translocation and increased glucose uptake in L6 myotubes. The effects of 3-O-acyl(-)-epicatechin were more potent than those of epicatechin, whereas 3-O-myristoyl-(+)-catechin (C-C14) and 3-O-palmitoyl-(+)-catechin (C-C16) did not promote glucose uptake or GLUT4 translocation, like (+)-catechin
381	Tea catechins	This study investigated the mechanisms by which tea might affect emulsification of food lipids, and consequently digestion and absorption. An in vitro small intestine model system containing dietary fat emulsified by phosphatidylcholine (PC) and bile salts was developed to simulate human small intestine conditions	Tea catechins from green and black tea inhibited lipase activity in a concentration-dependent manner with an 82% reduction in the presence of 2 mg total catechins from green tea. Interestingly, black tea inhibited lipase activity by 80% at 1 mg total catechins which was half of the green tea concentration. The main compounds responsible for these effects were identified as EGCG and ECG using HPLC
382	Polyphenol juice drinks	The aim of this study was to elucidate the acute effects of polyphenol juice drinks on markers of lipid metabolism after ingestion of a HFM. Fifteen healthy volunteers were enrolled and assigned in a crossover design to consume a HFM and 500 mL of different juices (2.B.3, 2.4.5, 457 or a placebo drink)	Following ingestion of an HFM, the plasma triglyceride concentration began to increase after 30 min, becoming significant at 2 h and reaching a peak at 4 h, and remaining significantly higher compared to baseline after 6 and 8 h of fat overloading. In the presence of beverage 457 the change in plasma TG was significantly lower compared to the HFM at 4, 6 and 8 h. Total plasma cholesterol (TC) levels increased 4 h after ingestion with a peak at 8 h. Ingestion of beverage 2.B.3 suppressed (100% inhibition) the increase in plasma cholesterol levels at 6 and 8 h
383	Black soybean (<i>Glycine max</i> L.) seed coat extract	The effect of black soybean seed coat (BSSC) on obesity was evaluated in C57BL/6 mice fed a HFD containing 30% (w/w) lard for 14 weeks	Body weight gain was significantly lowered in mice fed the HFD containing 1.0% BSSC compared with mice fed the HFD alone and decreased abdominal white adipose tissue weight in a dose-dependent manner. In the oral glucose tolerance test, BSSC improved impaired glucose tolerance at 15, 30, 60 and 120 min in mice fed the HFD. The gene expression levels of TNF- α and MCP-1 in mesenteric adipose tissue were remarkably decreased in mice fed the HFD containing BSSC compared with mice fed the HFD alone

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Table I. Cont. Summary of studies on polyphenols presented at the 4th International Conference on Polyphenols and Health.

Ref.	Polyphenols/plants/natural interventions	Study design	Outcome
384	Polyphenols	The role of oligo proanthocyanidin polyphenols as regulators of FoxO1a and their implications for diabetes and dementia were investigated	Data suggested that polyphenol extracts may not only have potential therapeutic value in the treatment of type 2 diabetes but also carry less risk of toxicity and other adverse effects than current drug therapies. The extracts may also have the potential to slow down amyloid plaque and neurofibrillary tangle formation and therefore be of value as an early intervention in Alzheimer's disease
385	<i>Curcubita pepo</i> and <i>Salvia hispanica</i>	The effects of <i>C. pepo</i> and <i>S. hispanica</i> ingestion on triglycerides, cholesterol levels and HDL levels were investigated in volunteers with metabolic syndrome	It was concluded that continuous and constant combination of phenolic compounds, essential fatty acids and fiber may offer benefits in reducing cardiovascular risk and improving insulin resistance, and consequently type 2 diabetes
