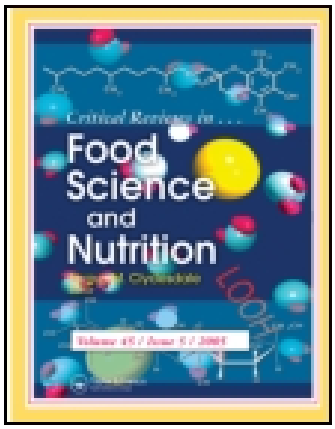

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Antioxidant Modulation of F2-Isoprostanes in Humans: A Systematic Review

Teresa Petrosino [a] & Mauro Serafini [a]
[a] Research Center on Agriculture, CRA-NUT , 00178 , Rome , Italy
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Antioxidant Modulation of F2-Isoprostanes in Humans: A Systematic Review

TERESA PETROSINO and MAURO SERAFINI
Research Center on Agriculture, CRA-NUT, 00178, Rome, Italy

F2-isoprostanes are a biomarker of lipid peroxidation, and their measurement has emerged as a reliable approach to assess oxidative stress. However, dietary intervention studies in humans have provided contrasting results following supplementation with antioxidant-rich foods or supplements. In this paper, we have systematically reviewed the evidence about the effect of supplementation with antioxidant-rich foods and galenic antioxidants on isoprostanes levels in humans. Moreover, the association with nonenzymatic antioxidant capacity (NEAC), a biomarker of endogenous antioxidant status, has also been investigated.

MEDLINE database was searched using the terms "(isoprostane OR isoP OR iso-PGF OR epi-PGF) AND (intervention* OR consumption* OR administration* OR supplementation*)," with limits activated "humans" and "English." Abstracts and full texts were screened, from which were selected human intervention studies reporting isoprostanes measurement in biological fluids. The total of the studies carried out with antioxidant-rich foods and antioxidant galenic supplements was 113, reporting 154 interventions. Results suggest that dietary antioxidants modulate successfully the levels of isoprostanes in less than 45% of the interventions. A correspondence between the effect on isoprostane and NEAC has been evidenced, and this correspondence suggests the importance of measuring different biomarkers to obtain a better outline of the redox events following supplementation.*

Keywords Oxidative stress, antioxidant capacity, human, plasma, plant foods, biomarkers

INTRODUCTION

Isoprostanes are prostaglandin-like compounds produced in vivo primarily by free radical-induced peroxidation of arachidonic acid esterified in the *sn*-2 position of phospholipids (Morrow et al., 1990). After their formation, isoprostanes are released from membrane phospholipids by the action of phospholipases and excreted in urine. There are different classes of isoprostanes, the most numerous of which are the analogues of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$). The mechanism by which isoprostanes are generated, involving the addition of two oxygen molecules to arachidonic acid to form a hydroperoxy-bycicloendoperoxy intermediate, makes possible four regioisomeric series of F_2-IsoP, depending on the position of hydroxyl in the side chain. They are named 5-, 8-, 12-, and 15-F_2-IsoP (Taber et al., 1997) even if other nomenclature systems have also been proposed (Rokach et al., 1997). The basic structures of the four main F_2-IsoP are reported in Fig. 1. Among these, the 5- and 15-series are the most abundant because the intermediates involved in the formation of the 8- and 12-series undergo further oxidation. In particular, the most extensively studied F_2-IsoP has been 15-F_{2t}-IsoP, also known as 8-iso-$PGF_{2\alpha}$ or $iPF_{2\alpha}$-III.

Isoprostanes have been found in many animal tissues and most biological fluids, including urine (in free form) and plasma (both free and esterified to lipoproteins). Different approaches can be used to assess their endogenous production: by measuring the free isoprostanes in biological fluids, by measuring the esterified forms in specific target sites such as biopsy specimens and plasma lipoproteins, and finally by measuring the major urinary metabolites. As far as quantification techniques are concerned, the two main analytical approaches adopted were, on one hand, gas- or liquid-chromatography coupled to mass-spectrometry and, on the other, immunological techniques. The latter have the advantage of lower costs and easier usage, but they are also susceptible to cross-reactivity problems, in consequence of which they are deemed to give only a semiquantitative estimation of isoprostanes levels. On the other hand, mass-spectrometric techniques require expensive equipments

Address correspondence to Mauro Serafini, Ph.D., Research Center on Agriculture, CRA-NUT, 00178 Rome, Italy. E-mail: serafini_mauro@yahoo.it

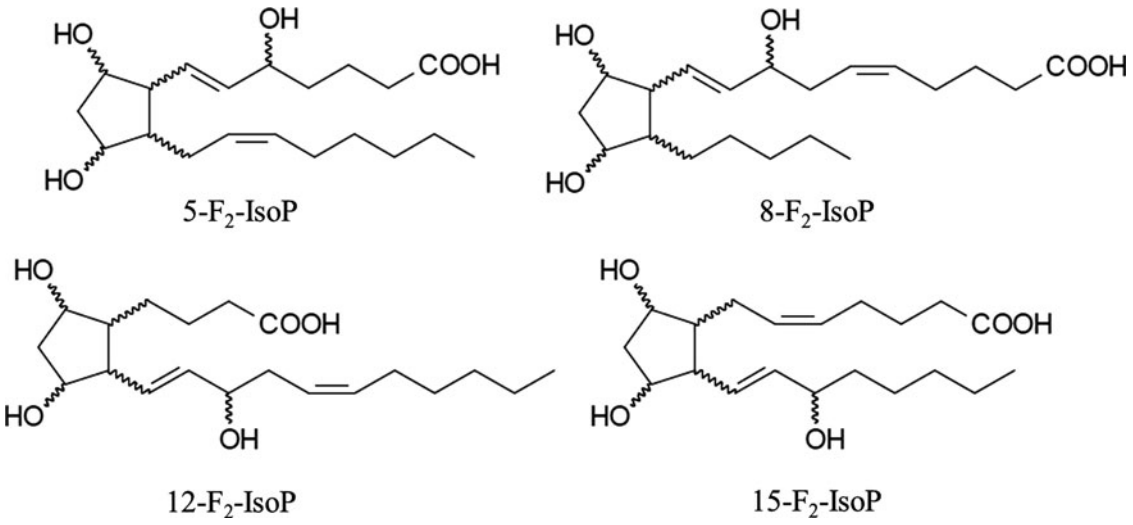

Figure 1 Basic structures of the four F2-IsoP series.

and expert users compensated by high sensitivity and specificity.

Quantification of isoprostanes is a sensitive and specific indicator of lipid peroxidation and emerges as one of the most reliable biomarker for assessing oxidative stress in vivo (Roberts and Morrow, 2000). Although isoprostanes are not a major product of lipid peroxidation, they are present in detectable quantities in all normal biological tissues and fluids. Their levels increase substantially in animal models of oxidant injury (Morrow et al., 1990) and are unaffected by lipid content of the diet (Richelle et al., 1999). In a recent multilaboratory study, the biomarkers of oxidative stress study (BOSS), quantification of plasma and urinary isoprostanes has emerged as an accurate method to assess in vivo oxidative injury (Kadiiska et al., 2005). Elevated levels of isoprostanes have been reported in patients affected by cardiovascular diseases and related risk factors (e.g., smoking, hypercholesterolemia, diabetes, obesity, metabolic syndrome), neurological diseases (e.g., Alzheimer's disease), lung, renal and liver diseases (Montuschi et al., 2007), and cancer (Barocas et al., 2011; Khadem-Ansari et al., 2011).

Nonenzymatic antioxidant capacity (NEAC), which is improperly defined "total" antioxidant capacity (TAC), is a biomarker of in vivo antioxidant status, being a measure of the cumulative action of all the antioxidant molecules, and it takes into account their synergistic interactions too (Serafini and Del Rio, 2004). As it requires inexpensive and easy-to-perform procedures, it has been widely used in human intervention studies, and a large number of assays for its measurement in biological matrices have been developed (Serafini and Del Rio, 2004). However, much criticism has been raised on the physiological meaning of NEAC and its link with dietary antioxidants (Bartosz, 2010). As we have recently shown, in a systematic review of all the dietary intervention studies with plant foods, plasma, or serum NEAC respond to dietary ingestion of antioxidant-rich foods, its efficacy depending on food type, study design, and health status of the subjects (Serafini et al., 2011) in accordance with previous evidences (Pitsavos et al., 2005; Rautiainen et al., 2008; Razquin et al., 2009).

Despite the large number of available evidences on the appropriateness of the use of isoprostanes as valuable markers of oxidative stress, no clear-cut evidence has been reached about the role of diet in their modulation. Supplementation with dietary antioxidants should impact the body by both reducing isoprostanes formation and/or boosting antioxidant defenses. However, dietary intervention studies in humans have provided conflicting results following supplementation with antioxidant-rich foods (O'Byrne et al., 2002; McAnulty et al., 2005; Miller et al., 2005; Flammer et al., 2007), highlighting the complexity of a mechanism still unraveled.

The aim of this work is to systematically review the evidence about the effect of supplementation with antioxidant-rich foods and galenic antioxidants on isoprostanes levels in human biological fluids. Moreover, we will investigate whether isoprostanes and NEAC are modulated in a comparable manner by dietary antioxidants.

STRATEGY SEARCH

A search for literature on intervention studies investigating the modulation of isoprostanes levels by dietary antioxidants was carried out. MEDLINE database was searched using the terms "(isoprostane* OR isoP OR iso-PGF OR epi-PGF) AND (intervention* OR consumption* OR administration* OR supplementation*)," with limits activated "humans" and "English." Abstracts and full texts were screened from which human acute and chronic intervention studies were selected, involving antioxidants and reporting isoprostanes measurement in plasma and/or urine. The studies conducted with antioxidant-rich foods (namely, fruit and fruit juices, tea, cocoa products, wine, olive oil, vegetables, dietary patterns, and other foods) and galenic supplements containing plant food extracts

or single antioxidants (vitamins, carotenoids, polyphenols) were examined. Interventions conducted in both healthy and pathological subjects were also included.

A total of 113 studies reporting 154 interventions were collected, and the results are presented in Tables 1–8 divided byantioxidant source: foods (Tables 1–6) or galenic preparations (Tables 7 and 8). As to the former, they were grouped according to different categories, namely, fruit and fruit juices (Table 1), tea (Table 2), cocoa products and wine (Table 3), vegetables and olive oils (Table 4). Food items not included in these categories were grouped together in Table 5 and referred to as "other foods." Finally, in Table 6 the interventions with different dietary patterns were reported. Regarding galenics, they were divided into preparations containing pure antioxidants (Table 7) and plant food extracts (Table 8). All the tables describe the type of food or supplement, number of intervention days, number of subjects, dose/day, and the effect on isoprostanes with quantification method used; effect on NEAC was also described for the studies in which this biomarker was measured.

Intervention Studies with Fruit and Fruit Juices

In Table 1, the results from acute and chronic intervention studies are recorded providing fruit and fruit juices as antioxidant source. A total of 11 studies reporting 13 interventions were collected: in the single acute intervention study, no effect on isoprostanes was reported. A decrease in plasma/serum and/or urine levels was observed in 6 of the 12 chronic interventions, and one study reported reduced urinary concentrations of an isoprostane's metabolite. Four of the chronic interventions inducing a change in plasma isoprostanes employed orange juice and were all from the same author (Sanchez-Moreno et al., 2003a, 2003b, 2004a): 500 mL/day of different types of orange juice were administered to 6 or 12 volunteers for two weeks, obtaining lower concentrations of plasma isoprostanes at the end of the study in all the interventions. However, in one of these studies (Sanchez-Moreno et al., 2003a), the consumption of orange juice produced a significant decrease of plasma isoprostanes but only in men. The consumption of two species of cactus fruit (Budinsky et al., 2001; Tesoriere et al., 2004) was also associated with a reduction of plasma isoprostanes. In the first study quoted (Tesoriere et al., 2004), 18 healthy volunteers received either 250 g of cactus pear fruit or 75 mg of vitamin C twice daily for two weeks: after supplementation with cactus pear, plasma levels of isoprostanes decreased significantly, while no effect was observed after vitamin C supplementation (see Table 7). In the second study (Budinsky et al., 2001), 250 g/day of prickly pear were given for four weeks to 15 young patients suffering from familial hypercholesterolemia (FH): in this case, significant decreases in plasma, serum, and urinary isoprostanes values were reported. Finally, in the study by Traustadottir et al. (2009), no changes were detected between placebo and tart cherry juice group in urinary isoprostanes, but significantly lower levels of the metabolite 2,3-dinor-15-F_{2t}-isoP (Table 1) were observed in subjects consuming cherry juice.

Among the reviewed studies, five interventions (one acute and four chronic) also provided NEAC measurements, and in two a concordant response between isoprostanes and NEAC was found. These interventions were both from McAnulty et al. (2005) and examined the effect of both acute ingestion and a three-week consumption of blueberries in chronic smokers, obtaining, as a result, no change in either isoprostanes levels or NEAC. In the remaining three chronic interventions was found no correspondence between the two biomarkers, obtaining an increase in serum NEAC without changes in urine isoprostanes (O'Byrne et al., 2002; Rankin et al., 2008) and a decrease of plasma isoprostanes with no effect on plasma NEAC (Tesoriere et al., 2004).

Intervention Studies with Tea

The results of acute and chronic interventions employing tea are described in Table 2. Seven studies providing black and/or green tea were collected for a total of 10 interventions (9 with tea only and 1 with black tea plus onion cake). Also in this case, only one acute intervention was reported while the others shared a long-term supplementation period. Quite surprisingly, no changes in isoprostanes levels were described, except in the study from Wolfram et al. (2002), where a decrease of plasma and serum isoprostanes after four weeks consumption of black tea was recorded in 12 healthy volunteers consuming 500 mL/day of tea, whereas no effect was observed after acute drinking of a single dose. The other interventions with tea reported no change in plasma or urinary concentration of isoprostanes, although they provided higher doses of tea (from 700 to 1250 mL), except one (300 mL).

Plasma NEAC was measured only in two studies (Davies et al., 2003; Widlansky et al., 2005), and no changes in both biomarkers were described. In the former (Davies et al., 2003), five cups/day of black tea were administered to 15 mildly hypercholesterolemic subjects for three weeks and, in the latter (Widlansky et al., 2005), 900 mL/day of black tea were given to 66 patients with coronary artery disease (CAD) for four weeks.

