Current Pharmaceutical Design, 2016, *22*, 6701-6715

REVIEW ARTICLE

Functional Foods for Health: The Interrelated Antioxidant and Anti-Inflammatory Role of Fruits, Vegetables, Herbs, Spices and Cocoa in Humans

Mauro Serafini* and Ilaria Peluso

Functional Foods and Metabolic Stress Prevention Laboratory, Centre for Food and Nutrition, Council for Agricultural Research and Economics, Rome, Italy

ARTICLE HISTORY

Received: September 8, 2015
Accepted: November 15, 2016

DOI: 10.2174/1381612823666161123094235

Abstract: The health benefits of plant food-based diets could be related to both integrated antioxidant and anti-inflammatory mechanisms exerted by a wide array of phytochemicals present in fruit, vegetables, herbs and spices. Therefore, there is mounting interest in identifying foods, food extracts and phytochemical formulations from plant sources which are able to efficiently modulate oxidative and inflammatory stress to prevent diet-related diseases. This paper reviews available evidence about the effect of supplementation with selected fruits, vegetables, herbs, spices and their extracts or galenic formulation on combined markers of redox and inflammatory status in humans.

Keywords: Antioxidants, human, functional foods, inflammation, oxidative stress, plant foods.

1. INTRODUCTION

The regulation of endogenous antioxidant defences, including superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX), involves the interaction with antioxidant responsive elements (ARE) which are present in the promoter regions of most of the genes inducible by oxidative stress [1]. In particular, nuclear factor-erythroid 2-related factor 2 (Nrf2) is the transcription factor responsible for both constitutive and inducible expression of ARE-regulated genes [2]. Under physiological conditions, Nrf2 is bound to kelch-like protein-1 (KEAP1) and is thereby sequestered in the cytoplasm; however, in the presence of oxidative stress, Nrf2 dissociates from KEAP1, translocates into the nucleus and induces the transcription of antioxidant enzymes. Oxidative stress represents also a key stimulus for the activation of nuclear factor- kappa B (NF-κB), which appears in the cytoplasm of non-stimulated cells forming a complex with its inhibitor IκB. Following stimulation, NF-κB is activated by phosphorylation and degradation of IκB, thus migrating to the nucleus, stimulating gene expression and inducing the synthesis of inflammatory cytokines. The close link between oxidative and inflammatory stress in the mechanisms of body defences against stress, is further highlighted in the oxidative burst of leucocytes, the innate immune response involving the activation of NADPH-oxidase (NOX) and myeloperoxidase (MPO) yielding a massive production of Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) [3]. However, the presence of an excessive and uncontrolled ROS and cytokines production, a condition defined as "low-grade chronic inflammation" takes place and is associated with pre-pathological conditions such as obesity and degenerative diseases [4, 5].

Inflammatory and oxidative stress can rise also as a direct consequence of unbalanced dietary life style, such as the ingestion of high fat and high carbohydrate meals [6, 7]. Increase in post-prandial lipopolysaccharide (LPS) and Toll-like receptor-4 (TLR4) is associated with increased levels of inflammatory cytokines, such as interleukin (IL)-6, IL-17 and tumor necrosis factor-alpha (TNF-α) [8], which in turn activate oxidative burst [9]. Given these premises, the importance of the diet, as inducer or preventer of inflammatory and oxidative stress, is paramount.

A large body of epidemiological and clinical evidence provides a solid rationale for the health benefits of diets based on foods of vegetable origin [10], thanks to their content of bioactive ingredients such as vitamins and flavonoids. In fact, flavonoids and their metabolites, in addition to their direct free radical scavenging capacity [11], impair the production of ROS and RNS by neutrophils and other phagocytic cells through the inhibition of NOX, MPO and inducible-Nitric Oxide Synthases (iNOS) [3]. However, herbs and spices used for culinary purposes also represent an excellent, source of phytochemicals [12, 13]. Antioxidant and anti-inflammatory activities have been reported in vitro and in animal models for ginger (*Zingiber officinale*) [14], milk thistle (*Silybum marianum*) [15], hawthorn (*Crataegus monogyna*) [16, 17], passion flower (*Passiflora edulis*) [18] and chamomile (*Matricaria chamomilla*) [19, 20]. Therefore the health benefits of plant food-based diets could be related to both integrated antioxidant and anti-inflammatory mechanisms exerted by a wide array of phytochemicals present in fruit, vegetables, herbs and spices [21-24]. On this basis, there is mounting interest in identifying foods, food extracts and phytochemicals formulations from plant sources which are able to efficiently modulate oxidative and inflammatory stress to prevent diet-related diseases [25]. This paper reviews available evidence about the effect of supplementation with selected fruits, vegetables, herbs, spices, cocoa, beverages with mixed plant food composition as well as extracts and galenic formulation, on combined markers of redox and inflammatory status in humans.