386	Yerba mate extract (<i>I. paraguariensis</i>)	The inhibitory effects of mate tea, a beverage rich in phosphatidylcholine (PC) and produced with leaves from <i>I. paraguariensis</i> , were evaluated in mice models of obesity. In an in vitro experiment, porcine and human pancreatic lipase activities were determined by measuring the rate of release of oleic acid from hydrolysis of emulsified olive oil. For in vivo experiments, animals were fed with a standard diet (SD, n = 10) or HFD (n = 30) for 16 weeks	The results showed that mate tea inhibited both porcine and human pancreatic lipase and induced potent inhibition of porcine lipase activity in the hydrolysis of substrate emulsified with taurocholate+PC (83 ± 3.8%) or PC alone (62 ± 4.3%). Mate tea prevented increases in body weight ($P < 0.05$) and decreased serum triglycerides and LDL-cholesterol concentrations at both doses (from 190.3 ± 5.7 to 135.0 ± 8.9 mg/dL and from 189.1 ± 7.3 to 129.3 ± 17.6 mg/dL, respectively)
387	Polyphenol-rich fractions of strawberry and apple	The effects of different classes of dietary polyphenols on intestinal glucose transport have been investigated using polarized Caco-2 intestinal cells	Results showed that several flavonoids were potent inhibitors of [¹⁴ C]-glucose transport with IC ₅₀ values of 19 µM, 197 µM and 307 µM for quercetin, phloridzin and pefargonidin 3-glucoside, respectively. The inhibition of GLUT2 by fractions of both strawberry and apple was greater than for SGLT1. The results suggest that some flavonoids inhibit glucose transport from the intestinal lumen into cells and also inhibit the release of GLUT2 on the basolateral side
388	Polyphenol juice drinks	This study investigated the effects of different polyphenol juice drinks (2.B.3; 2.4.5; 457) on plasma glucose and insulin levels in response to dietary stress induced by an HFM. Subjects consumed an HFM of 1351 kcal with placebo drink or one of the juices	Results showed that the HFM induced a peak in both glucose (+15.11 mg/dL) and insulin (+40.19 mU/L) at 0.5 h. None of the juice drinks affected the glucose increase induced by the HFM. It was concluded that acute ingestion of the 2.4.5 and 457 polyphenol juice drinks did not modify the increase in plasma glucose concentration and insulin response after ingestion of the HFM
389	4-Hydroxyderricin and xanthoangelol, prenylated chalcones from <i>Ashitaba</i> (<i>Angelica keiskei</i>)	This study investigated active food ingredients that can increase glucose uptake in skeletal muscles using the 2-deoxyglucose uptake assay in rat L6 muscle cells	Among the various compounds screened, 4-hydroxyderricin and xanthoangelol, prenylated chalcones from the root of the <i>Ashitaba</i> plant (<i>A. keiskei</i>), significantly increased 2-deoxyglucose uptake in rat L6 skeletal muscle cells without phosphorylation of PKC ζ /λ, Akt or AMPK

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Ref.	Polyphenols/plants/natural interventions	Study design	Outcome
390	Flavanoids	This study presented a method for examining and quantifying intermediate intracellular acyl-CoAs using HPLC-MS	Nutritionally induced changes in lipid metabolism were observed after ingestion of flavanoids, partly due to changes in the fatty acid β -oxidation pathway
391	Oolong tea polymerized polyphenols	The objective of this study was to determine if oolong tea polymerized polyphenols (OTPP) have an effect on blood triacylglycerides (TG). In a double-blind, randomized, repeated-measures study, 10 subjects were assigned to receive a fat-rich meal (sausage sandwich) and 350 mL of one of the following beverages: placebo containing oolong tea flavor and color (PD1 beverage); PD1 added to tea catechins at a concentration equivalent to that found in OTPP-enriched oolong tea (PD2 beverage) or OTPP-enriched oolong tea	In summary, OTPP-enriched oolong tea ingestion significantly reduced postprandial serum TG elevation that occurs after a fat-rich meal
392	Epigallocatechin gallate	This study investigated Akt modulation and forkhead box protein signaling by epigallocatechin gallate	EGCG activated the insulin-responsive PI3K/Akt pathway in HFFF2 human skin fibroblasts. EGCG significantly stimulated phosphorylation of Akt, whereas epicatechin, epigallocatechin and epicatechin gallate did not. This phosphorylation was abolished by the structurally unrelated PI3K inhibitors wortmannin and LY-2940002. EGCG also stimulated nuclear accumulation of forkhead box protein and DNA binding activity