Intervention Studies with Cocoa Products and Wine

In Table 3, acute and chronic intervention studies are grouped providing cocoa products and wine as a source of antioxidants. Regarding cocoa-based foods, a total of nine studies reporting 11 interventions were collected, of which 4 were acute and 7 were long-term interventions. A reduction of plasma/serum isoprostanes was reported in two of the four acute interventions. In the first one (Flammer et al., 2007) 40 g of a flavonoid-rich dark chocolate were administered to a group of 11 heart transplant recipients, in which was found, two hours after chocolate consumption, a significant reduction of isoprostane serum concentration. The second study (Wiswedel et al., 2004) investigated the effect of a high-flavanol cocoa drink (HFCD)

Table 1 Overview of the reviewed intervention studies in humans providing fruit and fruit juices: characteristics and results for F_2-IsoP and NEAC

Food	Days	Subjects	Dose/day	F_2-IsoP	NEAC	Reference
Blueberry	1	20 smokers	250 g	↔ Plasma (GC-MS)	↔ Plasma (FRAP)	McAnulty et al., 2005
Grape juice	14	15	10 mL/kg body weight	↔ Urine (ELISA)	↑ Serum (ORAC)	O'Byrne et al., 2002
Cactus pear (*Opuntiaficus-indica*)	14	18	500 g	↓ Plasma (GC-MS)	↔ Plasma (TEAC)	Tesoriere et al., 2004
Orange juice	14	12	500 mL	↓ Plasma (EIA) in men ↔ Plasma (EIA) in women		Sanchez-Moreno et al., 2003a
High-pressurized orange juice	14	12	500 mL	↓ Plasma (EIA)		Sanchez-Moreno et al., 2003b
Pulsed electric fields–processed orange juice	14	6	500 mL	↓ Plasma (EIA)		Sanchez-Moreno et al., 2004a
Freshly squeezed orange juice	14	6	500 mL	↓ Plasma (EIA)		Sanchez-Moreno et al., 2004a
Tart cherry juice	14	12 older	480 mL	↔ Urine (LC-MS/MS) ↓ Urine IsoP met (LC-MS/MS)		Traustadottir et al., 2009
Raisin	14	17 overweight	90 g	↔ Urine (ELISA)	↑ Serum (ORAC)	Rankin et al., 2008
Blueberry	21	20 smokers	250 g	↔ Plasma (GC-MS)	↔ Plasma (FRAP)	McAnulty et al., 2005
Mixed berry juice	28	18	700 mL	↔ Urine (GC-MS)		Weisel et al., 2006
Prickly pear (*Opuntiarobusta*)	28	15 with familiar hypercholesterolemia	250 g	↓ Plasma and serum (EIA) ↓ Urine (EIA)		Budinsky et al., 2001
Pomegranate juice	35	15 with chronic obstructive pulmonary disease	400 mL	↔ Urine (EIA)		Cerda et al., 2006

F_2-IsoP = F_2-isoprostanes, NEAC = nonenzymatic antioxidant capacity, ↑ = increase, ↔ = no change, ↓ = decrease, GC-MS = gas chromatography–mass spectrometry, ELISA = enzyme-linked immunosorbent assay, EIA = enzyme immunoassay, LC-MS/MS = liquid chromatography–mass spectrometry, IsoP met = isoprostanes metabolite, FRAP = ferric reducing antioxidant power, ORAC = oxygen radical antioxidant capacity, TEAC = Trolox equivalent antioxidant capacity.

compared with a low-flavanol cocoa drink (LFCD) on 10 subjects: although LFCD caused a slight increase in plasma isoprostanes two and four hours after intake (attributable to postprandial oxidative stress), this increase did not occur with HFCD. No effect on isoprostanes, despite the high polyphenol content of the tested products, was found in chronic interventions.

A high percentage of studies conducted with cocoa-based products reported also NEAC measurements. In three (of four) acute interventions, plasma/serum NEAC was assessed, and a concordant response with isoprostanes was obtained in one intervention only. In this study (Wang et al., 2000), different doses of a procyanidin-rich chocolate were administered to 10–13 subjects. Plasma NEAC and isoprostanes were measured at two and six hours after consumption, and, in both cases, no significant change for all doses was obtained. In the other studies (Wiswedel et al., 2004; Flammer et al., 2007), despite a decrease in isoprostanes, no effect was reported for NEAC. However, in the study of Flammer et al. (2007), both markers of antioxidant status [TRAP (total radical-trapping antioxidant parameter) and FRAP (ferric reducing antioxidant power)] showed a trend to increase after dark chocolate consumption although significance was not reached. Regarding chronic studies, five out of seven interventions reported NEAC measurements, all with a concordant response between the two biomarkers. In these studies, no change in both isoprostanes and NEAC was found after supplementation.

As far as dietary interventions with wine are concerned, only two studies reporting five chronic interventions were collected, and a decrease of isoprostanes levels was obtained in three of them. In the first study (Abu-Amsha Caccetta et al., 2001), 18 smokers consumed for two weeks, in random order, red wine, white wine (polyphenols control), or dealcoholized red wine (alcohol control): a reduction of plasma and urinary isoprostanes was observed only after the dealcoholized red wine ingestion. Different results were obtained by Pignatelli et al. (2006), reporting a decrease of urinary isoprostanes after 15-day consumption of both red and white wine.

None of the interventions with wine reported NEAC measurements.

Table 2 Overview of the reviewed intervention studies in humans providing tea: characteristics and results for F_2-IsoP and NEAC

Food	Days	Subjects	Dose/day	F_2-IsoP	NEAC	Reference
Black tea	1	12	500 mL	↔ Plasma and serum (RIA)		Wolfram et al., 2002
Black tea	7	13 with raised blood pressure	Five cups (one cup = 2 g in 200 mL)	↔ Urine (GC-MS)		Hodgson et al., 2002a
Green tea	7	13 with raised blood pressure	Five cups (one cup = 2 g in 200 mL)	↔ Urine (GC-MS)		Hodgson et al., 2002a
Green tea	14	22	Seven cups (one cup = 0.9 g in 100 mL)	↔ Urine (ELISA)		Hirano-Ohmori et al., 2005
Black tea	21	15 mildly hypercholesterolemic	Five cups	↔ Plasma (ELISA)	↔ Plasma (FRAP)	Davies et al., 2003
Black tea	28	66 with coronary artery disease	900 mL	↔ Urine (GC-MS)	↔ Plasma (ORAC and FRAP)	Widlansky et al., 2005
Black tea	28	12	500 mL	↓ Plasma and serum (RIA)		Wolfram et al., 2002
Black tea	28	10 with mildly raised total cholesterol and/or triacylglycerols	Five cups (one cup = 2 g in 250 mL)	↔ Urine (GC-MS)		Hodgson et al., 2002b
Black tea	28	22 with mildly raised total cholesterol and/or triacylglycerols	Five cups (one cup = 2 g in 250 mL)	↔ Urine (GC-MS)		Hodgson et al., 2002a
Onions and black tea	14	32	150 g of onion cake and 300 mL of black tea	↔ Plasma (GC-MS)		O'Reilly et al., 2001

F_2-IsoP = F_2-isoprostanes, NEAC = nonenzymatic antioxidant capacity, ↑ = increase, ↔ = no change, ↓ = decrease, RIA = radioimmunoassay, GC-MS = gas chromatography–mass spectrometry, ELISA = enzyme-linked immunosorbent assay, FRAP = ferric reducing antioxidant power, ORAC = oxygen radical antioxidant capacity.

Intervention Studies with Vegetables and Olive Oils

Results from acute and chronic intervention studies with vegetables and olive oils are described in Table 4. Only two acute interventions were collected, one with tomato sauce and one with olive oil. In both cases, an effect on urinary isoprostanes was found. In the first study (Lee et al., 2009), 150 g of tomato sauce were administrated to 10 volunteers, leading to a significant decrease of urinary isoprostanes 48 hours after ingestion, whereas no change was reported for plasma levels. Differences in urinary concentration of isoprostanes, following acute interventions, were also reported by the other study (Visioli et al., 2000), in which olive oils with different phenolic content were administered to six subjects: an inverse correlation was observed between phenolic content and urinary excretion of isoprostanes.

As to chronic interventions, a total of five studies reporting six interventions with vegetables as antioxidant source were collected: two of these were with a vegetable-soup (gazpacho) and four with tomato products. In both studies with gazpacho (Sanchez-Moreno et al., 2004b, 2006), a reduction in plasma isoprostanes concentrations was reported in 12 healthy subjects that consumed 500 mL/day of this vegetable-soup for two weeks. Scarce effects on isoprostanes were, instead, obtained in studies providing tomato products: only one out of four interventions reported a decrease in urinary levels after consumption of tomato in different forms (raw, sauce, paste) for three weeks (Visioli et al., 2003).

Finally, three studies were conducted with olive oil for a total of five interventions, and only one reported a decrease of plasma isoprostanes. This study (Cicero et al., 2008) actually drew data from another trial, the EUROLIVE study (Covas et al., 2006), a randomized crossover trial with three intervention periods of three weeks during which olive oils with different phenolic content were administered to 182–184 volunteers. The results related to these three interventions are also reported in Table 4 (Covas et al., 2006), and, as can be seen, no change in plasma isoprostanes levels was found after each intervention, independently from the phenolic content of the oil used. However, the study of Cicero et al. (2008) used only data from baseline and end point (last intervention). A comparison of these data showed a significant decrease in plasma isoprostanes from the beginning to the end of The Effect of Olive Oil on Oxidative Damage in European Populations (EUROLIVE) Study. From these results and despite the fact that no carryover was detected in the two-week washout periods, the authors suggested that a long-term consumption of olive oil is required to observe changes in isoprostanes levels.

In the abovementioned studies, NEAC was assessed in three chronic interventions with tomato products and one intervention with olive oil. A concordant response between isoprostanes and NEAC was obtained by Jacob et al. (2008), who conducted one intervention with tomato juice and one with tomato juice fortified with vitamin C, reporting in both cases no effect on urinary isoprostanes and plasma NEAC after two-week supplementation. However, they assessed NEAC also in urine,

Table 3 Overview of the reviewed intervention studies in humans providing cocoa products and wine: characteristics and results for F_2-IsoP and NEAC

Food	Days	Subjects	Dose/day	F_2-IsoP	NEAC	Reference
Flavonoid-rich dark chocolate	1	11 heart transplanted	40 g	↓ (2 h) serum (EIA)	↔ Serum (TRAP and FRAP)	Flammer et al., 2007
Procyanidin-rich chocolate	1	13 13 10	27 g 53 g 80 g	↔ Plasma (EIA)	↔ Plasma (chemiluminescence: luminol)	Wang et al., 2000
Polyphenols-rich dark chocolate	1	22 with prehypertension or stage 1 hypertension	6.3 g	↔ Plasma (EIA)		Taubert et al., 2007
High-flavanols cocoa drink	1	10	100 mL	↓(2 e 4 h) plasma (GC-MS)	↔ Plasma (TEAC)	Wiswedel et al., 2004
Flavonoid-rich dark chocolate	14	11	46 g	↔ Plasma (EIA)	↔ Plasma (ORAC)	Engler et al., 2004
Flavonoid-rich dark chocolate	14	20	45 g	↔ Serum (n.r.)		Shiina et al., 2009
Dark chocolate	21	15	75 g	↔ Plasma (GC-MS)	↔ Plasma (TRAP)	Mursu et al., 2004
Polyphenols-rich dark chocolate	21	15	75 g	↔ Plasma (GC-MS)	↔ Plasma (TRAP)	Mursu et al., 2004
Cocoa tablets	28	13	Six tablets	↔ Plasma (GC-MS)	↔ Plasma (TRAP)	Murphy et al., 2003
Dark chocolate and cocoa powder drink	42	25	36.90 g of dark chocolate and 30.95 g of cocoa powder drink	↔ Urine (ELISA)	↔ Plasma (ORAC)	Mathur et al., 2002
Polyphenols-rich dark chocolate	126	22 with prehypertension or stage 1 hypertension	6.3 g	↔ Plasma (EIA)		Taubert et al., 2007
Red wine	14	18 smokers	375 mL	↔ Plasma (GC-MS) ↔ Urine (GC-MS)		Abu-Amsha Caccetta et al., 2001
Dealcoholized red wine	14	17 smokers	500 mL	↓ Plasma (GC-MS) ↓ Urine (GC-MS)		Abu-Amsha Caccetta et al., 2001
White wine	14	18 smokers	375 mL	↔ Plasma (GC-MS) ↔ Urine (GC-MS)		Abu-Amsha Caccetta et al., 2001
Red wine	15	10	300 mL	↓ Urine (EIA)		Pignatelli et al., 2006
White wine	15	10	300 mL	↓ Urine (EIA)		Pignatelli et al., 2006

F_2-IsoP = F_2-isoprostanes, NEAC = nonenzymatic antioxidant capacity, ↑ = increase, ↔ = no change, ↓ = decrease, EIA = enzyme immunoassay, GC-MS = gas chromatography–mass spectrometry, ELISA = enzyme-linked immunosorbent assay, TRAP = total radical-trapping antioxidant parameter, FRAP = ferric reducing antioxidant power, TEAC = Trolox equivalent antioxidant capacity, ORAC = oxygen radical antioxidant capacity, n.r. = not reported.

obtaining in this case different results: while urinary NEAC was not enhanced after consumption of the normal tomato juice, it increased significantly with the fortified juice. On the other hand, either in the intervention with tomato (Visioli et al., 2003) and in that with olive oil (Visioli et al., 2005), no correspondence between the two biomarkers was found. In the former (Visioli et al., 2003), a decrease of urinary isoprostanes was obtained without any change in plasma NEAC. In the latter (Visioli et al., 2005), on the contrary, urinary isoprostanes were not affected by olive oil consumption, whereas an increase of plasma NEAC was reported.

Intervention Studies with Other Foods

In Table 5, acute and chronic studies are reported conducting with plant food items that are not included in the categories illustrated above. Only two acute interventions were found (both conducted with foods containing soy isoflavones), and just one reported an effect on isoprostanes. In this study (Lee et al., 2006), the authors investigated the antioxidant effects of dark soy sauce (DSS) on 24 subjects and found that, when compared with placebo, DSS had greater impact on lowering both total and free plasma isoprostanes, with levels differing significantly at three and four hours (respectively, for total and free forms). Urinary excretion was also evaluated, but no significant difference was found between DSS and the placebo at any time.