2. OVERVIEW OF IDENTIFIED STUDIES

We performed a search on MEDLINE and Google Scholar Databases for literature of human studies by using the search terms: (fruit* OR vegetable* OR herb* OR spice* OR cocoa) AND antioxidant AND (cytokines OR CRP) AND (subjects OR patients).

A total of 88 interventions from 74 studies reporting both markers of redox/oxidative and inflammatory status after consumption of plant-derived products were collected. Dietary interventions were grouped according to different categories, specifically vegetables

*Address correspondence to this author at the Functional Foods and Metabolic Stress Prevention Laboratory, Centre for Food and Nutrition, Council for Agricultural Research and Economics, Via Ardeatina 546, 00176 Rome, Italy; Tel: +39-065149451; E-mail: serafini_mauro@yahoo.it

1873-4286/16 $58.00+.00

Table 1. Overview of the reviewed intervention studies with vegetables and vegetable extracts in humans: characteristics, study design and effect on markers of redox, oxidative and inflammatory status.

Treatment	Dose/day Standardization	Subjects (healthy status and no.)	Study design and duration	Markers of red-ox/ oxidative status	Markers of inflammatory status	Refs.
Carrot (juice)	16 fl oz	Healthy 17	Longitudinal, 3 months	NEAC↑ MDA↓	CRP and IL-1↔	[26]
Tomato (juice)	280 ml (11.6 mg of lycopene/100 ml)	Healthy women 25	Longitudinal, 2 months	TBARS ↓ NEAC ↔	Adiponectin ↑	[27]
Tomato-derived Lyc-O-Mato (capsules)	45 mg lycopene	Asthmatic 79	Parallel, 14 weeks	IsoP↔	CRP ↑ IL-6, IL-8 and TNF-α ↔	[28]
Tomato-derived Lyc-O-Mato (capsules).	30 mg lycopene	Obese 8	Longitudinal, 4 weeks	Dienes ↔	CRP, TNF-α and IL-6 ↔	[29]
Tomato-derived Lyc-O-Mato (drink).	250 ml (5.7 mg of lycopene, 3.7 mg of phytoene, 2.7 mg of phytofluene, 1 mg of β-carotene, and 1.8 mg α-tocopherol)	Healthy 26	Crossover, 26 days	IsoP↔	TNF-α and IFN-γ ex vivo ↓	[30]
Tomato-derived Lyc-O-Mato (extract)	80 mg lycopene	Healthy 18 males	Longitudinal, 1 week; postprandial (3h)	MDA ↔ MDA ↔	CRP↔ CRP↔	[31]

CRP: C reactive protein; IFN-γ: interferon gamma; IL: interleukin; IsoP: isoprostanes; MDA: malondialdehyde; NEAC: non-enzymatic antioxidant capacity; TBARS: thiobarbituric acid reactive substances; TNF-α: tumor necrosis factor alfa.

(Table **1**) [26-31], fruits (Table **2**) [32-54], grape seeds (Table **3**) [55-59], herbs (Table **4**) [60-65], green tea (Table **5**) [66-70], spices (Table **6**) [71-78], beverages with mixed composition (Table **7**) [8, 79-82] extracts with mixed composition (Table **8**) [83-93] and cocoa products (Table **9**) [66, 94-97]. Selection of the plant foods was performed on the basis of available human data on both oxidative and inflammatory markers: for example, raspberry, blackberry and olives were not included due to the lack of combined information. Of these interventions, 69 were given over a long-term (from five days to 1 year). Studies were extremely variable in their experimental design: 44 were parallel, 17 were cross-over and 13 were longitudinal studies. The number of participants enrolled in individual trials ranged from 8 [29, 45] to 121 [73], and enrolled subjects were characterized by extremely variable features and health status: either healthy subjects or patients with asthma, cancer, infections, hemodialysis, rheumatoid arthritis, sepsis, acute respiratory distress syndrome, cardiovascular disease (CVD, hypertension, diabetes, dyslipidemia and metabolic syndrome and subjects with risk factors for CVD (i.e. smoking habit, overweight/obesity, old age). A limited number of studies evaluated the effect of the tested product in acute models of oxidative stress such as postprandial status (high energy meal, two studies) or physical exercise (five studies).