393	Tocotrienol	The aim of this study was to explore the effect of tocotrienol on thermal and mechanical hyperalgesia, allodynia, oxidative-nitrosative stress, inflammation and apoptosis in streptozotocin-induced experimental diabetes	Streptozotocin-induced diabetic rats developed neuropathy which was evident from a significant increase in hyperalgesia and allodynia associated with enhanced oxidative-nitrosative stress, release of inflammatory mediators (TNF- α , IL-1 β , TGF-1 β) and caspase-3. Chronic treatment with tocotrienol significantly attenuated these changes. Data suggested that suppression of the NF- κ B signaling pathway and caspase-3 by tocotrienol could prevent diabetic neuropathy
394	Epigallocatechin-3-gallate	Green tea and its major polyphenol EGCG were investigated for the prevention of chronic diseases including obesity and the metabolic syndrome using the high fat-fed C57b16/J mouse model	Results demonstrated that treatment with EGCG (3.2 mg/g diet) for 16 weeks reduced body weight gain, body fat, fasting blood glucose and plasma cholesterol by 41%, 37%, 25% and 24%, respectively, compared to control mice
395	(-)-Epicatechin, (+)-catechin and procyanidin B2	This aim of this study was to determine the rate of sucrose hydrolysis by Caco-2 cells in the absence and presence of cocoa extracts and various polyphenols present in chocolate and cocoa	The addition of cocoa extract inhibited sucrose hydrolysis by Caco-2 cells. (-)-Epicatechin, (+)-catechin and procyanidin B2, major components of cocoa, also substantially inhibited sucrose hydrolysis in Caco-2 cells. These results demonstrated that intestinal hydrolysis of sucrose by α -glucosidase enzymes could be inhibited by cocoa polyphenols, thereby reducing the rate of glucose release
396	<i>Leucosyke capitellata</i> leaves	This study was designed to evaluate the antihyperglycemic effects of <i>L. capitellata</i> leaf extract on blood glucose levels in diabetic rats and to determine the effect of the extract on insulin secretion using RIN-m5F rat pancreatic β -cells	Results showed that the <i>L. capitellata</i> leaf extract (dose range equivalent to 0.1-2.0 mg/mL) was capable of enhancing basal insulin secretion (at 2 mmol/L glucose) by 14-147% compared to the untreated RIN-m5F cell lines. In addition, the extract (1 mg/mL) increased insulin secretion

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Ref.	Polyphenols/plants/natural interventions	Study design	Outcome
397	Oligonol	A randomized, double-blind clinical trial evaluated the potential effect of oligonol intake on the suppression of postprandial hyperglycemia	Results showed that administration of oligonol resulted in suppression of blood glucose levels in 7 cases, minimal suppression in 3 cases and relative increase in 2 cases
398	Polyphenol juice drinks	This study investigated polyphenol juice drinks (2.B.3, 2, 4.5, 457), with different levels of in vitro total antioxidant capacity, to determine whether they could modulate the antioxidant response induced by postprandial stress	Ingestion of the drinks directly increased plasma antioxidant defenses with an efficiency mirroring in vitro total antioxidant capacity
399	Polyphenol juice drinks	The effects of polyphenol juice drinks on HFM-induced cytokine production were evaluated in overweight subjects	Results showed that ingestion of an HFM induced an increase in the inflammatory cytokines TNF- α and IL-6. TNF- α increases ranged from 34% at 0.5 h to 76% at 8 h and IL-6 increases ranged from 53% at 0.5 h to 200% at 8 h, both compared to baseline levels. When the HFM was consumed with the polyphenol juice drinks there was significant inhibition of TNF- α endogenous response to the stressor meal with all of the beverages. Beverage 2.4.5 significantly reduced IL-6 responses in the early phase of inflammatory response to the HFM