As to chronic studies, 11 were collected, reporting 11 interventions with different foods, and in 6, a decrease in isoprostanes levels was found. Three of the 11 chronic interventions were with soy-based products. In two of these, urinary measurements were carried out after consumption of soy milk for different periods, 4 weeks (Nhan et al., 2005) and 16 weeks (Ryan-Borchers et al., 2006), obtaining in both cases no effects on isoprostanes

Table 4 Overview of the reviewed intervention studies in humans providing vegetables and olive oils: characteristics and results for F_2-IsoP and NEAC

Food	Days	Subjects	Dose/day	F_2-IsoP	NEAC	Reference
Tomato sauce	1	10	150 g	↔ Plasma (GC-MS) ↓ (48 h) urine (GC-MS)		Lee et al., 2009
Olive oils (with four different phenolic contents)	1	6	50 mL containing 487.5, 975, 1462.5, and 1950 mg/L of total phenols	↓ Urine with increasing phenolic content (EIA)		Visioli et al., 2000
High-pressurized gazpacho	14	12	500 mL	↓ Plasma (EIA)		Sanchez-Moreno et al., 2004b
Gazpacho	14	12	500 mL	↓ Plasma (EIA)		Sanchez-Moreno et al., 2006
Tomato juice	14	12	500 mL	↔ Urine (EIA)	↔ Plasma and urine (TEAC and FRAP)	Jacob et al., 2008
Tomato juice fortified with vitamin C	14	12	500 mL enriched with 870 mg/L of vitamin C	↔ Urine (EIA)	↔ Plasma ↑ Urine (TEAC and FRAP)	Jacob et al., 2008
Tomato products	21	12	100 g fresh tomato (two days/week) + 60 g tomato sauce (three days/week) + 15 g tomato paste (two days/week), with 5-g olive oil/serving	↓ Urine (EIA)	↔ Plasma (kit)	Visioli et al., 2003
Tomato-based drink (Lyc-o-Mato)	26	26	250 mL	↔ Urine (LC-MS/MS)		Riso et al., 2006
LPC Olive oil	21	182	25 mL	↔ Plasma (LC-MS/MS)		Covas et al., 2006
MPC Olive oil	21	184	25 mL	↔ Plasma (LC-MS/MS)		Covas et al., 2006
HPC Olive oil	21	183	25 mL	↔ Plasma (LC-MS/MS)		Covas et al., 2006
EVOO	49	22 mildly dyslipidemic	40 mL	↔ Urine (EIA)	↑ Plasma (kit)	Visioli et al., 2005
Olive oil	63	182	25 mL	↓ Plasma (LC-MS/MS)		Cicero et al., 2008

F_2-IsoP = F_2-isoprostanes, NEAC = nonenzymatic antioxidant capacity, ↑ = increase, ↔ = no change, ↓ = decrease, LPC = low-phenolic content, MPC = medium-phenolic content, HPC = high-phenolic content, EVOO = extra-virgin olive oil, GC-MS = gas chromatography–mass spectrometry, EIA = enzyme immunoassay, LC-MS/MS = liquid chromatography–mass spectrometry, TEAC = Trolox equivalent antioxidant capacity, FRAP = ferric reducing antioxidant power.

levels. On the contrary, a reduction of plasma isoprostanes was observed by Wiseman et al. (2000) after the consumption of a vegetarian burger with soy protein high in isoflavones for 17 days. No change in plasma isoprostanes was detected in 22 smokers after the administration of a vegetable burger plus a fruit drink for three weeks (van den Berg et al., 2001).

Only two studies provided coffee, both reporting an effect on isoprostanes. In the first one (Kempf et al., 2010), 47 volunteers with an elevated risk of type 2 diabetes were given sequentially two different doses of coffee (four and eight cups/day) for four weeks each, leading to a significant decrease in serum concentration of isoprostanes for the eight cups/day dose. In the second study (Ochiai et al., 2009), an eight weeks administration of 184 mL/day of hydroxyhydroquinone (HHQ)-reduced coffee (containing 300 mg of chlorogenic acids) to nine subjects with mild hypertension and vascular failure led to a significant decrease of urinary isoprostanes.

Two intervention studies were conducted with nuts and almonds, producing positive results as well. A reduction of plasma isoprostanes concentrations in 17 hypercholesterolemic subjects was observed by Garg et al. (2007) after consumption of macadamia nuts for four weeks; the amount of nuts consumed ranged between 40 and 90 g/day depending on subject's energy intake (approximately 15% of the total daily intake provided by macadamia nuts). Urinary levels of isoprostanes were, instead, reduced in 27 hyperlipidemic volunteers eating almonds (at two different doses) for four weeks, in comparison with the control group (Jenkins et al., 2008).

Other products tested in the reviewed studies included sesame bars, baked products containing ground flaxseed, and spreads supplemented with vitamin E and carotenoids. Among these, a change in isoprostanes levels was observed only in the last case (Upritchard et al., 2003), in which the effect of moderate doses of vitamin E and carotenoids, incorporated into a commercial spread, was studied. Twenty-five g/day of two fortified spreads (spread A: 43 mg α-tocopherol equivalents + 0.45 mg carotenoids, or spread B: 111 mg α-tocopherol equivalents + 1.24 mg carotenoids) were consumed for 11 weeks by 33 healthy volunteers. A significant reduction of plasma total isoprostanes as well as an increase of plasma NEAC was reported in subjects

Table 5 Overview of the reviewed acute and chronic intervention studies in humans providing "other foods" containing antioxidants: characteristics and results for F_2-IsoP and NEAC

Food	Days	Subjects	Dose/day	F_2-IsoP	NEAC	Reference
Dark soy sauce	1	24	30 mL	↔ Urine (GC-MS) ↓ (3h) plasma total (GC-MS) ↓ (4h) plasma free (GC-MS)		Lee et al., 2006
Low-fat test meal with soy isoflavones	1	22 postmenopausal women	60 g of half-sugar orange spread with 80 mg of soy isoflavones	↔ Plasma (GC-MS)		Hall et al., 2008
Vegetarian burger with soy protein high in isoflavones	17	24	One burger	↓ Plasma (GC-MS)		Wiseman et al., 2000
Soy milk	28	8	36-oz	↔ Urine (ELISA)		Nhan et al., 2005
Soy milk	112	18 postmenopausal women	706 mL	↔ Urine (EIA)		Ryan-Borchers et al., 2006
Vegetable burger and fruit drink	21	22 smokers	100 g of vegetable burger and 330 mL of fruit drink	↔ Plasma (GC-MS)	↑ Plasma (TEAC)	van den Berg et al., 2001
Coffee	28	47 with elevated risk of type 2 diabetes	Four cups, eight cups (one cup = 150 mL)	↓ Serum (EIA) for eight cups/day dose		Kempf et al., 2010
HHQ-reduced coffee	56	9 with mild hypertension and vascular failure	184 mL	↓ Urine (n.r.)		Ochiai et al., 2009
Macadamia Nut	28	17 hypercholesterolemic	40–90 g (15% of total energy intake)	↓ Plasma (EIA)		Garg et al., 2007
Almonds	28	27 hyperlipidemic	73 ± 3 g (full-dose) 37 ± 2 g (half-dose)	↓ Urine (GC-MS)		Jenkins et al., 2008
Sesame bars	35	33 overweight or obese	One bar containing ∼ 25 g sesam seeds	↔ Plasma (GC-MS)		Wu et al., 2009
Baked products containing ground flaxseed	70	30 hypercholesterolemic	40 g	↔ Urine (LC-MS/MS)		Bloedon et al., 2008
Spread supplemented with vitamin E and carotenoids	77	33	25 g containing: A) 43 mg α-tocopherol equivalents + 0.45 mg carotenoids B) 111 mg α-tocopherol equivalents + 1.24 mg carotenoids	↓ Plasma only for spread B (LC-MS/MS)	↑ Plasma only for spread B (FRAP)	Upritchard et al., 2003

F_2-IsoP = F_2-isoprostanes, NEAC = nonenzymatic antioxidant capacity, ↑ = increase, ↔ = no change, ↓ = decrease, HHQ = hydroxyhydroquinone, GC-MS = gas chromatography–mass spectrometry, ELISA = enzyme-linked immunosorbent assay, EIA = enzyme immunoassay, LC-MS/MS = liquid chromatography–mass spectrometry, TEAC = Trolox equivalent antioxidant capacity, FRAP = ferric reducing antioxidant power, n.r. = not reported.

assigned to spread B. Besides this intervention, plasma NEAC was assessed only in another study, obtaining contrasting results: Although consumption of a vegetable burger plus fruit drink produced no effect on isoprostanes, an increase of plasma NEAC was instead reported (van den Berg et al., 2001).

Intervention Studies with Dietary Patterns

The results from long-term interventions conducted with different dietary patterns are reported in Table 6. A total of eight studies reporting 10 interventions were collected, and in four, a reduction of isoprostanes levels was observed. Two of these studies, conducted by Thompson et al. (1999, 2005), investigated the effect of diets rich in fruit and vegetables for relatively short periods (two and four weeks) reporting in both cases a reduction in urinary concentrations of isoprostanes. However, opposite results were obtained by Chen et al. (2004) based on a considerably longer intervention period (one year) with a high-fruit/vegetable diet that brought no change in plasma isoprostanes levels. The other studies reporting an effect on urinary isoprostanes were from Crujeiras et al. (2007) and Miller et al. (2005). In the first one, 15 obese subjects followed for eight weeks, a hypocaloric diet enriched in legumes (Crujeiras et al., 2007), whereas in the second one (Miller et al., 2005) 51 healthy individuals were assigned for three months to a diet rich in fruits, vegetables, and low-fat dairy products and reduced in fat, saturated fat, and cholesterol. This last intervention

Table 6 Overview of the reviewed intervention studies in humans providing dietary patterns: characteristics and results for F_2-IsoP and NEAC

Food	Days	Subjects	Dose/day	F_2-IsoP	NEAC	Reference
Diet high in fruit and vegetables	14	28	12 servings of fruit and vegetables	↓ Urine (ELISA)		Thompson et al., 1999
DASH diet	21	19	∼ Eight servings of fruit and vegetables	↔ Urine (GC-MS)		Al-Solaiman et al., 2009
Diet high in fruit and vegetables	28	246	9.2 servings of fruit and vegetables	↓ Urine (ELISA)		Thompson et al., 2005
Diet with soy protein enriched in isoflavones	42	42 hypercholesterolemic	50 mg isoflavones/1000 kcal	↔ Urine (EIA)	↔ Plasma (BODIPY/MeO-AMVN)	Vega-Lopez et al., 2005
Diet with animal protein enriched in isoflavones	42	42 hypercholesterolemic	50 mg isoflavones/1000 kcal	↔ Urine (EIA)	↔ Plasma (BODIPY/MeO-AMVN)	Vega-Lopez et al., 2005
Hypocaloric diet enriched in legumes	56	15 obese	Legume servings four days/week	↓ Urine (ELISA)	↔ Plasma (kit)	Crujeiras et al., 2007
DASH diet	90	51	Diet rich in fruits, vegetables, and low-fat dairy products	↓ Urine (EIA)	↑ Serum (ORAC) at months 2 and 3	Miller et al., 2005
Lupin-enriched diet	112	37 overweight and obese	∼ 4 × 40 g slices of lupin kernel flour-enriched bread (15–20% of daily energy intake)	↔ Plasma (GC-MS) ↔ Urine (GC-MS)		Yang et al., 2010
High-fruit and vegetables diet	365	122	Nine servings of fruit and vegetables	↔ Plasma (EIA)		Chen et al., 2004
Low-fat/high-fruit and vegetables diet	365	122	Nine servings of fruit and vegetables + low fat intake (15% of total energy)	↔ Plasma (EIA)		Chen et al., 2004

F_2-IsoP = F_2-isoprostanes, NEAC = nonenzymatic antioxidant capacity, ↑ = increase, ↔ = no change, ↓ = decrease, ELISA = enzyme-linked immunosorbent assay, GC-MS = gas chromatography–mass spectrometry, EIA = enzyme immunoassay, BODIPY = 4,4-difluoro-5-(4-phenyl-1,3-butadienyl)-4-bora-3a,4a-diaza-s-indacene-3-undecanoic acid, MeO-AMVN = 2,2′-azobis(4-methoxy-2,4-dimethylvaleronitrile), ORAC = oxygen radical antioxidant capacity.

was conducted as an ancillary study within the Dietary Approaches to Stop Hypertension-Sodium (DASH-sodium) trial, assessing the effects of dietary patterns and sodium intake on blood pressure (Sacks et al., 2001). In another study by Al-Solaiman et al. (2009), DASH diet resulted, instead, ineffective in lowering isoprostanes levels: in this study, the effects of DASH and low-sodium-DASH (LS-DASH) diets were compared in 19 volunteers during three-week dietary periods, obtaining no change in urinary concentration, following DASH diet, and a decrease after LS-DASH only in salt-sensitive subjects.

Among the collected studies, NEAC was assessed in four interventions. In one of these (Crujeiras et al., 2007), a correspondence between isoprostanes and NEAC was not found since, despite a decrease of urinary isoprostanes, no effect was reported on plasma NEAC. On the other hand, a concordant response between the two biomarkers was obtained in the other three interventions. In one case (Miller et al., 2005), an effect on both biomarkers was reported, whereas in the two interventions conducted by Vega-Lopez et al. (2005), neither isoprostanes nor NEAC levels changed.

Intervention Studies with Galenic Preparations Containing Pure Antioxidants

In Table 7, the results from intervention studies with galenic preparations containing pure antioxidants (both alone and in combinations) are presented. A total of 41 studies reporting 55 interventions were collected, with four acute interventions (one with vitamin C and three with polyphenols). Most of the chronic studies were conducted with preparations containing vitamins; only one study utilized pure lycopene, whereas few others interventions tested polyphenols (see Table 7). Although none of the acute interventions affected isoprostanes concentration, an effect was reported in 23 chronic interventions on 51. In Table 7, in the beginning the chronic interventions are reported providing single antioxidants (vitamin C, vitamin E and others), and then those with combinations of two, three, or more antioxidants. In the first group, 10 interventions with vitamin C alone were collected, 5 of which reported a reduction of plasma or urine isoprostanes after supplementation. One of these studies was by Reilly et al. (1996), who investigated the effects of five-day dosing with vitamin C, vitamin E and their combination on

Table 7 Overview of the reviewed intervention studies in humans providing galenic preparations containing pure antioxidants: characteristics and results for F_2-IsoP and NEAC