As expected, multiple biomarkers were used to monitor different aspects of redox/oxidative and inflammatory status in biological fluids and cells. Markers of redox status included non- enzymatic antioxidant capacity (NEAC, n=29), reduced glutathione (GSH, n=8) or ratio of reduced/oxidized glutathione (GSH/GSSG) (n=1), antioxidant enzymes (n=29) (e.g. SOD, CAT and GPX), markers of lipid peroxidation (n=77) [i.e. oxidized low density lipoproteins (oxLDL), isoprostanes (IsoP), malondialdehyde (MDA), thiobarbituric acid reactive substances (TBARS), peroxides, 4-hydroxy-nonenal (4-HNE) and conjugated dienes], pro-oxidant- antioxidant balance (PAB, n=1), 8-hydroxy-2'–deoxyguanosine (8-OHdG, n=2) and markers of protein oxidation (n=15). Inflammatory markers included C-reactive protein (CRP, n=69), heat shock protein 70 (HSP70, n=1), inflammatory cytokines (n=49), adiponectin (n=8) and markers of innate immunity-mediated ROS generation (n=10) [i.e. the oxidative burst, subunit p22phox of the NOX, iNOS and MPO].

3. STUDIES ON COMBINED ANTIOXIDANT AND ANTI-INFLAMMATORY EFFECT OF VEGETABLES AND VEGETABLE EXTRACTS

Table **1** describes the reviewed intervention studies on the combined antioxidant and anti-inflammatory effects of vegetables and vegetable extracts.

Three months of supplementation with carrot [26] juice decrease marker of lipid oxidation, increase plasma antioxidant defenses but did not show any effect on inflammatory markers in healthy subjects. On the contrary, drinking 280 mL of tomato juice for two months [27] decreased markers of lipid oxidation, without affecting antioxidant capacity status, but increasing the anti-inflammatory adiponectin in healthy subjects. On the other hand, tomato-derived Lyc-o-Mato supplement did not affect peroxidation markers, neither in the form of drink [30] nor as supplement [28, 31]. Besides Lyc-o-Mato increased CRP production in asthmatic subjects [28] without affecting plasma cytokines concentration in obese and asthmatic subjects [28, 29], but decreasing the ex-vivo production of interferon (IFN)-γ and TNF-α in healthy subjects [30].

Although only 28.6% (2/7) of the interventions improved the markers of red-ox or inflammatory status, however it must be taken into account that some of the intervention studies were not controlled for placebo [26, 27, 29, 31] and 4 studies out of seven were conducted on healthy subjects, supposedly not affected by oxidative/inflammatory chronic conditions.

4. STUDIES WITH FRUITS, FRUIT JUICES, GRAPE SEEDS AND THEIR EXTRACTS

Within juice (Table **2**), pomegranate juice (100cc/day, 1 year) [48] and concentrated juice (50g/day, four weeks) [44] decreased IL-6 [44, 48, 51] or MPO [50, 51], concomitantly increasing NEAC [44] or decreasing lipo-peroxidation and protein oxidation markers [48, 50] in type 2 diabetic patients [44], hemodialysis subjects [50, 51] and overweight/obese subjects [48].

Cranberry juice (0.7 liters for 60 days in parallel design) significantly reduced markers of protein and lipid oxidation and increased the anti-inflammatory adiponectin in patients with metabolic syndrome [35].

In the study by Basu *et al.* [34], 480 mL of cranberry juice, in a similar period of time (8 weeks) and in patients with metabolic syndrome, decreased oxidative stress markers (oxLDL and MDA), increase plasma NEAC and in agreement with results from Simao's [35], the juice did not affect CRP and IL-6 levels, while adiponectin levels were not measured in this study. On the contrary, when cranberry was given as dried powder for 6 months, it neither affected the markers of redox/oxidative status nor CRP in men with urinary tract infections [33]. Bilberry juice, in a parallel study on subjects with at least one risk factor for CVD was effective in modulating inflammatory markers without any impact on redox status or lipid oxidation [32]. On the contrary, in type 2 diabetic patients, freeze-dried strawberry 50g/day consumption for 6 weeks decreased CRP and MDA and increased NEAC [42].