400	Yerba mate extract (<i>I. paraguariensis</i>)	The aim of this study was to evaluate the effects of yerba mate extract (1.0 g/kg) upon liver cytokine expression and insulin signaling pathways in obese mice fed an HFD. The liver was examined to morphologically determine the mRNA levels of TNF- α , IL-6 and iNOS. IRS/Akt signaling was determined by immunoblotting	The yerba mate extract improved basal glucose and triglyceride blood levels. Liver testing revealed that there was an improvement in triglycerides in response to insulin administration. The molecular analysis of insulin signaling revealed restoration of insulin substrate receptor IRS-1 and Akt phosphorylation in response to insulin after the yerba mate intervention. The hepatic expression of TNF- α , IL-6 and iNOS was inhibited
401	Epigallocatechin-3-gallate	This study examined the mechanism by which EGCG induces GLUT4 translocation in rat L6 myotubes. EGCG-stimulated phosphorylation of PI3K, PKC ζ / λ and Thr308 of Akt, which are involved in the insulin signaling pathway, was also investigated	EGCG did not phosphorylate Ser473 of Akt or IR β . These results indicated that EGCG promoted GLUT4 translocation via a PI3K-dependent pathway in rat L6 myotubes. A single oral dose of EGCG of 75 mg/kg slightly increased the amount of glycogen in skeletal muscle of rats
402	Quercetin and resveratrol	The objective of this study was to characterize mitochondriotropic derivatives of two model polyphenols, quercetin and resveratrol, and their effects on mitochondria	Two quercetin derivatives, 3-(4-O-triphenyl-phosphoniumbutyl)quercetin iodide (Q3BTPI) and its tetracetylated analogue (QTA3BTPI), were characterized. When used in the 10-20- μ M range these compounds acted as co-inducers of mitochondrial permeability transition, as well as inhibitors of the respiratory chain and mitochondrial ATP synthase. Q3BTPI behaved as an uncoupler of isolated mitochondria, causing depolarization and stimulating oxygen consumption. The compounds caused loss of fluorescence from the mitochondria of tetramethylrhodamine methyl ester-loaded Hep G2 and Jurkat cells

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Ref.	Polyphenols/plants/natural interventions	Study design	Outcome
403	<i>Theobroma cacao</i> L.	This study assessed the neuroprotective effect of cocoa polyphenols on SY-SY5Y human neuroblastoma cells exposed to ischemic damage	Phenolic-rich extracts of both unroasted and roasted cocoa prevented celecoxib-induced cell growth inhibition in MLP29 liver cells due to accumulation of G1 cells and cell death. Death prevented by cocoa had signs of apoptosis and activation of BAX expression together with downregulation of Bcl-2 released cytochrome c in the cytosol with activation of caspase-3
404	Vitamin E, α -tocopherol and tocotrienol	The aim of this study was to investigate the effect of both isoforms of vitamin E, α -tocopherol (100 mg/kg, oral gavage) and tocotrienol (50, 100 and 200 mg/kg, oral gavage) against alcohol-induced neuropathic pain in rats	Ethanol-treated animals showed a significant decrease in nociceptive threshold, as evident by decreased tail flick latency (thermal hyperalgesia) and decreased paw withdrawal threshold in the Randall-Sellito test (mechanical hyperalgesia) and von-Frey hair test (mechanical allodynia), along with reduction in nerve glutathione and superoxide dismutase levels. TNF- α and IL-1 β levels were also significantly increased in both serum and sciatic nerve of ethanol-treated rats. Treatment with α -tocopherol and tocotrienol for 10 weeks significantly improved all of the above functional and biochemical deficits in a dose-dependent manner, with more potent effects observed with tocotrienol
405	Resveratrol	The effect of chronic resveratrol administration on cognitive function was investigated in a nonhuman primate, the gray mouse lemur, with an average longevity of 8 years	Resveratrol treatment had no effect on exploratory behavior compared to control feeding. None of the animals showed any decrease in cognitive performance from middle to adult age. Executive memory performance estimated by spontaneous spatial alternation was significantly increased in resveratrol-treated animals at both ages
406	Polyphenols	A new method to directly identify bioactive compounds from polyphenolic fractions was developed	Methodology was developed for three different protein targets: poly-L-proline, ovalbumin and β -amyloid peptide