Supplement	Days	Subjects	Dose/day	F_2-IsoP	NEAC	Reference
Vitamin C	1	26	2 g	↔ Plasma (GC-MS) ↔ Urine (GC-MS)		Kelly et al., 2008
Quercetin	1	12	200 mg	↔ Plasma (GC-MS) ↔ Urine (GC-MS)		Loke et al., 2008
Epicatechin	1	12	200 mg	↔ Plasma (GC-MS) ↔ Urine (GC-MS)		Loke et al., 2008
Epigallocatechin gallate	1	12	200 mg	↔ Plasma (GC-MS) ↔ Urine (GC-MS)		Loke et al., 2008
Vitamin C	5	5 heavy smokers	2 g	↓ Urine (GC-MS)		Reilly et al., 1996
Vitamin C	14	18	150 mg	↔ Plasma (GC-MS)	↔ Plasma (TEAC)	Tesoriere et al., 2004
Vitamin C	17	11 smokers	1000 mg	↔ Plasma (GC-MS)		Bruno et al., 2006
Vitamin C	17	13	1000 mg	↔ Plasma (GC-MS)		Bruno et al., 2006
Vitamin C	42	19 hypertensive	500 mg	↔ Plasma (GC-MS) ↔ Urine (GC-MS)		Ward et al., 2005
Vitamin C	56	10 in hemodialysis	250 mg (three days/week postdialysis)	↔ Plasma (GC-MS)		Chan et al., 2006
Vitamin C	60	46	500 mg	↓ Urine (EIA)	↑ Serum (ORAC)	Huang et al., 2002
Vitamin C	60	128	1000 mg	↓ Plasma (GC-MS)		Block et al., 2008
Vitamin C	60	42 smokers	515 mg	↓ Plasma in subjects with BMI > 26.6 (GC-MS)		Dietrich et al., 2002
Vitamin C	60	22 passive smokers	515 mg	↓ Plasma (GC-MS)		Dietrich et al., 2003
Vitamin E	5	5 moderate smokers	100 IU	↔ urine (GC-MS)		Reilly et al., 1996
Vitamin E	5	7 heavy smokers	800 IU	↔ Urine (GC-MS)		Reilly et al., 1996
Vitamin E (*l*-α-tocopheryl acetate)	14	10 with type 2 diabetes	600 mg	↓ Urine (RIA)		Davì et al., 1999
RRR-α-tocopherol	14	17	400 IU	↔ Urine (ELISA)	↑ Serum (ORAC)	O'Byrne et al., 2002
Vitamin E (*d,l*-α-tocopheryl acetate)	21	11 smokers 12 smokers 11 smokers	300 mg 600 mg 1200 mg	↔ Urine (RIA)		Patrignani et al., 2000
RRR-α-tocopherol	42	18 with type 2 diabetes	500 mg	↓ Plasma (GC-MS) ↔ Urine (GC-MS)		Wu et al., 2007
Mixed tocopherols rich in γ-tocopherol	42	19 with type 2 diabetes	500 mg	↓ Plasma (GC-MS) ↔ Urine (GC-MS)		Wu et al., 2007
Vitamin E (*d*-α-tocopherol)	56	5	200, 400, 800, 1200, 2000 IU	↔ Urine (GC-MS)		Meagher et al., 2001
Vitamin E	56	8 with chronic kidney disease	800 IU	↔ Plasma (ELISA)		Saran et al., 2003
Vitamin E (*RRR*-α-tocopheryl acetate)	60	45	400 IU	↓ Urine (EIA)	↔ Serum (ORAC)	Huang et al., 2002
Vitamin E (*RRR*-α-tocopherol)	60	130	800 IU	↓ Plasma (GC-MS)		Block et al., 2008
Vitamin E (*RRR*-α-tocopherol)	70	20 older	1000 IU	↔ Plasma (GC-MS)		Simons et al., 1999
Vitamin E (*RRR*-α-tocopherol)	84	26 with advanced heart failure	671.2 mg (1000 IU)	↔ Plasma (EIA)		Keith et al., 2001
Vitamin E (*all rac*-α-tocopherol)	90	50 with type 2 diabetes	1200 IU	↓ Urine (EIA and GC-MS)		Devaraj et al., 2001
Vitamin E (*RRR*-α-tocopheryl acetate)	112	35 hypercholesterolemic	100, 200, 400, 800, 1600, 3200 IU	↓ Plasma for 1600 and 3200 IU doses (GC-MS)		Roberts et al., 2007
Vitamin E (*RRR*-α-tocopheryl acetate)	140	8 hypercholesterolemic	3200 IU	↓ Plasma after 112 days (GC-MS)		Roberts et al., 2007
Vitamin E	180	39 overweight	800 IU for months 1–3, 1200 IU for months 4—6	↓ Plasma (LC-MS/MS)		Sutherland et al., 2007

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Table 7 Overview of the reviewed intervention studies in humans providing galenic preparations containing pure antioxidants: characteristics and results for F_2-IsoP and NEAC *(Continued)*

Supplement	Days	Subjects	Dose/day	F_2-IsoP	NEAC	Reference
Vitamin E (*RRR*-α-tocopherol)	730	44 with coronary artery disease	1200 IU	↓ Urine (n.r.)		Devaraj et al., 2007
Rutin	42	8	500 mg	↔ Urine (ELISA)	↔ Plasma (FRAP)	Boyle et al., 2000
Lycopene	56	21 with mildly raised cholesterol 17 with mildly raised cholesterol 21 with mildly raised cholesterol	6.5 mg 15 mg 30 mg	↔ Urine (EIA)		Devaraj et al., 2008
Pycnogenol	90	49 elderly	150 mg	↓ Plasma (GC-MS)		Ryan et al., 2008
Genistein	730	198 osteopenic, postmenopausal women	54 mg	↓ Urine (EIA)		Atteritano et al., 2007
Vitamins C + E	5	4 heavy smokers	2 g vitamin C + 800 IU vitamin E	↓ Urine (GC-MS)		Reilly et al., 1996
Vitamins E + C	28	28 with Crohn's disease	800 IU vitamin E + 1000 mg vitamin C	↓ Plasma (EIA)		Aghdassi et al., 2003
Vitamins C + E	28	13 with impaired fasting glucose	1000 mg vitamin C + 1000 IU vitamin E	↓ Plasma (EIA)		Rizzo et al., 2008
Vitamins C + E	42	12	1000 mg vitamin C + 300 mg *RRR*-α-tocopheryl acetate	↔ Plasma (GC-MS)		Mastaloudis et al., 2004
Vitamins C + E	56	55 with essential hypertension	1 g vitamin C + 400 IU vitamin E	↓ Plasma (ELISA)	↑ Plasma (FRAP)	Rodrigo et al., 2008
Vitamins C + E	60	46	500 mg vitamin C + 400 IU vitamin E	↓ Urine (EIA)	↔ Serum (ORAC)	Huang et al., 2002
Vitamins E + C	84	75 with dementia or mild cognitive impairment	500 mg vitamin E + 200 mg vitamin C	↔ Urine (LC-MS/MS)		Clarke et al., 2003
Vitamins C + E	180	11 with coronary artery disease	1000 mg vitamin C + 800 IU vitamin E	↔ Plasma (GC-MS)		Kinlay et al., 2004
γ-tocopherol + DHA	56	31 in hemodialysis	308 mg γ-tocopherol + 800 mg DHA	↔ Plasma (GC-MS)		Himmelfarb et al., 2007
Quercetin + vitamin C	84	334 333	500 mg quercetin + 125 mg vitamin C 1000 mg quercetin + 250 mg vitamin C	↔ Plasma (GC-MS)	↔ Plasma (FRAP and ORAC)	Shanely et al., 2010
Vitamin C + α-lipoic acid + vitamin E	60	39 smokers	515 mg vitamin C + 95 mg α-lipoic acid + 371 mg of *RRR*-α-tocopherol, 171 mg of *RRR*-γ-tocopherol, 50 mg of α-tocotrienol, 184 mg of γ-tocotrienol, 18 mg of δ-tocotrienol	↔ Plasma (GC-MS)		Dietrich et al., 2002
Vitamin C + α-lipoic acid + vitamin E	60	21 passive smokers	515 mg vitamin C + 95 mg α-lipoic acid + 371 mg of *RRR*-α-tocopherol, 171 mg of *RRR*-γ-tocopherol, 50 mg of α-tocotrienol, 184 mg of γ-tocotrienol, 18 mg of δ-tocotrienol	↓ Plasma (GC-MS)		Dietrich et al., 2003

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Table 7 Overview of the reviewed intervention studies in humans providing galenic preparations containing pure antioxidants: characteristics and results for F_2-IsoP and NEAC *(Continued)*

Supplement	Days	Subjects	Dose/day	F_2-IsoP	NEAC	Reference
Vitamin C + vitamin E + folic acid	90	18 smokers	272 mg vitamin C + 31 mg *all rac*-α-tocopherol + 400 μg folic acid	↔ Urine (GC-MS)		Jacob et al., 2003
Vitamin C + vitamin E + folic acid	90	17	272 mg vitamin C + 31 mg *all rac*-α-tocopherol + 400 μg folic acid	↔ Urine (GC-MS)		Jacob et al., 2003
Daidzein + genistein + glycitein	112	15 postmenopausal women	30 mg daidzein + 33 mg genistein + 7 mg glycitein	↔ Urine (EIA)		Ryan-Borchers et al., 2006
Vitamin E + vitamin C + vitamin B6 + vitamin B12 + folic acid	56	20 in hemodialysis	800 IU vitamin E + 250 mg vitamin C + 100 mg vitamin B6 + 250 μg vitamin B12 + 10 mg folic acid	↔ Plasma (ELISA)		Kamgar et al., 2009
Vitamin E + vitamin C + β-carotene + selenium + vitamin A	56	22 with cystic fibrosis	200 mg vitamin E + 300 mg vitamin C + 25 mg β-carotene + 90 μg selenium + 500 μg vitamin A	↔ Plasma (EIA)		Wood et al., 2003
β-carotene + vitamin C + vitamin E + zinc + selenium + garlic	28	36 allergic	9 mg β-carotene + 1500 mg vitamin C + 130 mg vitamin E + 45 mg zinc + 76 μg selenium + 150 mg garlic	↔ Plasma (GC-MS)	↔ Serum (AIOR: uroporphyrin I/ AAPH)	Dunstan et al., 2007
Vitamin C + vitamin E + β-carotene + vitamin B6 + zinc + selenium + fish oil	34	7 smokers	500 mg vitamin C + 30 mg vitamin E + 3 mg β-carotene + 5 mg vitamin B6 + 10 mg zinc + 100 μg selenium + 5.6 g lipids	↔ Urine (n.r.)		Nitta et al., 2007

F_2-IsoP = F_2-isoprostanes, NEAC = nonenzymatic antioxidant capacity, ↑ = increase, ↔ = no change, ↓ = decrease, DHA = docosahexaenoic acid, IU = International Units, BMI = body mass index, GC-MS = gas chromatography–mass spectrometry, EIA = enzyme immunoassay, RIA = radioimmunoassay, ELISA = enzyme-linked immunosorbent assay, LC-MS/MS = liquid chromatography–mass spectrometry, TEAC = Trolox equivalent antioxidant capacity, ORAC = oxygen radical antioxidant capacity, FRAP = ferric reducing antioxidant power, AIOR = antioxidant inhibition of radicals, AAPH = 2,2′-azobis(2-amidinopropane) dihydrochloride, n.r. = not reported.

four–seven smokers only. In this case, while both vitamin C and vitamin C plus E interventions suppressed urinary isoprostanes concentration, vitamin E alone had no effect. A decrease of urinary isoprostanes was also reported by Huang et al. (2002) in a study where a two-month supplementation with vitamin E, vitamin, C and their combination were compared. Although all the interventions produced a reduction of urinary isoprostanes, no synergistic effect of these two vitamins was observed by the authors. In another study (Block et al., 2008), evaluating two-month supplementation with either vitamin C or vitamin E, a significant interaction with baseline levels was found. Whereas in the overall sample, a decrease of plasma isoprostanes was reported following both interventions, when the subjects were grouped according to their baseline levels the results changed: for baseline concentrations < 50 pg/mL no reduction was observed, whereas, for higher levels, plasma isoprostanes were significantly reduced for vitamin C only. A significant interaction between body mass index (BMI) and treatment group was, instead, found by Dietrich et al. (2002). They investigated the effect of two-month intervention with vitamin C on 42 smokers and found that, while in subjects with BMI > 26.6 plasma isoprostanes decreased significantly after supplementation, there was no significant treatment effect in volunteers with BMI below that value. These results were consistent with the previous study, since subjects with higher BMI had also more elevated baseline levels of isoprostanes. In the same study (Dietrich et al., 2002), the authors conducted a second intervention on 39 smokers with an antioxidant mixture containing vitamin C, α-lipoic acid, and vitamin E obtaining in this case no effect on plasma isoprostanes, regardless of subjects' BMI. A slightly different result was found by the same authors in another study (Dietrich et al., 2003) where both vitamin C alone and a mixture of vitamin C, α-lipoic acid, and vitamin E reduced plasma isoprostane concentrations after two months of supplementation in passive smokers.

Eighteen interventions were collected providing supplementation with vitamin E alone, and in 10, a decrease of isoprostanes concentration in plasma or urine was found. Two of these were the abovedescribed interventions conducted by Huang et al.

Table 8 Overview of the reviewed intervention studies in humans providing galenic preparations containing plant food extracts: characteristics and results for F2-IsoP and NEAC

Supplement	Days	Subjects	Dose/day	F_2-IsoP	NEAC	Reference
Decaffeinated green tea extract	14	9	Four capsules (844 mg of catechins)	↔ Urine (GC-MS)		Donovan et al., 2005
Green tea extract	28	20	3 g (corresponding to 10 cups)	↔ Urine (RIA)		Freese et al., 1999
Garlic extract	14	10 smokers	5 mL	↓ Plasma (EIA) ↓ Urine (EIA)		Dillon et al., 2002
Garlic extract	14	10	5 mL	↓ Plasma (EIA) ↓ Urine (EIA)		Dillon et al., 2002
Garlic pearls	56	20 with essential hypertension	500 mg	↓ Plasma (ELISA) ↓ Urine (ELISA)	↑ Plasma (FRAP)	Dhawan and Jain, 2004
Garlic pearls	56	20	500 mg	↔ Plasma (ELISA) ↔ Urine (ELISA)	↔ Plasma (FRAP)	Dhawan and Jain, 2004
Soy extract	21	12	50 mg for women and 100 mg for men	↔ Plasma (EIA)		Djuric et al., 2001
Soya beans extract	84	50 with prior ischemic stroke	80 mg	↔ Serum (n.r.)		Chan et al., 2008
Subterranean clover extract	56	30 with high-normal blood pressure	55 mg	↔ Urine (GC-MS)		Hodgson et al., 1999
Olive leaf capsule	28	14	Three capsules	↔ Urine (ELISA)		Kendall et al., 2009
Olive leaf liquid extract	28	12	15 mL	↔ Urine (ELISA)		Kendall et al., 2009
Mixed α- plus γ-tocotrienol extract from palm oil	28	17 hypercholesterolemic	200 mg of total tocotrienols	↔ Urine (RIA)		Mustad et al., 2002
High γ-tocotrienol extract from rice bran oil	28	17 hypercholesterolemic	200 mg of total tocotrienols	↔ Urine (RIA)		Mustad et al., 2002
P-25 complex tocotrienol extract from rice bran oil	28	16 hypercholesterolemic	200 mg of total tocotrienols	↔ Urine (RIA)		Mustad et al., 2002
Safflower seed extract	28	20	2.1 g	↓ Urine (EIA)		Koyama et al., 2009
Fruit and vegetables gummy supplements	21	20 children (5–10 years)	Six capsules (three of fruit supplement and three of vegetables supplement)	↔ Urine (EIA)	↔ Urine (ORAC)	Stewart et al., 2002
Standardized extracts of fruits and berries	28	22 hypercholesterolemic	2700 mg	↓ Urine (ELISA)		Abidov et al., 2006
Lyophilized grape powder	28	20 postmenopausal women	36 g (equivalent to 200 g of fresh grapes)	↓ Urine (EIA)		Zern et al., 2005
Lyophilized grape powder	28	24 premenopausal women	36 g (equivalent to 200 g of fresh grapes)	↓ Urine (EIA)		Zern et al., 2005
Grape polyphenol extract	42	11 smokers with chronic obstructive pulmonary disease	Three tablets (540 mg of polyphenols)	↓ Urine (EIA)		Santus et al., 2005
Grape polyphenol extract	42	9	Three tablets (540 mg of polyphenols)	↔ Urine (EIA)		Santus et al., 2005
Grape-seed polyphenols	42	16 hypertensive	1000 mg	↔ Plasma (GC-MS) ↔ Urine (GC-MS)		Ward et al., 2005
Grape-seed polyphenols + vitamin C	42	16 hypertensive	1000 mg of polyphenols + 500 mg of vitamin C	↔ Plasma (GC-MS) ↔ Urine (GC-MS)		Ward et al., 2005
Emblica officinalis (Amla) extract	120	17 uremic	Three tablets (450 mg of Amla extract)	↓ Plasma (ELISA)	↑ Plasma (n.r.)	Chen et al., 2009

F_2-IsoP = F_2-isoprostanes, NEAC = nonenzymatic antioxidant capacity, ↑ = increase, ↔ = no change, ↓ = decrease, GC-MS = gas chromatography–mass spectrometry, RIA = radioimmunoassay, EIA = enzyme immunoassay, ELISA = enzyme-linked immunosorbent assay, FRAP = ferric reducing antioxidant power, ORAC = oxygen radical antioxidant capacity, n.r. = not reported.