One and half rio red grapefruit consumption for 6 weeks in parallel design, failed to display any effect on isoprostanes and CRP levels neither in obese nor in subjects with metabolic syndrome [54]. However, it is extremely interesting to notice that subjects with high baseline isoprostanes levels experienced a significant reduction in response to grapefruit consumption, highlighting once more the importance of a detectable oxidative/inflammatory stress for a significant effect [54, 98]. Marotta *et al.* [38, 39] showed that supplementation with 9 and 6 g of fermented papaya for 6 months in patients with HCV-related cirrhosis translated in an improvement of marker of redox status, in a decrease in marker of oxidative stress and in a parallel anti-inflammatory effect on TNF-α and TNF-α *ex vivo* production. In a different group of subjects, chronic consumption of 9 g of fermented papaya for 3 months decreased TNF-α and IL-6, increase Hsp-70 without changes in antioxidant enzymes in elderly subjects [37]. A quite surprising increase of oxidative burst in PBMN was described in Type 2 diabetic obese after supplementation with 9 g of sachets of fermented papaya [36]. Barona *et al.* [43] observed an increase of iNOS in subjects without dyslipidemia and a decrease in those individuals with dyslipidemia after 4 weeks of consumption of 46 g of freeze-dried whole grape powder. Also plasma adiponectin concentrations followed opposite outcomes based on dyslipidemia category (Table **2**), whereas IL-6, IL-8, TNF-α, SOD, GPX, oxLDL and IsoP did not differ significantly between treatment periods regardless of dyslipidemia classification. On the contrary GPX increased in patients with Rheumatoid Arthritis after the consumption of pomegranate extract (500 mg) for 8 weeks [50].

Table **3** describes intervention trials with grape seeds in different forms: as capsules [55, 57], tablets [58] or added in yoghurt [56].

In the study by Kar *et al.* [58] where 600 mg of grape seeds extract was given to 32 diabetics for 4 weeks, showed a combined effect in increasing antioxidant status (GSH), and decreasing inflammation (CRP). In agreement with Kar's findings, 200 mg of monomeric and oligomeric flavanols from grape seeds increased the GSH/GSSG ratio and decreased TNF-α in smokers. Higher doses of grape seed extract, 1300 mg and 2 g, did not show any effect on selected markers of redox, oxidative and inflammatory status [55, 56]. Nevertheless, two grams of grape seeds extracts displayed an antioxidant effect, decreasing isoprostanes and lipid oxidation, after fructose ingestion in overweight obese patients [57].

5. STUDIES WITH HERBS, GREEN TEA AND THEIR EXTRACTS

Overall, herb extracts are extremely effective in modulating oxidative and inflammatory status as shown in four studies out of the five identified (Table **4**).

Ginseng-based steroid Rg1 (5 mg) decreased lipid oxidation and inflammatory TNF-α in healthy subjects after exercise [60] and ginsenosides, intravenously injected, decreased lipid oxidation and IL-6 and LPS production [62].

On the contrary, capsules of ginseng extracts did not affect CRP levels and antioxidant status [61]. Between the selected herbs, extracts of Silybum marianum (milk thistle) decreased CRP in subjects with Type 2 diabetes in concomitance with an increase in NEAC and antioxidant enzymes (SOD and GPX), as well as with decreases in MDA levels [63]. Also the hydro alcoholic nettle (*Urtica dioica*) extract, 100 mg/kg of body weight for 8 weeks supplementation, increased NEAC and decreased IL-6 and CRP in patients with type 2 diabetes [64, 65].

Green tea extracts modulate both markers of oxidation and inflammation, as shown in three studies out of the four identified; at least one marker of inflammation was actively improved in all studies (Table **5**).

In particular, in hemodialysis patients the decrease in peroxides levels of two different doses of green tea extract (455 and 910 mg) was associated with the reduction of markers of inflammation IL8 and TNF-α receptor, CRP and TNF-α both after acute and chronic consumption [70]. Similar results were obtained with 1 g of green tea extract in a longitudinal study of 3 and 6 months with a decline in oxLDL and of p22phox [69]. Furthermore green tea extract (379 mg) increased NEAC, concomitantly with a reduction of TNF-α and CRP after 3 months of supplementation in obese and hypertensive patients [68].