407	Epicatechin	This study investigated whether epicatechin has greater bioavailability than catechin and if it is protective against brain ischemic damage in a mouse model of cerebral artery occlusion (MCAO)	The epicatechin-associated neuroprotection (both anatomically and behaviorally) was mostly abolished in mice lacking the antioxidant enzyme HO-1 or the transcriptional factor Nrf2. These results suggest that epicatechin exerts part of its beneficial effects via activation of the Nrf2/ARE-mediated pathway and an increase in one of its key regulators, the neuroprotective HO-1 enzyme
408	<i>Rosmarinus officinalis</i> flavanoids	The substances that induce nerve growth factor (NGF)-like effects in rat pheochromocytoma PC-12 cells, including quercetin, apigenin 7-O-glucoside and luteolin, were investigated in an in vitro model for neuronal differentiation	Exposure of PC-12 cells to these flavanoids showed that luteolin was the most potent, with the lowest cytotoxicity. The percentage of cells with synapses longer than 2 times the body of the cell was around 42% for luteolin compared to 32% for treated cells with NGF at 50 ng/mL following 3 days of incubation. Additionally, luteolin increased acetylcholinesterase (AChE) activity up to 133% of control and improved the synthesis of total choline by 1.5-fold of control. A specific inhibitor of MAPK, U-0126, prevented cell differentiation and AChE activity

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Ref.	Polyphenols/plants/natural interventions	Study design	Outcome
409	Curcumin	The effect of curcumin feeding on the age-dependent decline in mitochondrial function in the brain of SAMPs mice was investigated	Results showed that murine brain cells preincubated with curcumin prior to addition of the stressor Fe2+ concentration-dependently prevented mitochondrial dysfunction. Curcumin supplementation (500 mg/kg diet) of SAMPs mice for 5 months reversed the age-dependent decline in mitochondrial membrane potential, and ATP production was observed in SAMPs mice fed a curcumin-free control diet but did not alter mitochondrial membrane fluidity or biomarkers of oxidative stress
410	Sesamol	In this study the role of a novel carrier system for the polyphenolic lignan sesamol was investigated in menopause-related biochemical and behavioral paradigms	Results showed that solid lipid nanoparticles (SLN) were the suitable carrier to deliver effective amounts of sesamol to the brain. Sesamol-loaded SLNs prepared by the microemulsification method had an average particle size of 122 nm with a zeta potential of -25 mV, total drug content of 98.54 ± 0.43% and entrapment efficiency of 72.01 ± 0.36. An in vitro experiment demonstrated a Fickian release (n = 0.43) with an initial phase of fast release with first-order kinetics followed by a sustained release up to 24 h (71%). SLNs produced a much higher concentration of drug in both plasma and brain. Respective C _{max} values of SLNs in plasma and brain were 1.32-fold and 3.4-fold higher than free sesamol
411	Blueberry juice	The effect of blueberry juice consumption on dark vision was recently examined in a randomized, placebo-controlled, double-blind, crossover trial (N = 59). The juice or placebo was consumed daily for 12 weeks. Vision was tested at prescribed intervals using PC-based tests to determine rate of dark adaptation, dark-adapted visual acuity and contrast sensitivity, and recovery of visual acuity after exposure to bright light	No juice-related difference was found in any test except the rate of recovery of visual acuity after bright light exposure. Blueberry juice consumption may benefit individuals who operate in low light with interruptions by bright light. Light-induced retinopathy, which employs prescribed exposure to bright light to induce damage, apoptosis and remodeling in retinal photoreceptors, was used as an in vivo model, in which the blueberry juice protected rat retinae against damage