(2002) and Block et al. (2008) in healthy subjects. A change in isoprostanes levels of diabetic volunteers after vitamin E supplementation was obtained, instead, by Davì et al. (1999); Wu et al. (2007); and Devaraj et al. (2001). In the first study (Davì et al., 1999), authors reported a reduction of urinary isoprostanes after two weeks of vitamin E consumption. In the study by Wu et al. (2007), the effects of six-week intervention with either α-tocopherol or mixed tocopherols (rich in γ-tocopherol) were compared obtaining the same results: both interventions produced a reduction of plasma concentrations while no effect was found on urinary isoprostanes. Similar results to the study of Davì et al. (1999) were obtained by Devaraj et al. (2001): also in this case a decrease of urinary isoprostanes levels was found after supplementation with vitamin E in type 2 diabetic subjects. This study included patients either with and without macrovascular complications: when these two subgroups were considered separately, the reduction was significant after three-month supplementation only in diabetic patients with macrovascular complications. The same authors also reported decreased levels of urinary isoprostanes after two years of vitamin E consumption in 44 patients with stable CAD (Devaraj et al., 2007). Other long-term interventions with vitamin E leading to a reduction of isoprostanes levels were by Sutherland et al. (2007) and Roberts et al. (2007). In the first study (Sutherland et al., 2007), 39 overweight subjects were supplemented for six months with vitamin E (receiving a 800 IU daily dose for months 1–3 and 1200 IU for months 4–6), and during the intervention period plasma isoprostanes concentrations decreased significantly. In the second case (Roberts et al., 2007), two studies were undertaken on hypercholesterolemic subjects; a time-course study was first performed in participants supplemented with 3200 IU/day of vitamin E for 20 weeks, and the results obtained from this intervention were thereafter used to perform a subsequent dose-ranging study. In the time-course study, a significant reduction of plasma isoprostanes did not occur until after 16 weeks of supplementation, and this period of time was therefore chosen for the dose-ranging study. Thus, participants were supplemented for 16 weeks with 100, 200, 400, 800, 1600, or 3200 IU/day of vitamin E, obtaining a linear trend between the dosage and percentage of reduction in plasma isoprostanes concentrations, which reached significance at doses of 1600 and 3200 IU.

Finally, four chronic interventions providing single antioxidants different from vitamins were collected, one with lycopene and three with polyphenols. Decreased concentration of plasma isoprostanes was found in elderly subjects after three months of supplementation with Pycnogenol (Ryan et al., 2008) while two years of supplementation with genistein reduced isoprostanes urinary excretion in 198 osteopenic, postmenopausal women (Atteritano et al., 2007).

Regarding galenic preparations containing combinations of different antioxidants, eight interventions providing vitamin C plus E were collected with five reporting an effect on isoprostanes. Besides a decrease of urinary isoprostanes found in the two previously described studies by Reilly et al. (1996) and Huang et al. (2002), plasma concentrations of isoprostanes were reduced after interventions providing both vitamins in subjects with Crohn's disease (Aghdassi et al., 2003), impaired fasting glucose (Rizzo et al., 2008) and essential hypertension (Rodrigo et al., 2008). Among the other interventions with combinations of three or more antioxidants, only the one by Dietrich et al. (2003) reported a decrease of plasma isoprostanes.

In all these studies, NEAC was assessed in only 9 chronic interventions of 51, and in 6, a concordant result with isoprostanes was reported. Two of these interventions provided vitamin C but, whereas in the first (Tesoriere et al., 2004) two-week supplementation with a daily dose of 150 mg produced no change in both isoprostanes and NEAC, in the second one (Huang et al., 2002) two-month administration of 500 mg/day of vitamin C resulted in a decrease of isoprostanes concentration and in a corresponding increase of serum NEAC. Another study reporting a concordant response between isoprostanes and NEAC was conducted with rutin (Boyle et al., 2000), obtaining no effect on both biomarkers after six weeks of supplementation. Reduced isoprostanes levels and increased plasma NEAC were, instead, reported by Rodrigo et al. (2008) after an eight-week intervention with vitamins C plus E in hypertensive subjects. Finally, the remaining two interventions, in which a correspondence between isoprostanes and NEAC was found, reported no effect on both biomarkers. In the first (Shanely et al., 2010), two different doses of quercetin plus vitamin C were administrated to a large number of subjects for 12 weeks, whereas in the second (Dunstan et al., 2007), a supplement containing different antioxidants was given to allergic patients for four weeks.

Intervention Studies with Galenic Preparations Containing Plant Food Extracts

Intervention studies with galenic preparations containing plant food extracts are described in Table 8. A total of 16 long-term intervention studies reporting 24 interventions were collected, in 9 of which there was observed a decrease of plasma and/or urine isoprostanes. Two studies provided green tea extracts, but no effect on isoprostanes was found. On the contrary, three of the four interventions conducted with garlic products reported a decrease of plasma and urinary isoprostanes. Two of these were from Dillon et al. (2002): they investigated the effect of two-week supplementation with aged garlic extract on 10 smokers and on 10 nonsmokers volunteers, obtaining reduced plasma and urinary concentrations of isoprostanes in both groups. In a second study from Dhawan and Jain (2004), garlic pearls (containing garlic oil) were administrated for eight weeks to 20 hypertensive subjects and 20 healthy volunteers (used as a control): in this case, a reduction in plasma and urinary isoprostanes was found only for hypertensive group, which showed more elevated baseline levels. Other interventions were conducted with isoflavonoids-rich extracts (from soy and subterranean clover), olive leaf extracts, tocotrienol supplements (from different oils), fruit and vegetables supplements, but in all of these cases, no change in isoprostanes concentration

was reported after supplementation. A reduction in urinary isoprostanes was, instead, found after the consumption of safflower seed extract (Koyama et al., 2009) and of a supplement containing extracts of fruits and berries (Abidov et al., 2006). The same results were also obtained in three interventions providing grape polyphenols: in the first two (Zern et al., 2005), the authors administered a lyophilized grape powder to 24 pre- and 20 postmenopausal women during four weeks, whereas in the third (Santus et al., 2005), 11 smokers with chronic obstructive pulmonary disease were given, for six weeks, a standardized polyphenol extract obtained from the skin of selected grapes. In the last study (Santus et al., 2005), the same extract was consumed also by nine healthy controls, but a significant decrease in isoprostanes excretion was found only in smokers with baseline levels higher than controls. Finally, in the study by Chen et al. (2009), a decrease of plasma isoprostanes was reported after four months of consumption of *Emblica officinalis* (Amla or Indian goosberry) extract.

Among the collected studies, NEAC was assessed in only four interventions, in all of which a concordant response with isoprostanes was found. In the interventions conducted by Dhawan and Jain (2004), consumption of garlic pearls produced a decrease of isoprostanes and a correspondent increase of NEAC in hypertensive subjects but not in healthy controls. No effect on isoprostanes and NEAC urinary levels was described by Stewart et al. (2002) after a three-week supplementation with fruit and vegetable gummy supplements in 20 children. The last study reporting NEAC measurement was published by Chen et al. (2009), where an increase of plasma NEAC was found together with a reduction of plasma isoprostanes after supplementation with Amla extract.

CONCLUSIONS

A systematic review has been conducted in this paper of the available evidences from literature on the link between isoprostanes and dietary antioxidants. Although isoprostanes are considered a reliable and established marker of lipid peroxidation, the number of dietary intervention studies reporting their measurements is not very high when compared with other biomarkers such as NEAC (Serafini et al., 2011). Both foods and galenics were considered, and a total of 154 interventions were collected. Of these, only 14 were acute interventions: 10 conducted with foods and 4 with galenics. A decrease of isoprostanes levels was found in half of the interventions with foods (5/10) while none of the galenic preparations (all containing pure antioxidants) affected isoprostanes levels. Given the scarce number of interventions, no certain conclusion can be drawn. Perhaps, the short period of exposure to antioxidants (just one portion or one dose in a day) might not be enough to modify levels of isoprostanes in biological fluids.

As to chronic studies, after grouping the interventions according to the antioxidant source (foods or galenics), the following results were obtained: the 37% (24/65) of interventions with foods and the 43% (32/75) of interventions with galenics reported a decrease of isoprostanes levels after supplementation. Putting together food and supplements, the percentage was 40% (56/140). When the results were analyzed by single categories of foods, a large variability was observed for fruit, fruit juices, wine, vegetables, olive oil, and dietary patterns with a percentage of positive results balancing the negative results, thus making hard to draw any conclusion. However, it is important to mention the lack of effect obtained in long-term intervention studies with tea and chocolate. Despite the high content in antioxidant molecules such as catechin and procyanidins, only one intervention (black tea) on a total of nine for tea and seven for chocolate was effective in reducing isoprostanes plasma levels. From these figures, it seems that isoprostanes are inconsistently modulated by antioxidant-rich foods and supplements. Nevertheless, some considerations are essential. First of all, it should be considered the high heterogeneity of the reviewed studies, involving not only very different sources of supplementation but also different doses, length of supplementation, and study design. Sometimes a negative result can be due to the use of an inappropriate antioxidant or dose, to a short period of supplementation or to inadequate sample size, all factors playing a significant role on the result of the study.

It should also be considered that, despite the high antioxidant content of certain foods, supporting an in vivo efficacy, they might not always act as antioxidants in humans. Despite the fact that the assessment of the content of bioactive molecules and of the antioxidant capacity of a food is an important step to characterize the food under an antioxidant point of view, this set of data is not predictive of the effect after long-term ingestion in humans. We might distinguish between an "intrinsic" antioxidant potential, linked to the food's composition and an "extrinsic" antioxidant activity linked to the real ability of the food to modulate markers of oxidative stress in vivo. The outcome of a dietary intervention study may also depend on the "health" status of subjects involved; as previously stated, elevated levels of isoprostanes have been reported in individuals with diseases, or related risk factors, in which oxidative stress is involved. These subjects are supposed to have a higher need of antioxidants and, thus, to better respond to dietary intervention. The studies of Dhawan and Jain (2004) and Santus et al. (2005) confirm this hypothesis: in both studies supplementation (in the first case with garlic pearls and in the second with grape polyphenols extract) resulted effective in lowering isoprostanes levels only in pathological subjects who showed higher baseline levels, whereas administration of the same galenic preparations to healthy controls produced no significant change. In another study by Block et al. (2008), a significant interaction between baseline levels of isoprostanes and treatment effect of vitamin C was found. In the same way, a significant interaction with BMI was reported by Dietrich et al. (2002) in a study evaluating the effect of vitamin C on smokers: isoprostanes decreased significantly only in subjects with higher BMI, who also had more elevated baseline levels. Furthermore, as recently reviewed by our group, the effect of dietary antioxidants on plasma endogenous antioxidant defenses is much more effective in people affected

by disease and/or characterized by risk factors associated with oxidative stress (Serafini et al., 2011). Anyhow, notwithstanding these results, in other interventions a correlation between treatment effect and "oxidative status" of subjects was not found, leaving the debate open.

Besides the differences attributable to these factors, the quantification technique utilized represents an important source of variability. As previously stated, since isoprostanes were first characterized in humans, several methods have been developed for their measurement, but in most cases, they were applied without a proper standardization. Studies where isoprostanes have been measured by gas chromatography–mass spectrometry or liquid chromatography–mass spectrometry techniques give a more reliable and precise information compared with enzyme-linked immunosorbent assay-based methodologies. It should also be mentioned that isoprostanes, despite the large number of evidences suggesting their use as optimal markers of oxidative stress, might not be a proper marker in healthy subjects lacking an oxidative stress condition. Moreover, isoprostanes assess a specific aspect of oxidative stress related to arachidonic acid cascade and might not be a stress predictor for all the cellular districts where oxidative stress takes place.

The results about the potential link between isoprostanes and NEAC are presented in Fig. 2. Notwithstanding the quite low percentage of the effect in the reviewed studies, we found a relationship between isoprostanes and endogenous antioxidant defenses. Measurements of both biomarkers were conducted in a total of 38 interventions: among these only 4 were acute interventions (3 providing cocoa products and 1 blueberry), whereas 34 were chronic interventions (21 conducted with foods and 13 with galenic preparations). Given the scarce number of acute interventions, only the chronic ones were reported in Fig. 2, and they were grouped according to the antioxidant source: foods and galenics. In both cases, a high percentage of interventions with concordant results between isoprostanes and NEAC was found: 67% (14 on 21) for foods and 77% (10 on 13) for galenics. These results suggest that these two biomarkers respond in a similar way to dietary antioxidants, since in most cases where the intervention worked for isoprostanes (decreasing their levels) it also produced an increase of NEAC; likewise, most of the interventions with no effect on isoprostanes also resulted ineffective on NEAC. As to the interventions with not concordant response between the two biomarkers, in one half an effect was reported only for isoprostanes and in the other half only for NEAC. Although further studies are needed, it has nevertheless been found from the available data a corresponding response between isoprostanes and NEAC after antioxidant supplementation.