6. STUDIES WITH SPICES EXTRACTS

Spices often used for culinary purposes, namely curcumin and ginger, showed the capability to improve both oxidative stress and inflammatory status (Table **6**).

Capsules of curcuminoids decreased lipid oxidation and CRP levels in patients undergoing coronary artery bypass [73]. Decrease of CRP and IL-8 concentration but with no antioxidant effect, was obtained with 200 mg of curcumin in healthy subjects [71].

Studies conducted with ginger involved patients with Type 2 diabetes [77], subjects on peritoneal dialysis [76], or patients with acute respiratory distress syndrome [78]. In two of these studies, ginger consumption improved redox and inflammatory markers. In another 4-week study on diabetic patients, with a randomized, controlled design, turmeric (2g) as an adjunct to standard metformin therapy determined a significant reduction in lipid peroxidation and MDA, reduced CRP and enhanced total antioxidant status [74].

7. STUDIES WITH BEVERAGES AND EXTRACTS WITH MIXED PLANT FOOD COMPOSITION

Among different beverages, a mixed fruits juice did not affect neither TBARS nor CRP levels in healthy subjects after 12 weeks of 120 ml daily [79], whereas ingestion of 300 mL of citrus-based

Table 2. Overview of the reviewed intervention studies with fruits, fruit juices and fruits extracts in humans: characteristics, study design and effect on markers of redox, oxidative and inflammatory status.

Treatment	Dose/day Standardization	Subjects (healthy status and no.)	Study design and Duration	Markers of red-ox/ oxidative status	Markers of inflammatory status	Refs.
Bilberry (juice)	330 ml	At least one risk factor for cardiovascular disease 62	Parallel, 4 weeks	NEAC, lipid peroxidation and GSH ↔	CRP and IL-6 ↓ IL-1, IL-2, IL-12, IL-17 and IFN-γ ↔ TNF-α ↑	[32]
Cranberries (dried powder)	1500 mg	Men with urinary tract infection 42	Parallel, 6 months	NEAC, SOD, MDA, GSH, GPX, CAT and AOPP ↔	CRP ↔	[33]
Cranberry (juice)	480 ml (polyphenols 458 mg)	Metabolic syndrome 31	Parallel, 8 weeks	NEAC ↑ MDA ↓ oxLDL,↓	CRP↔ IL6↔	[34]
Cranberry (juice)	0,7 litres (polyphenols 104mg/100ml)	Metabolic syndrome 56	Parallel, 60 days	Lipid peroxidation and AOPP ↓	Adiponectin ↑ CRP, TNF-α, IL-1 and IL-6 ↔	[35]
Fermented papaya (sachets)	9 g	Type 2 diabetic obese 17	Longitudinal, 2 and 6 weeks	4-HNE ↔ Carbonils ↔	Oxidative burst ↑	[36]
Fermented papaya (supplement).	9 g	Elderly 40	Crossover, 3 months	SOD, GPX and GSH ↔	TNF-α and IL-6 ↓ CRP ↔ Hsp-70 ↑	[37]
Fermented papaya (supplement).	9 g	HCV-related cirrhosis 50	Longitudinal, 6 months	GSH and GPX↑ MDA and 8-OHdG↓	TNF-α↓	[38]
Fermented papaya (supplement).	6 g	HCV-related cirrhosis 32	Parallel, 6 months	4-HNE ↓ GSH ↑	TNF-α ex vivo ↓	[39]
Freeze-dried Strawberry	50g (polyphenols 2.0g)	Women with metabolic syndrome 16	Longitudinal, 4 weeks	4-HNE, MDA ↓ oxLDL ↔	CRP and adiponectin ↔	[40]
Freeze-dried strawberry	25 g (low) (polyphenols 1.0g) 50g (high) (polyphenols 2.0g)	Obese with elevated serum lipids 60	Parallel, 12 weeks	MDA and HNE ↓ MDA and HNE ↓	CRP ↔ CRP ↔	[41]
Freeze-dried strawberry	50g (polyphenols 2.0g)	Type 2 diabetic 36	Parallel, 6 weeks	NEAC ↑ MDA ↓	CRP ↓	[42]
Freeze-dried whole grape (powder)	46 g (polyphenols 580 mg/100 g)	Dyslipidemia 11 Non-dyslipidemia 13	Crossover, 4 weeks	oxLDL, IsoP, SOD and GPX↔ oxLDL, IsoP, SOD and GPX↔	TNF-α, IL-6, IL-8 and NOX↔ adiponectin↑ iNOS↓ TNF-α, IL-6, IL-8 and NOX↔ adiponectin↓ iNOS↑	[43]

(Table 2) Contd....