412	Resveratrol	A double-blind, placebo-controlled, crossover study in 22 healthy volunteers was performed to assess the alteration in cerebral blood flow and oxygenation parameters after resveratrol administration	Results showed that resveratrol administration resulted in a dose-dependent increase in cerebral blood flow during task performance, as measured by total concentration of hemoglobin
413	Grape seed extract	This study investigated the effect of dietary grape extract on neurogenesis in transgenic mice where green fluorescent protein was used as a marker for neurogenesis	Preliminary data showed that the degree of neurogenesis in the pups exposed to grape seed extract in the mother's milk was reduced compared to that detected in pups that were not exposed to the extract
414	Concord grape juice	Neurocognitive effects in 12 elderly adults with early memory decline but not dementia were investigated in a randomized, double-blind, placebo-controlled trial with concord grape juice supplementation for 12 weeks. Measures of memory, body composition and metabolic function were obtained prior to and during the final week of the intervention	Results demonstrated a significant improvement in verbal learning; there were nonsignificant trends towards enhanced verbal recall. There was no appreciable effect on symptoms of depression or weight and waist circumference. There was also no effect on fasting glucose, although a small increase in fasting insulin was observed for those consuming grape juice

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415	Flavonoid	This study reviewed flavonoid randomized clinical trials with respect to the types of cognitive domain and the types of tests used in flavonoid research	Findings from animal studies suggested that spatial working memory is sensitive to flavonoid intake; however, this hypothesis has only been investigated in a third of the randomized, controlled trials in humans
416	Fruits and vegetables	An 18-week, randomized, parallel-group, 3-arm controlled dietary intervention trial was performed to establish a dose-response relationship between consumption of fruits and vegetables and cognition status. Low fruit and vegetable consumers at risk of cardiovascular disease were randomly assigned to one of three groups: high flavonoid (HF), low flavonoid (LF) or control. All participants completed the Mini-Mental State Examination (MMSE) in order to determine cognitive status	Results indicated that all participants scored 24-30 points on the MMSE, indicating that the population was not cognitively impaired at baseline, and no significant differences were found among dietary groups
417	Coffee	This study was designed to evaluate the cardiovascular changes occurring approximately 30 min after consuming espresso coffee containing 130 mg caffeine, decaffeinated espresso coffee or a caffeine capsule containing 130 mg caffeine, and to test whether these cardiovascular changes are modulated by posture	Results demonstrated that caffeine affected the vascular system whereas espresso coffee affected heart activity. Decaffeinated coffee impacted the cardiovascular system differently than regular naturally caffeinated coffee. Conclusions were that a change in posture could either increase or decrease a drug's pharmacological activity, and changes in the cardiovascular system after consuming the isolated phytochemical caffeine cannot be generalized to drinking coffee
418	Resveratrol	This study examined the effect of resveratrol on the mitochondrial antioxidant enzyme manganese superoxide dismutase (MnSOD) and cellular stress resistance	Results showed that chronic resveratrol exposure induced an up to 6-fold upregulation of MnSOD in cultured cell lines from mice and humans. This induction correlated to an increase in cellular stress resistance and significantly reduced the rate of cell replication
419	Flavanoids	This study investigated the ability of a number of flavonoids to modulate NF- κ B signaling in primary mouse cortical astrocytes using luciferase reporter assays	Results showed that NF- κ B-mediated transcription was increased after addition of LPS (4 μ g/mL). However, treatment of primary cortical astrocytes with the flavonoids (-)-epicatechin, kaempferol, naringenin, chrysin, hesperetin, (+)-catechin and luteolin (100 nM-1 μ M) did not have any significant effect on NF- κ B activation