Given the complexity of processes regulating oxidative status of organism and on the basis of our findings, the use of more than one biomarker could be the better approach in intervention studies with antioxidants. To assess the efficacy of supplementation, it should be verified if the body antioxidant defenses have been increased by food/supplement, and if oxidative damage has been reduced, which can be achieved by

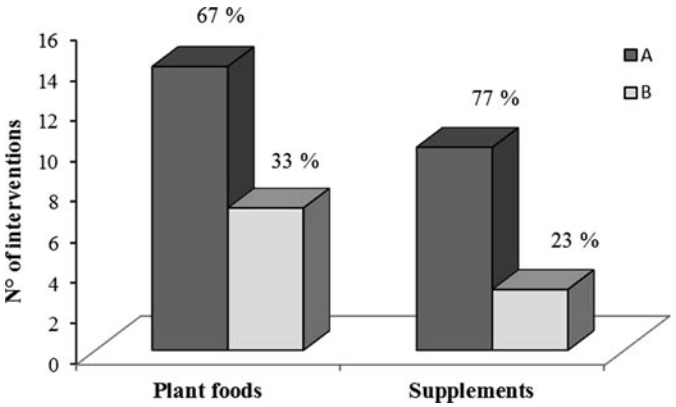

Figure 2 Number of long-term dietary intervention studies in humans providing antioxidant-rich plant foods or antioxidant supplements with concordant (A: lack of change for both biomarkers or increase in NEAC and decrease in isoprostanes) and not concordant (B: change in only one of the two biomarkers) response between isoprostanes and NEAC.

using biomarkers of antioxidant protection, such as NEAC, and biomarkers of oxidative stress such as isoprostanes, which represent the two faces of the same coin. As concerns the latter, some issues should be addressed: first of all an adequate standardization of quantification techniques is required, not only for immunoassays but also for the many chromatographic/mass spectrometric methods developed. Moreover, no standard protocol is available for handling and storage of biological samples, and confusion exists regarding the different isomers to be measured and their metabolism, confusion that is also increased by the several nomenclature systems adopted by different laboratories. Another aspect that should be considered is the definition of a "physiological" range for isoprostanes: indeed, although some authors (Morrow et al., 1990; Fam and Morrow, 2003; Milne et al., 2007) have defined the normal levels of isoprostanes in healthy subjects, in the reviewed studies there has been observed a far wider range of baseline levels, thus making impossible, at present, the identification of physiological cut-off levels.

In agreement with previous evidences (Serafini et al., 2011; Visioli et al., 2011), there is not enough data to claim a direct role of polyphenols in the dietary modulation of oxidative stress. However, the antioxidant effect of polyphenols might take place through different mechanisms such as an induction of specific redox transcription factors or in the oxidative reactions taking place during digestion. More evidences in humans, involving new techniques such as metabolomics associated with a detailed screening of the bioavailability and sites of action of main metabolites, are required.

In conclusion, although isoprostanes are considered as the golden standard for assessing oxidative stress in disease state, the review of the available evidence suggests that dietary antioxidants modulate the levels of isoprostanes in a percentage lower than 45% of interventions. Variables such as methodology and the existence of mechanisms of homeostatic control of redox status in vivo might explain some of the observed variability. In the future, methodological issues should be overcome, an

identification of physiological range for isoprostanes in humans is highly needed, and alternative markers of oxidative stress should be identified as well. Further studies are required to better understand the role of dietary antioxidants in modulating oxidative stress in humans.

REFERENCES

Abidov, M., Jimenez Del Rio, M., Ramazanov, A., Kalyuzhin, O. and Chkhikvishvili, I. (2006). Efficiency of pharmacologically-active antioxidant phytomedicine radical fruits in treatment hypercholesteremia at men. *Georgian Med. News*. 78–83.

Abu-Amsha Caccetta, R., Burke, V., Mori, T. A., Beilin, L. J., Puddey, I. B. and Croft, K. D. (2001). Red wine polyphenols, in the absence of alcohol, reduce lipid peroxidative stress in smoking subjects. *Free Radic. Biol. Med.* **30**:636–642.

Aghdassi, E., Wendland, B. E., Steinhart, A. H., Wolman, S. L., Jeejeebhoy, K. and Allard, J. P. (2003). Antioxidant vitamin supplementation in Crohn's disease decreases oxidative stress. a randomized controlled trial. *Am. J. Gastroenterol.* **98**:348–353.

Al-Solaiman, Y., Jesri, A., Zhao, Y., Morrow, J. D. and Egan, B. M. (2009). Low-Sodium DASH reduces oxidative stress and improves vascular function in salt-sensitive humans. *J. Hum. Hypertens.* **23**:826–835.

Atteritano, M., Marini, H., Minutoli, L., Polito, F., Bitto, A., Altavilla, D., Mazzaferro, S., D'Anna, R., Cannata, M. L., Gaudio, A., Frisina, A., Frisina, N., Corrado, F., Cancellieri, F., Lubrano, C., Bonaiuto, M., Adamo, E. B. and Squadrito, F. (2007). Effects of the phytoestrogen genistein on some predictors of cardiovascular risk in osteopenic, postmenopausal women: A two-year randomized, double-blind, placebo-controlled study. *J. Clin. Endocrinol. Metab.* **92**:3068–3075.

Barocas, D. A., Motley, S., Cookson, M. S., Chang, S. S., Penson, D. F., Dai, Q., Milne, G., Roberts, L. J., 2nd, Morrow, J., Concepcion, R. S., Smith, J. A., Jr. and Fowke, J. H. (2011). Oxidative stress measured by urine F2-isoprostane level is associated with prostate cancer. *J. Urol.* **185**:2102–2107.

Bartosz, G. (2010). Non-enzymatic antioxidant capacity assays: Limitations of use in biomedicine. *Free Radic. Res.* **44**:711–720.

Block, G., Jensen, C. D., Morrow, J. D., Holland, N., Norkus, E. P., Milne, G. L., Hudes, M., Dalvi, T. B., Crawford, P. B., Fung, E. B., Schumacher, L. and Harmatz, P. (2008). The effect of vitamins C and E on biomarkers of oxidative stress depends on baseline level. *Free Radic. Biol. Med.* **45**: 377–384.

Bloedon, L. T., Balikai, S., Chittams, J., Cunnane, S. C., Berlin, J. A., Rader, D. J. and Szapary, P. O. (2008). Flaxseed and cardiovascular risk factors: Results from a double blind, randomized, controlled clinical trial. *J. Am. Coll. Nutr.* **27**:65–74.

Boyle, S. P., Dobson, V. L., Duthie, S. J., Hinselwood, D. C., Kyle, J. A. and Collins, A. R. (2000). Bioavailability and efficiency of rutin as an antioxidant: A human supplementation study. *Eur. J. Clin. Nutr.* **54**: 774–782.

Bruno, R. S., Leonard, S. W., Atkinson, J., Montine, T. J., Ramakrishnan, R., Bray, T. M. and Traber, M. G. (2006). Faster plasma vitamin E disappearance in smokers is normalized by vitamin C supplementation. *Free Radic. Biol. Med.* **40**:689–697.

Budinsky, A., Wolfram, R., Oguogho, A., Efthimiou, Y., Stamatopoulos, Y. and Sinzinger, H. (2001). Regular ingestion of opuntia robusta lowers oxidation injury. *Prostaglandins Leukot Essent Fatty Acids*. **65**:45–50.

Cerda, B., Soto, C., Albaladejo, M. D., Martinez, P., Sanchez-Gascon, F., Tomas-Barberan, F. and Espin, J. C. (2006). Pomegranate juice supplementation in chronic obstructive pulmonary disease: A 5-week randomized, double-blind, placebo-controlled trial. *Eur. J. Clin. Nutr.* **60**:245–253.

Chan, D., Irish, A., Croft, K. D. and Dogra, G. (2006). Effect of ascorbic acid supplementation on plasma isoprostanes in haemodialysis patients. *Nephrol. Dial Transplant*. **21**:234–235.

Chan, Y. H., Lau, K. K., Yiu, K. H., Li, S. W., Chan, H. T., Fong, D. Y., Tam, S., Lau, C. P. and Tse, H. F. (2008). Reduction of C-reactive protein with isoflavone supplement reverses endothelial dysfunction in patients with ischaemic stroke. *Eur. Heart J.* **29**:2800–2807.

Chen, G., Heilbrun, L. K., Venkatramanamoorthy, R., Maranci, V., Redd, J. N., Klurfeld, D. M. and Djuric, Z. (2004). Effects of low-fat and/or high-fruit-and-vegetable diets on plasma levels of 8-isoprostane-F2alpha in the Nutrition and Breast Health study. *Nutr. Cancer.* **50**:155–160.

Chen, T. S., Liou, S. Y. and Chang, Y. L. (2009). Supplementation of Emblica officinalis (Amla) extract reduces oxidative stress in uremic patients. *Am. J. Chin Med.* **37**:19–25.

Cicero, A. F., Nascetti, S., Lopez-Sabater, M. C., Elosua, R., Salonen, J. T., Nyyssonen, K., Poulsen, H. E., Zunft, H. J., Kiesewetter, H., de la Torre, K., Covas, M. I., Kaikkonen, J., Mursu, J., Koenbick, C., Baumler, H. and Gaddi, A. V. (2008). Changes in LDL fatty acid composition as a response to olive oil treatment are inversely related to lipid oxidative damage: The EUROLIVE study. *J. Am. Coll. Nutr.* **27**:314–320.

Clarke, R., Harrison, G. and Richards, S. (2003). Effect of vitamins and aspirin on markers of platelet activation, oxidative stress and homocysteine in people at high risk of dementia. *J. Intern. Med.* **254**:67–75.

Covas, M. I., Nyyssonen, K., Poulsen, H. E., Kaikkonen, J., Zunft, H. J., Kiesewetter, H., Gaddi, A., de la Torre, R., Mursu, J., Baumler, H., Nascetti, S., Salonen, J. T., Fito, M., Virtanen, J. and Marrugat, J. (2006). The effect of polyphenols in olive oil on heart disease risk factors: A randomized trial. *Ann. Intern. Med.* **145**:333–341.

Crujeiras, A. B., Parra, D., Abete, I. and Martinez, J. A. (2007). A hypocaloric diet enriched in legumes specifically mitigates lipid peroxidation in obese subjects. *Free Radic. Res.* **41**:498–506.

Davì, G., Ciabattoni, G., Consoli, A., Mezzetti, A., Falco, A., Santarone, S., Pennese, E., Vitacolonna, E., Bucciarelli, T., Costantini, F., Capani, F. and Patrono, C. (1999). In vivo formation of 8-iso-prostaglandin f2alpha and platelet activation in diabetes mellitus: Effects of improved metabolic control and vitamin E supplementation. *Circulation*. **99**:224–229.

Davies, M. J., Judd, J. T., Baer, D. J., Clevidence, B. A., Paul, D. R., Edwards, A. J., Wiseman, S. A., Muesing, R. A. and Chen, S. C. (2003). Black tea consumption reduces total and LDL cholesterol in mildly hypercholesterolemic adults. *J. Nutr.* **133**:3298S–3302S.

Devaraj, S., Hirany, S. V., Burk, R. F. and Jialal, I. (2001). Divergence between LDL oxidative susceptibility and urinary F(2)-isoprostanes as measures of oxidative stress in type 2 diabetes. *Clin. Chem.* **47**:1974–1979.

Devaraj, S., Mathur, S., Basu, A., Aung, H. H., Vasu, V. T., Meyers, S. and Jialal, I. (2008). A dose-response study on the effects of purified lycopene supplementation on biomarkers of oxidative stress. *J. Am. Coll. Nutr.* **27**: 267–273.

Devaraj, S., Tang, R., Adams-Huet, B., Harris, A., Seenivasan, T., de Lemos, J. A. and Jialal, I. (2007). Effect of high-dose alpha-tocopherol supplementation on biomarkers of oxidative stress and inflammation and carotid atherosclerosis in patients with coronary artery disease. *Am. J. Clin. Nutr.* **86**:1392–1398.

Dhawan, V. and Jain, S. (2004). Effect of garlic supplementation on oxidized low density lipoproteins and lipid peroxidation in patients of essential hypertension. *Mol. Cell Biochem.* **266**:109–115.

Dietrich, M., Block, G., Benowitz, N. L., Morrow, J. D., Hudes, M., Jacob, P., 3rd, Norkus, E. P. and Packer, L. (2003). Vitamin C supplementation decreases oxidative stress biomarker f2-isoprostanes in plasma of nonsmokers exposed to environmental tobacco smoke. *Nutr. Cancer.* **45**:176–184.

Dietrich, M., Block, G., Hudes, M., Morrow, J. D., Norkus, E. P., Traber, M. G., Cross, C. E. and Packer, L. (2002). Antioxidant supplementation decreases lipid peroxidation biomarker F(2)-isoprostanes in plasma of smokers. *Cancer Epidemiol. Biomarkers Prev.* **11**:7–13.

Dillon, S. A., Lowe, G. M., Billington, D. and Rahman, K. (2002). Dietary supplementation with aged garlic extract reduces plasma and urine concentrations of 8-iso-prostaglandin F(2 alpha) in smoking and nonsmoking men and women. *J. Nutr.* **132**:168–171.

Djuric, Z., Chen, G., Doerge, D. R., Heilbrun, L. K. and Kucuk, O. (2001). Effect of soy isoflavone supplementation on markers of oxidative stress in men and women. *Cancer Lett.* **172**:1–6.

Donovan, J. L., DeVane, C. L., Chavin, K. D., Oates, J. C., Njoku, C., Patrick, K. S., Fiorini, R. N. and Markowitz, J. S. (2005). Oral administration of a decaffeinated green tea (Camellia sinensis) extract did not alter urinary 8-epi-prostaglandin F(2 alpha), a biomarker for in-vivo lipid peroxidation. *J. Pharm. Pharmacol.* **57**:1365–1369.

Dunstan, J. A., Breckler, L., Hale, J., Lehmann, H., Franklin, P., Lyons, G., Ching, S. Y., Mori, T. A., Barden, A. and Prescott, S. L. (2007). Supplementation with vitamins C, E, beta-carotene and selenium has no effect on anti-oxidant status and immune responses in allergic adults: A randomized controlled trial. *Clin. Exp. Allergy.* **37**:180–187.

Engler, M. B., Engler, M. M., Chen, C. Y., Malloy, M. J., Browne, A., Chiu, E. Y., Kwak, H. K., Milbury, P., Paul, S. M., Blumberg, J. and Mietus-Snyder, M. L. (2004). Flavonoid-rich dark chocolate improves endothelial function and increases plasma epicatechin concentrations in healthy adults. *J. Am. Coll. Nutr.* **23**:197–204.

Fam, S. S. and Morrow, J. D. (2003). The isoprostanes: Unique products of arachidonic acid oxidation-a review. *Curr. Med. Chem.* **10**:1723–1740.

Flammer, A. J., Hermann, F., Sudano, I., Spieker, L., Hermann, M., Cooper, K. A., Serafini, M., Luscher, T. F., Ruschitzka, F., Noll, G. and Corti, R. (2007). Dark chocolate improves coronary vasomotion and reduces platelet reactivity. *Circulation.* **116**:2376–2382.