Treatment	Dose/day Standardization	Subjects (healthy status and no.)	Study design and Duration	Markers of red-ox/ oxidative status	Markers of inflammatory status	Refs.
Pomegranate (concentrated juice)	50 g (polyphenols 6.3 mg/100 g).	Type 2 diabetic 31	Longitudinal, 4 weeks	NEAC ↑	IL-6 and adiponectin ↓ TNF-α and CRP ↔	[44]
Pomegranate (capsules)	2 capsules (1.5g polyphenol).	obese with type 2 diabetes 8 healthy 9	Longitudinal, 4 weeks	4-HNE, MDA ↓ oxLDL ↔ 4-HNE, MDA, oxLDL ↔	CRP ↔ CRP ↔	[45]
Pomegranate (extract)	1g (600–755 mg of gallic acid equivalents)	Hemodialysis 33	Parallel, 6 months	NEAC, AOPP, 8-OHdG and ox-LDL↔	IL-6 and CRP ↔	[46]
Pomegranate (extract)	2 capsules (500 mg, 40% ellagic acid)	Rheumatoid arthritis 55	Parallel, 8 weeks	MDA ↔ GPX ↑	CRP ↔	[47]
Pomegranate (extract)	100mg	Overweight/obese 42	Parallel, 30 days	MDA ↓	CRP and IL-6 ↓	[48]
Pomegranate juice + pomegranate (extract)	100 mL Juice 1,050 mg extract	Hemodialysis 20	Crossover 4 weeks juce followed by 4 weeks extract or 4 weeks extract followed by 4 weeks juice), immediately before each dialysis treatment	IsoP ↔	CRP and IL-6 ↔	[49]
Pomegranate (juice)	100ml (polyphenols 0.7mmol/100 cc juice).	Hemodialysis 27	Parallel, during the first hour of a dialysis session	AOPP ↓	MPO ↓	[50]
Pomegranate (juice)	100 cc (polyphenols 0.7mmol/100 cc juice).	Hemodialysis 49	Parallel, during each dialysis (3 times/ week), 1 year	MDA, AOPP and carbonyls ↓	TNF-α, IL-6 and MPO ↓	[51]
Red grape (concentrated juice)	100ml (polyphenols 0.64 g)	Hemodialysis 38 Healthy 15	Parallel, 2 weeks	NEAC ↑ oxLDL ↓ NEAC ↑ oxLDL ↓	CRP ↔ CRP ↔	[52]
Red grape (concentrated juice)	100ml (polyphenols 0.64 g)	Hemodialysis 16	Parallel, 2 weeks	oxLDL ↓	CRP ↔ ROS ↓	[53]
Rio red grapefruit	Half 3 times/day	Obese 74 Metabolic syndrome 29	Parallel, 6 weeks	IsoP ↔ IsoP ↔	CRP ↔ CRP ↔	[54]

4-HNE: 4-hydroxynonenal; 8-OHdG: 8-hydroxy-2' –deoxyguanosine; AOPP: advanced oxidation protein products; CAT: catalase; CRP: C reactive protein; GPX: glutathione peroxidase; GSH: reduced glutathione; Hsp-70: heat shock protein 70; IFN-γ: interferon gamma; IL: interleukin; iNOS: inducible nitric oxide synthase; IsoP: isoprostanes; MDA: malondialdehyde; NEAC: non-enzymatic antioxidant capacity; NOX: NADPH-oxidase; oxLDL: oxidized low density lipoproteins; ROS: reactive oxygen species; SOD: superoxide dismutase; TNF-α: tumor necrosis factor alfa; HCV: Hepatitis C Virus.

Table 3. Overview of the reviewed intervention studies with grape seeds in humans: characteristics, study design and effect on markers of redox, oxidative and inflammatory status.