420	α -Tocopherol and tocotrienol	This study compared the effects of α -tocopherol and tocotrienol against chronic alcohol-induced cognitive dysfunction in rats. Male Wistar rats were given ethanol (10 g/kg p.o.) for 10 weeks and treated with α -tocopherol and tocotrienol for 10 weeks	The rats were sacrificed at the end of 10-week treatment and cytoplasmic fractions of cerebral cortex and hippocampus were prepared for the quantification of AChE activity, oxidative-nitrosative stress parameters and TNF- α and IL-1 β levels. Beginning at week 6, ethanol-treated rats exhibited a significant increase in transfer latency in behavioral paradigms which correlated with enhanced AChE activity, increased oxidative-nitrosative stress, TNF- α and IL-1 β levels in different brain regions. Coadministration of α -tocopherol or tocotrienol significantly and dose-dependently prevented these behavioral, biochemical and molecular changes. However, the effects were more pronounced with tocotrienol

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421	Naringenin	This study investigated the anti-inflammatory effects of different flavonoid subclasses (flavanones, flavanols and anthocyanidins) in primary mixed glial cell cultures and neuron/glial co-culture models	The flavanones naringenin and hesperetin and the flavanols (+)-catechin and (-)-epicatechin, but not the anthocyanidins cyanidin and pelargonidin, attenuated LPS/IFN- γ -induced TNF- α production in glial cells. Pretreatment of glial cells with naringenin resulted in a significant inhibition of LPS/IFN- γ -induced iNOS expression at concentrations of 0.03 μ mol/L and higher, whereas all other flavonoids exerted no inhibition
422	α -Viniferin and resveratrol	The aim of this study was to compare the effects of α -viniferin and resveratrol on cultured vascular smooth muscle cells (SMCs) and endothelial cells (ECs) and their role in the development of atherosclerosis	α -Viniferin at a low micromolar concentration exhibited more potent antiproliferative activity than resveratrol in SMCs, whereas both compounds enhanced wound repair of ECs. Viniferin pretreatment of ECs afforded remarkable protection against hydrogen peroxide-induced cytotoxicity in a cell-counting assay. Moreover, incubation of ECs with resveratrol and α -viniferin time-dependently induced phosphorylation of HO-1 protein with a peak effect at 12 and 24 h, respectively. Notably, both compounds increased catalase and glutathione activities
423	Fisetin	The anti-inflammatory effect of fisetin in the brain was studied using the N9 microglial cell line and a double-transgenic mice model of AD	Results showed that fisetin can reduce bacterial LPS-induced microglial activation. Fisetin was very effective at blocking LPS-induced NO production, measured as accumulation of nitrite in the culture medium, and reduced LPS-induced increases in iNOS and TNF- α expression. In double-transgenic mice oral administration of fisetin attenuated the decrease in cognitive function and prevented an increase in proinflammatory chemokines and their receptors, including CCL2, CCL5, CXCL1, CXCR5 and TNF- α . In the transient MCAO model of stroke in mice, fisetin not only reduced infarct size but also prevented both the early proliferation of microglia and the subsequent massive accumulation of neutrophils, an event implicated in postischemic brain injury
424	Dihydroxybenzoic acid	This study was designed to examine four biologically relevant isomers of dihydroxybenzoic acid (DHBA), which are present in blood after the consumption of a fruit- or vegetable-containing meal, for their ability to protect cells from hydrogen peroxide-induced oxidative damage and the mechanisms underlying this protection	Pretreatment of the oxidatively sensitive neuronal cell line SH-SY5Y with 3,4-DHBA (a major metabolite of cyanidin-based anthocyanins) was shown to protect from hydrogen peroxide-induced cell death, and to decrease internal oxidative stress and reduce cell death signaling