Freese, R., Basu, S., Hietanen, E., Nair, J., Nakachi, K., Bartsch, H. and Mutanen, M. (1999). Green tea extract decreases plasma malondialdehyde concentration but does not affect other indicators of oxidative stress, nitric oxide production, or hemostatic factors during a high-linoleic acid diet in healthy females. *Eur. J. Nutr.* **38**:149–157.

Garg, M. L., Blake, R. J., Wills, R. B. and Clayton, E. H. (2007). Macadamia nut consumption modulates favourably risk factors for coronary artery disease in hypercholesterolemic subjects. *Lipids.* **42**:583–587.

Hall, W. L., Formanuik, N. L., Harnpanich, D., Cheung, M., Talbot, D., Chowienczyk, P. J. and Sanders, T. A. (2008). A meal enriched with soy isoflavones increases nitric oxide-mediated vasodilation in healthy postmenopausal women. *J. Nutr.* **138**:1288–1292.

Himmelfarb, J., Phinney, S., Ikizler, T. A., Kane, J., McMonagle, E. and Miller, G. (2007). Gamma-tocopherol and docosahexaenoic acid decrease inflammation in dialysis patients. *J. Ren Nutr.* **17**:296–304.

Hirano-Ohmori, R., Takahashi, R., Momiyama, Y., Taniguchi, H., Yonemura, A., Tamai, S., Umegaki, K., Nakamura, H., Kondo, K. and Ohsuzu, F. (2005). Green tea consumption and serum malondialdehyde-modified LDL concentrations in healthy subjects. *J. Am. Coll. Nutr.* **24**:342–346.

Hodgson, J. M., Croft, K. D., Mori, T. A., Burke, V., Beilin, L. J. and Puddey, I. B. (2002a). Regular ingestion of tea does not inhibit in vivo lipid peroxidation in humans. *J. Nutr.* **132**:55–58.

Hodgson, J. M., Puddey, I. B., Burke, V., Watts, G. F. and Beilin, L. J. (2002b). Regular ingestion of black tea improves brachial artery vasodilator function. *Clin. Sci. (Lond).* **102**:195–201.

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

Huang, H. Y., Appel, L. J., Croft, K. D., Miller, E. R., 3rd, Mori, T. A. and Puddey, I. B. (2002). Effects of vitamin C and vitamin E on in vivo lipid peroxidation: Results of a randomized controlled trial. *Am. J. Clin. Nutr.* **76**:549–555.

Jacob, R. A., Aiello, G. M., Stephensen, C. B., Blumberg, J. B., Milbury, P. E., Wallock, L. M. and Ames, B. N. (2003). Moderate antioxidant supplementation has no effect on biomarkers of oxidant damage in healthy men with low fruit and vegetable intakes. *J. Nutr.* **133**:740–743.

Jacob, K., Periago, M. J., Bohm, V. and Berruezo, G. R. (2008). Influence of lycopene and vitamin C from tomato juice on biomarkers of oxidative stress and inflammation. *Br. J. Nutr.* **99**:137–146.

Jenkins, D. J., Kendall, C. W., Marchie, A., Josse, A. R., Nguyen, T. H., Faulkner, D. A., Lapsley, K. G. and Blumberg, J. (2008). Almonds reduce biomarkers of lipid peroxidation in older hyperlipidemic subjects. *J. Nutr.* **138**:908–913.

Kadiiska, M. B., Gladen, B. C., Baird, D. D., Germolec, D., Graham, L. B., Parker, C. E., Nyska, A., Wachsman, J. T., Ames, B. N., Basu, S., Brot, N., Fitzgerald, G. A., Floyd, R. A., George, M., Heinecke, J. W., Hatch, G. E., Hensley, K., Lawson, J. A., Marnett, L. J., Morrow, J. D., Murray, D. M., Plastaras, J., Roberts, L. J., 2nd, Rokach, J., Shigenaga, M. K., Sohal, R. S., Sun, J., Tice, R. R., Van Thiel, D. H., Wellner, D., Walter, P. B., Tomer, K. B., Mason, R. P. and Barrett, J. C. (2005). Biomarkers of oxidative stress study II: Are oxidation products of lipids, proteins, and DNA markers of CCl4 poisoning? *Free Radic. Biol. Med.* **38**:698–710.

Kamgar, M., Zaldivar, F., Vaziri, N. D. and Pahl, M. V. (2009). Antioxidant therapy does not ameliorate oxidative stress and inflammation in patients with end-stage renal disease. *J. Natl. Med. Assoc.* **101**:336–344.

Keith, M. E., Jeejeebhoy, K. N., Langer, A., Kurian, R., Barr, A., O'Kelly, B. and Sole, M. J. (2001). A controlled clinical trial of vitamin E supplementation in patients with congestive heart failure. *Am. J. Clin. Nutr.* **73**:219–224.

Kelly, R. P., Poo Yeo, K., Isaac, H. B., Lee, C. Y., Huang, S. H., Teng, L., Halliwell, B. and Wise, S. D. (2008). Lack of effect of acute oral ingestion of vitamin C on oxidative stress, arterial stiffness or blood pressure in healthy subjects. *Free Radic. Res.* **42**:514–522.

Kempf, K., Herder, C., Erlund, I., Kolb, H., Martin, S., Carstensen, M., Koenig, W., Sundvall, J., Bidel, S., Kuha, S. and Tuomilehto, J. (2010). Effects of coffee consumption on subclinical inflammation and other risk factors for type 2 diabetes: A clinical trial. *Am. J. Clin. Nutr.* **91**:950–957.

Kendall, M., Batterham, M., Obied, H., Prenzler, P. D., Ryan, D. and Robards, K. (2009). Zero effect of multiple dosage of olive leaf supplements on urinary biomarkers of oxidative stress in healthy humans. *Nutrition.* **25**:270–280.

Khadem-Ansari, M. H., Shahsavari, Z., Rasmi, Y. and Mahmoodlo, R. (2011). Elevated levels of urinary 8-hydroxy-2′-deoxyguanosine and 8-isoprostane in esophageal squamous cell carcinoma. *J. Carcinog.* **10**:14.

Kinlay, S., Behrendt, D., Fang, J. C., Delagrange, D., Morrow, J., Witztum, J. L., Rifai, N., Selwyn, A. P., Creager, M. A. and Ganz, P. (2004). Long-term effect of combined vitamins E and C on coronary and peripheral endothelial function. *J. Am. Coll. Cardiol.* **43**:629–634.

Koyama, N., Suzuki, K., Furukawa, Y., Arisaka, H., Seki, T., Kuribayashi, K., Ishii, K., Sukegawa, E. and Takahashi, M. (2009). Effects of safflower seed extract supplementation on oxidation and cardiovascular risk markers in healthy human volunteers. *Br. J. Nutr.* **101**:568–575.

Lee, C. Y., Isaac, H. B., Huang, S. H., Long, L. H., Wang, H., Gruber, J., Ong, C. N., Kelly, R. P. and Halliwell, B. (2009). Limited antioxidant effect after consumption of a single dose of tomato sauce by young males, despite a rise in plasma lycopene. *Free Radic. Res.* **43**:622–628.

Lee, C. Y., Isaac, H. B., Wang, H., Huang, S. H., Long, L. H., Jenner, A. M., Kelly, R. P. and Halliwell, B. (2006). Cautions in the use of biomarkers of oxidative damage; the vascular and antioxidant effects of dark soy sauce in humans. *Biochem. Biophys. Res. Commun.* **344**:906–911.

Loke, W. M., Hodgson, J. M., Proudfoot, J. M., McKinley, A. J., Puddey, I. B. and Croft, K. D. (2008). Pure dietary flavonoids quercetin and (−)-epicatechin augment nitric oxide products and reduce endothelin-1 acutely in healthy men. *Am. J. Clin. Nutr.* **88**:1018–1025.

Mastaloudis, A., Morrow, J. D., Hopkins, D. W., Devaraj, S. and Traber, M. G. (2004). Antioxidant supplementation prevents exercise-induced lipid peroxidation, but not inflammation, in ultramarathon runners. *Free Radic. Biol. Med.* **36**:1329–1341.

Mathur, S., Devaraj, S., Grundy, S. M. and Jialal, I. (2002). Cocoa products decrease low density lipoprotein oxidative susceptibility but do not affect biomarkers of inflammation in humans. *J. Nutr.* **132**:3663–3667.

McAnulty, S. R., McAnulty, L. S., Morrow, J. D., Khardouni, D., Shooter, L., Monk, J., Gross, S. and Brown, V. (2005). Effect of daily fruit ingestion on angiotensin converting enzyme activity, blood pressure and oxidative stress in chronic smokers. *Free Radic. Res.* **39**:1241–1248.

Meagher, E. A., Barry, O. P., Lawson, J. A., Rokach, J. and FitzGerald, G. A. (2001). Effects of vitamin E on lipid peroxidation in healthy persons. *JAMA.* **285**:1178–1182.

Miller, E. R., 3rd, Erlinger, T. P., Sacks, F. M., Svetkey, L. P., Charleston, J., Lin, P. H. and Appel, L. J. (2005). A dietary pattern that lowers oxidative stress increases antibodies to oxidized LDL: Results from a randomized controlled feeding study. *Atherosclerosis.* **183**:175–182.

Milne, G. L., Yin, H., Brooks, J. D., Sanchez, S., Jackson Roberts, L., 2nd and Morrow, J. D. (2007). Quantification of F2-isoprostanes in biological fluids and tissues as a measure of oxidant stress. *Methods Enzymol*. **433**:113–126.

Montuschi, P., Barnes, P. and Roberts, L. J., 2nd. (2007). Insights into oxidative stress: The isoprostanes. *Curr. Med. Chem.* **14**:703–717.

Morrow, J. D., Hill, K. E., Burk, R. F., Nammour, T. M., Badr, K. F. and Roberts, L. J., 2nd. (1990). A series of prostaglandin F2-like compounds are produced in vivo in humans by a non-cyclooxygenase, free radical-catalyzed mechanism. *Proc. Natl. Acad. Sci. USA*. **87**:9383–9387.

Murphy, K. J., Chronopoulos, A. K., Singh, I., Francis, M. A., Moriarty, H., Pike, M. J., Turner, A. H., Mann, N. J. and Sinclair, A. J. (2003). Dietary flavanols and procyanidin oligomers from cocoa (Theobroma cacao) inhibit platelet function. *Am. J. Clin. Nutr.* **77**:1466–1473.

Mursu, J., Voutilainen, S., Nurmi, T., Rissanen, T. H., Virtanen, J. K., Kaikkonen, J., Nyyssonen, K. and Salonen, J. T. (2004). Dark chocolate consumption increases HDL cholesterol concentration and chocolate fatty acids may inhibit lipid peroxidation in healthy humans. *Free Radic. Biol. Med.* **37**:1351–1359.

Mustad, V. A., Smith, C. A., Ruey, P. P., Edens, N. K. and DeMichele, S. J. (2002). Supplementation with 3 compositionally different tocotrienol supplements does not improve cardiovascular disease risk factors in men and women with hypercholesterolemia. *Am. J. Clin. Nutr.* **76**:1237–1243.

Nhan, S., Anderson, K. E., Nagamani, M., Grady, J. J. and Lu, L. J. (2005). Effect of a soymilk supplement containing isoflavones on urinary F2 isoprostane levels in premenopausal women. *Nutr. Cancer.* **53**:73–81.

Nitta, H., Kinoyama, M., Watanabe, A., Shirao, K., Kihara, H. and Arai, M. (2007). Effects of nutritional supplementation with antioxidant vitamins and minerals and fish oil on antioxidant status and psychosocial stress in smokers: An open trial. *Clin. Exp. Med.* **7**:179–183.

O'Byrne, D. J., Devaraj, S., Grundy, S. M. and Jialal, I. (2002). Comparison of the antioxidant effects of Concord grape juice flavonoids alpha-tocopherol on markers of oxidative stress in healthy adults. *Am. J. Clin. Nutr.* **76**:1367–1374.

Ochiai, R., Chikama, A., Kataoka, K., Tokimitsu, I., Maekawa, Y., Ohishi, M., Rakugi, H. and Mikami, H. (2009). Effects of hydroxyhydroquinone-reduced coffee on vasoreactivity and blood pressure. *Hypertens Res.* **32**:969–974.

O'Reilly, J. D., Mallet, A. I., McAnlis, G. T., Young, I. S., Halliwell, B., Sanders, T. A. and Wiseman, H. (2001). Consumption of flavonoids in onions and black tea: Lack of effect on F2-isoprostanes and autoantibodies to oxidized LDL in healthy humans. *Am. J. Clin. Nutr.* **73**:1040–1044.

Patrignani, P., Panara, M. R., Tacconelli, S., Seta, F., Bucciarelli, T., Ciabattoni, G., Alessandrini, P., Mezzetti, A., Santini, G., Sciulli, M. G., Cipollone, F., Davi, G., Gallina, P., Bon, G. B. and Patrono, C. (2000). Effects of vitamin E supplementation on F(2)-isoprostane and thromboxane biosynthesis in healthy cigarette smokers. *Circulation*. **102**:539–545.

Pignatelli, P., Ghiselli, A., Buchetti, B., Carnevale, R., Natella, F., Germano, G., Fimognari, F., Di Santo, S., Lenti, L. and Violi, F. (2006). Polyphenols synergistically inhibit oxidative stress in subjects given red and white wine. *Atherosclerosis*. **188**:77–83.

Pitsavos, C., Panagiotakos, D. B., Tzima, N., Chrysohoou, C., Economou, M., Zampelas, A. and Stefanadis, C. (2005). Adherence to the Mediterranean diet is associated with total antioxidant capacity in healthy adults: The ATTICA study. *Am. J. Clin. Nutr.* **82**:694–699.

Rankin, J. W., Andreae, M. C., Oliver Chen, C. Y. and O'Keefe, S. F. (2008). Effect of raisin consumption on oxidative stress and inflammation in obesity. *Diabetes Obes. Metab.* **10**:1086–1096.

Rautiainen, S., Serafini, M., Morgenstern, R., Prior, R. L. and Wolk, A. (2008). The validity and reproducibility of food-frequency questionnaire-based total antioxidant capacity estimates in Swedish women. *Am. J. Clin. Nutr.* **87**:1247–1253.

Razquin, C., Martinez, J. A., Martinez-Gonzalez, M. A., Mitjavila, M. T., Estruch, R. and Marti, A. (2009). A 3 years follow-up of a Mediterranean diet rich in virgin olive oil is associated with high plasma antioxidant capacity and reduced body weight gain. *Eur. J. Clin. Nutr.* **63**:1387–1393.

Reilly, M., Delanty, N., Lawson, J. A. and FitzGerald, G. A. (1996). Modulation of oxidant stress in vivo in chronic cigarette smokers. *Circulation*. **94**:19–25.

Richelle, M., Turini, M. E., Guidoux, R., Tavazzi, I., Metairon, S. and Fay, L. B. (1999). Urinary isoprostane excretion is not confounded by the lipid content of the diet. *FEBS Lett.* **459**:259–262.