Treatment	Dose/day Standardization	Subjects (healthy status and no.)	Study design and duration	Markers of red-ox/ oxidative status	Markers of inflammatory status	Refs.
Grape seeds (capsules)	1300 mg	CVD risk factors 50	Crossover, 1 month	NEAC, MDA and IsoP↔	CRP and IL-6 ↔	[55]
Grape seed extract (added in yoghurt)	2 g	CVDrisk factors 35	Crossover, 4 weeks	oxLDL and IsoP↔	CRP↔	[56]
Grape seed extract (capsules)	2 g	Overweight/obese first degree relatives of type 2 diabetic patients 38	Parallel, 8 weeks + 6d fructose	week 8: carbonils ↓ IsoP and TBARS ↔ after fructose: IsoP and TBARS↓	week 8: CRP ↔ after fructose: CRP ↔	[57]
Grape seed extract (tablets)	600 mg	Type 2 diabetes 32	Crossover, 4 weeks	NEAC ↔ GSH ↑	CRP ↓	[58]
Monomeric and oligomeric flavanols from grape seeds (capsules)	200 mg	Male smokers 25	Parallel, 8 weeks	NEAC, SOD, CAT, GPX and IsoP↔ GSH/GSSG ↑	CRP ↔ TNF-α ↓	[59]

CAT: catalase; CRP: C reactive protein; CVD: cardiovascular; GPX: glutathione peroxidase; GSH: reduced glutathione; GSSG: oxidized glutathione; IL: interleukin; IsoP: isoprostanes; MDA: malondialdehyde; NEAC: non-enzymatic antioxidant capacity; oxLDL: oxidized low density lipoproteins; SOD: superoxide dismutase; TBARS: thiobarbituric acid reactive substances; TNF-α: tumor necrosis factor alfa.

Table 4. Overview of the reviewed intervention studies with herbs extracts in humans: characteristics, study design and effect on markers of redox, oxidative and inflammatory status.

Treatment	Dose/day Standardization	Study design and duration	Study design and duration	Markers of red-ox/ oxidative status	Markers of inflammatory status	Refs.
Ginseng based steroid Rg1 (capsule)	5 mg Rg1	Healthy 12	Crossover, one night and one hour before exercise	TBARS ↓	IL6 ↔ TNF- α ↓	[60]
Ginseng extract (capsule)	250 mg, four capsules/day (7 mg ginsenosides)	Hyperlipidemic 36	Parallel, 8 weeks	PAB ↔	CRP↔	[61]
Ginsenosides (intravenously)	1.5 mL/kg (equal to 1.35 mg/kg ginsenosides and 0.15 mg/kg aconite alkaloid).	Children undergoing heart surgery for congenital heart defects 24	Parallel, 2 minutes before the start of cardiopulmonary bypass (CPB) and throughout the course of CPB.	MDA (1 and 2h after reperfusion) ↓	IL-6 and LPS (1 and 2h after reperfusion)↓	[62]
Silybum marianum (L.) Gaertn. (silymarin) extract (tablets)	140 mg silymarin three times/day	Type 2 diabetes 40	Parallel, 45 days	SOD↑ GPX↑ NEAC ↑ MDA↓	CRP↓	[63]
Nettle (*Urtica dioica*) (extract)	100 mg /kg of body weight	50 type 2 diabetes	Parallel, 8 weeks	NEAC ↑ SOD ↑ MDA↔ GPX↔	CRP and IL-6↓ TNF-α ↔	[64, 65]

CRP: C reactive protein; GPX: glutathione peroxidase; IL: interleukin; NEAC: non-enzymatic antioxidant capacity; LPS: lipopolysaccharide; MDA: malondialdehyde; PAB: Pro-oxidant- Antioxidant Balance; SOD: superoxide dismutase; TBARS: thiobarbituric acid reactive substances; TNF-α: tumor necrosis factor α.

Table 5. Overview of the reviewed intervention studies with green tea and green tea extracts in humans: characteristics, study design and effect on markers of redox, oxidative and inflammatory status.

Treatment	Dose/day Standardization	Subjects (healthy status and no.)	Study design and duration	Markers of red-ox/ oxidative status	Markers of inflammatory status	Refs.
Green tea (Beverage)	2.4 g instant green tea (297.9 mg catechins)	Obese 19	Crossover, 5 days	IsoP ↓	CRP and IL6 ↔	[66]
Green tea extract (Beverage)	159 mg total catechins in 450ml	Male cyclists 9	Crossover, 21 days, After exercise (2h)	oxLDL and TBARS ↔ After exercise: oxLDLand TBARS ↔	CRP ↓ IL6 ↔ After exercise: CRP and IL6 ↔	[67]
Green tea extract (capsule)	379 mg (208 mg EGCG)	Obese, hypertensive patients 9	Parallel, 3 months	NEAC ↑	TNF-α ↓ CRP ↓	[68]
Green tea extract (capsule)	1 g (483 mg of Camelia Sinensis powder and 100 mg of leaf extracts for a total of 68 mg catechins)	Chronic dialysis 20	Longitudinal, 3 and 6 months	oxLDL ↓ (only in 9 patients)	P22phox ↓	[69]
Green tea extract (Tablets)	455 and 910 mg of catechins during a single hemodialysis session.	Haemodialysis patients 44	Crossover, bolus, 1 and 3h post-dialysis Parallel, 7 months	peroxides ↓ peroxides ↓	IL-8 and TNF-α receptor↓ CRP and TNF-α↓	[70]