Riso, P., Visioli, F., Grande, S., Guarnieri, S., Gardana, C., Simonetti, P. and Porrini, M. (2006). Effect of a tomato-based drink on markers of inflammation, immunomodulation, and oxidative stress. *J. Agric. Food Chem.* **54**:2563–2566.

Rizzo, M. R., Abbatecola, A. M., Barbieri, M., Vietri, M. T., Cioffi, M., Grella, R., Molinari, A., Forsey, R., Powell, J. and Paolisso, G. (2008). Evidence for anti-inflammatory effects of combined administration of vitamin E and C in older persons with impaired fasting glucose: Impact on insulin action. *J. Am. Coll. Nutr.* **27**:505–511.

Roberts, L. J. and Morrow, J. D. (2000). Measurement of F(2)-isoprostanes as an index of oxidative stress in vivo. *Free Radic. Biol. Med.* **28**:505–513.

Roberts, L. J., 2nd, Oates, J. A., Linton, M. F., Fazio, S., Meador, B. P., Gross, M. D., Shyr, Y. and Morrow, J. D. (2007). The relationship between dose of vitamin E and suppression of oxidative stress in humans. *Free Radic. Biol. Med.* **43**:1388–1393.

Rodrigo, R., Prat, H., Passalacqua, W., Araya, J. and Bachler, J. P. (2008). Decrease in oxidative stress through supplementation of vitamins C and E is associated with a reduction in blood pressure in patients with essential hypertension. *Clin. Sci. (Lond).* **114**:625–634.

Rokach, J., Khanapure, S. P., Hwang, S. W., Adiyaman, M., Lawson, J. A. and FitzGerald, G. A. (1997). Nomenclature of isoprostanes: A proposal. *Prostaglandins*. **54**:853–873.

Ryan, J., Croft, K., Mori, T., Wesnes, K., Spong, J., Downey, L., Kure, C., Lloyd, J. and Stough, C. (2008). An examination of the effects of the antioxidant Pycnogenol on cognitive performance, serum lipid profile, endocrinological and oxidative stress biomarkers in an elderly population. *J. Psychopharmacol.* **22**:553–562.

Ryan-Borchers, T. A., Park, J. S., Chew, B. P., McGuire, M. K., Fournier, L. R. and Beerman, K. A. (2006). Soy isoflavones modulate immune function in healthy postmenopausal women. *Am. J. Clin. Nutr.* **83**:1118–1125.

Sacks, F. M., Svetkey, L. P., Vollmer, W. M., Appel, L. J., Bray, G. A., Harsha, D., Obarzanek, E., Conlin, P. R., Miller, E. R., 3rd, Simons-Morton, D. G., Karanja, N. and Lin, P. H. (2001). Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. *N. Engl. J. Med.* **344**:3–10.

Sanchez-Moreno, C., Cano, M. P., de Ancos, B., Plaza, L., Olmedilla, B., Granado, F., Elez-Martinez, P., Martin-Belloso, O. and Martin, A. (2004a). Pulsed electric fields-processed orange juice consumption increases plasma vitamin C and decreases F2-isoprostanes in healthy humans. *J. Nutr. Biochem.* **15**:601–607.

Sanchez-Moreno, C., Cano, M. P., de Ancos, B., Plaza, L., Olmedilla, B., Granado, F. and Martin, A. (2003a). Effect of orange juice intake on vitamin C concentrations and biomarkers of antioxidant status in humans. *Am. J. Clin. Nutr.* **78**:454–460.

Sanchez-Moreno, C., Cano, M. P., de Ancos, B., Plaza, L., Olmedilla, B., Granado, F. and Martin, A. (2003b). High-pressurized orange juice consumption affects plasma vitamin C, antioxidative status and inflammatory markers in healthy humans. *J. Nutr.* **133**:2204–2209.

Sanchez-Moreno, C., Cano, M. P., de Ancos, B., Plaza, L., Olmedilla, B., Granado, F. and Martin, A. (2004b). Consumption of high-pressurized vegetable soup increases plasma vitamin C and decreases oxidative stress and inflammatory biomarkers in healthy humans. *J. Nutr.* **134**:3021–3025.

Sanchez-Moreno, C., Cano, M. P., de Ancos, B., Plaza, L., Olmedilla, B., Granado, F. and Martin, A. (2006). Mediterranean vegetable soup consumption increases plasma vitamin C and decreases F2-isoprostanes, prostaglandin E2 and monocyte chemotactic protein-1 in healthy humans. *J. Nutr. Biochem.* **17**:183–189.

Santus, P., Sola, A., Carlucci, P., Fumagalli, F., Di Gennaro, A., Mondoni, M., Carnini, C., Centanni, S. and Sala, A. (2005). Lipid peroxidation and 5-lipoxygenase activity in chronic obstructive pulmonary disease. *Am. J. Respir Crit. Care Med.* **171**:838–843.

Saran, R., Novak, J. E., Desai, A., Abdulhayoglu, E., Warren, J. S., Bustami, R., Handelman, G. J., Barbato, D., Weitzel, W., D'Alecy, L. G. and

Rajagopalan, S. (2003). Impact of vitamin E on plasma asymmetric dimethylarginine (ADMA) in chronic kidney disease (CKD): A pilot study. *Nephrol. Dial Transplant.* **18**:2415–2420.

Serafini, M. and Del Rio, D. (2004). Understanding the association between dietary antioxidants, redox status and disease: Is the total antioxidant capacity the right tool? *Redox. Rep.* **9**:145–152.

Serafini, M., Miglio, C., Peluso, I. and Petrosino, T. (2011). Modulation of plasma non enzymatic antioxidant capacity (NEAC) by plant foods: The role of polyphenols. *Curr. Top Med. Chem.* **11**:1821–1846.

Shanely, R. A., Knab, A. M., Nieman, D. C., Jin, F., McAnulty, S. R. and Landram, M. J. (2010). Quercetin supplementation does not alter antioxidant status in humans. *Free Radic. Res.* **44**:224–231.

Shiina, Y., Funabashi, N., Lee, K., Murayama, T., Nakamura, K., Wakatsuki, Y., Daimon, M. and Komuro, I. (2009). Acute effect of oral flavonoid-rich dark chocolate intake on coronary circulation, as compared with non-flavonoid white chocolate, by transthoracic Doppler echocardiography in healthy adults. *Int. J. Cardiol.* **131**:424–429.

Simons, L. A., von Konigsmark, M., Simons, J., Stocker, R. and Celermajer, D. S. (1999). Vitamin E ingestion does not improve arterial endothelial dysfunction in older adults. *Atherosclerosis.* **143**:193–199.

Stewart, R. J., Askew, E. W., McDonald, C. M., Metos, J., Jackson, W. D., Balon, T. W. and Prior, R. L. (2002). Antioxidant status of young children: Response to an antioxidant supplement. *J. Am. Diet Assoc.* **102**:1652–1657.

Sutherland, W. H., Manning, P. J., Walker, R. J., de Jong, S. A., Ryalls, A. R. and Berry, E. A. (2007). Vitamin E supplementation and plasma 8-isoprostane and adiponectin in overweight subjects. *Obesity (Silver Spring).* **15**:386–391.

Taber, D. F., Morrow, J. D. and Roberts, L. J., 2nd (1997). A nomenclature system for the isoprostanes. *Prostaglandins.* **53**:63–67.

Taubert, D., Roesen, R., Lehmann, C., Jung, N. and Schomig, E. (2007). Effects of low habitual cocoa intake on blood pressure and bioactive nitric oxide: A randomized controlled trial. *JAMA.* **298**:49–60.

Tesoriere, L., Butera, D., Pintaudi, A. M., Allegra, M. and Livrea, M. A. (2004). Supplementation with cactus pear (Opuntia ficus-indica) fruit decreases oxidative stress in healthy humans: A comparative study with vitamin C. *Am. J. Clin. Nutr.* **80**:391–395.

Thompson, H. J., Heimendinger, J., Haegele, A., Sedlacek, S. M., Gillette, C., O'Neill, C., Wolfe, P. and Conry, C. (1999). Effect of increased vegetable and fruit consumption on markers of oxidative cellular damage. *Carcinogenesis.* **20**:2261–2266.

Thompson, H. J., Heimendinger, J., Sedlacek, S., Haegele, A., Diker, A., O'Neill, C., Meinecke, B., Wolfe, P., Zhu, Z. and Jiang, W. (2005). 8-Isoprostane F2alpha excretion is reduced in women by increased vegetable and fruit intake. *Am. J. Clin. Nutr.* **82**:768–776.

Traustadottir, T., Davies, S. S., Stock, A. A., Su, Y., Heward, C. B., Roberts, L. J., 2nd and Harman, S. M. (2009). Tart cherry juice decreases oxidative stress in healthy older men and women. *J. Nutr.* **139**:1896–1900.

Upritchard, J. E., Schuurman, C. R., Wiersma, A., Tijburg, L. B., Coolen, S. A., Rijken, P. J. and Wiseman, S. A. (2003). Spread supplemented with moderate doses of vitamin E and carotenoids reduces lipid peroxidation in healthy, nonsmoking adults. *Am. J. Clin. Nutr.* **78**:985–992.

van den Berg, R., van Vliet, T., Broekmans, W. M., Cnubben, N. H., Vaes, W. H., Roza, L., Haenen, G. R., Bast, A. and van den Berg, H. (2001). A vegetable/fruit concentrate with high antioxidant capacity has no effect on biomarkers of antioxidant status in male smokers. *J. Nutr.* **131**:1714–1722.

Vega-Lopez, S., Yeum, K. J., Lecker, J. L., Ausman, L. M., Johnson, E. J., Devaraj, S., Jialal, I. and Lichtenstein, A. H. (2005). Plasma antioxidant capacity in response to diets high in soy or animal protein with or without isoflavones. *Am. J. Clin Nutr.* **81**:43–49.

Visioli, F., Alarcon de la Lastra, C., Andres-Lacueva, C., Aviram, M., Calhau, C., Cassano, A., D'Archivio, M., Faria, A., Favé, G., Fogliano, V., Llorach, R., Vitaglione, P., Zoratti, M. and Edeas, M. (2011). Polyphenols and human health: A prospectus. *Crit. Rev. Food Sci. Nutr.* **51**:524–546.

Visioli, F., Caruso, D., Galli, C., Viappiani, S., Galli, G. and Sala, A. (2000). Olive oils rich in natural catecholic phenols decrease isoprostane excretion in humans. *Biochem. Biophys. Res. Commun.* **278**:797–799.

Visioli, F., Caruso, D., Grande, S., Bosisio, R., Villa, M., Galli, G., Sirtori, C. and Galli, C. (2005). Virgin Olive Oil Study (VOLOS): Vasoprotective potential of extra virgin olive oil in mildly dyslipidemic patients. *Eur. J. Nutr.* **44**:121–127.

Visioli, F., Riso, P., Grande, S., Galli, C. and Porrini, M. (2003). Protective activity of tomato products on in vivo markers of lipid oxidation. *Eur. J. Nutr.* **42**:201–206.

Wang, J. F., Schramm, D. D., Holt, R. R., Ensunsa, J. L., Fraga, C. G., Schmitz, H. H. and Keen, C. L. (2000). A dose-response effect from chocolate consumption on plasma epicatechin and oxidative damage. *J. Nutr.* **130**:2115S–2119S.

Ward, N. C., Hodgson, J. M., Croft, K. D., Burke, V., Beilin, L. J. and Puddey, I. B. (2005). The combination of vitamin C and grape-seed polyphenols increases blood pressure: A randomized, double-blind, placebo-controlled trial. *J. Hypertens.* **23**:427–434.

Weisel, T., Baum, M., Eisenbrand, G., Dietrich, H., Will, F., Stockis, J. P., Kulling, S., Rufer, C., Johannes, C. and Janzowski, C. (2006). An anthocyanin/polyphenolic-rich fruit juice reduces oxidative DNA damage and increases glutathione level in healthy probands. *Biotechnol. J.* **1**:388–397.

Widlansky, M. E., Duffy, S. J., Hamburg, N. M., Gokce, N., Warden, B. A., Wiseman, S., Keaney, J. F., Jr., Frei, B. and Vita, J. A. (2005). Effects of black tea consumption on plasma catechins and markers of oxidative stress and inflammation in patients with coronary artery disease. *Free Radic. Biol. Med.* **38**:499–506.

Wiseman, H., O'Reilly, J. D., Adlercreutz, H., Mallet, A. I., Bowey, E. A., Rowland, I. R. and Sanders, T. A. (2000). Isoflavone phytoestrogens consumed in soy decrease F(2)-isoprostane concentrations and increase resistance of low-density lipoprotein to oxidation in humans. *Am. J. Clin. Nutr.* **72**:395–400.

Wiswedel, I., Hirsch, D., Kropf, S., Gruening, M., Pfister, E., Schewe, T. and Sies, H. (2004). Flavanol-rich cocoa drink lowers plasma F(2)-isoprostane concentrations in humans. *Free Radic. Biol. Med.* **37**:411–421.

Wolfram, R. M., Oguogho, A., Efthimiou, Y., Budinsky, A. C. and Sinzinger, H. (2002). Effect of black tea on (iso-)prostaglandins and platelet aggregation in healthy volunteers. *Prostaglandins Leukot Essent Fatty Acids.* **66**:529–533.

Wood, L. G., Fitzgerald, D. A., Lee, A. K. and Garg, M. L. (2003). Improved antioxidant and fatty acid status of patients with cystic fibrosis after antioxidant supplementation is linked to improved lung function. *Am. J. Clin. Nutr.* **77**:150–159.

Wu, J. H., Hodgson, J. M., Puddey, I. B., Belski, R., Burke, V. and Croft, K. D. (2009). Sesame supplementation does not improve cardiovascular disease risk markers in overweight men and women. *Nutr. Metab. Cardiovasc. Dis.* **19**:774–780.

Wu, J. H., Ward, N. C., Indrawan, A. P., Almeida, C. A., Hodgson, J. M., Proudfoot, J. M., Puddey, I. B. and Croft, K. D. (2007). Effects of alpha-tocopherol and mixed tocopherol supplementation on markers of oxidative stress and inflammation in type 2 diabetes. *Clin. Chem.* **53**:511–519.

Yang, X., Croft, K. D., Lee, Y. P., Mori, T. A., Puddey, I. B., Sipsas, S., Barden, A., Swinny, E. and Hodgson, J. M. (2010). The effects of a lupin-enriched diet on oxidative stress and factors influencing vascular function in overweight subjects. *Antioxid Redox Signal.* **13**:1517–1524.

Zern, T. L., Wood, R. J., Greene, C., West, K. L., Liu, Y., Aggarwal, D., Shachter, N. S. and Fernandez, M. L. (2005). Grape polyphenols exert a cardioprotective effect in pre- and postmenopausal women by lowering plasma lipids and reducing oxidative stress. *J. Nutr.* **135**:1911–1917.