CRP: C reactive protein; EGCG: epigallocatechingallate; IL: interleukin; IsoP: isoprostanes; NEAC: non-enzymatic antioxidant capacity; oxLDL: oxidized low density lipoproteins; TBARS: thiobarbituric acid reactive substances; TNF-α: tumor necrosis factor alfa.

Table 6. Overview of the reviewed intervention studies with spices extracts in humans: characteristics, study design and effect on markers of redox, oxidative and inflammatory status.

Treatment	Dose/day Standardization	Subjects (healthy status and no.)	Study design and duration	Markers of red-ox/ oxidative status	Markers of inflammatory status	Refs.
Curcumin (phytosome)	200 mg	Healthy 19	Parallel, 48 hours prior and 24 hours after running test	NEAC↔ CAT ↔ GPX ↔	CRP ↓ (24h) IL-8 ↓ (2h) MPO ↔	[71]
Curcumin extracts (powder)	400 mg (80 mg curcumin)	Healthy 38	Parallel, 4 weeks	NEAC↑ CAT↑ SOD ↔	CRP ↔ MPO↑	[72]
Curcuminoids (capsules)	4 g	Undergoing coronary artery bypass grafting 121	Parallel, 3 days before the surgery and 5 days after surgery	MDA↓	CRP↓	[73]
Turmeric (capsules)	2 g	Type 2 diabetes on metformin therapy 60	Parallel, 4 weeks.	NEAC ↑ MDA↓ GSH, GPX, CAT and carbonyls ↔	CRP↓	[74]
Turmeric (capsules)	2.8 g	Overweight and obese women 98	Parallel, 4 weeks	IsoP and oxLDL↔	CRP, IL-6, IL-8 and TNF-α ↔	[75]
Ginger (capsule)	1000 mg	Peritoneal dialysis 36	Parallel, 10 weeks	MDA↔	CRP↔	[76]

(Table 6) Contd....

Treatment	Dose/day Standardization	Subjects (healthy status and no.)	Study design and duration	Markers of red-ox/ oxidative status	Markers of inflammatory status	Refs.
Ginger (capsules)	3 g	Type 2 diabetes 45	Parallel, 3 months	NEAC↑ MDA↓	CRP↓	[77]
Ginger extract (enteral feeding)	120 mg	Acute respiratory distress syndrome 32	Parallel, 5 and 10 days	GSH (day 5)↑	IL-1 ↔ IL-6 (day 5)↓ TNF-α ↔	[78]

CAT: catalase; CRP: C reactive protein; GPX: glutathione peroxidase; GSH: reduced glutathione; IL: interleukin; IsoP: isoprostanes; MDA: malondialdehyde; MPO: myeloperoxidase; NEAC: non-enzymatic antioxidant capacity; oxLDL: oxidized low density lipoproteins; SOD: superoxide dismutase; TNF--α: tumor necrosis factor alfa.

Table 7. Overview of the reviewed intervention studies with beverages with mixed plant food composition in humans: characteristics, study design and effect on markers of redox, oxidative and inflammatory status.

Treatment	Dose/day Standardization	Subjects (healthy status and no.)	Study design and duration	Markers of red-ox/ oxidative status	Markers of inflammatory status	Refs.
Mixed fruit beverage[a]	120 ml	Healthy 14	Longitudinal, 12 weeks	TBARS ↔	CRP↔	[79]
Citrus-based juice with melanocarpa[b].	300 ml	Metabolic syndrome 33	Parallel, 6 months	oxLDL↓	CRP↓	[80]
Mixed fruit and vegetable beverage[b]	360 mg/L polyphenols; 170 mg total proanthocyanidins and 9 mg anthocyanins in single dose	Healthy 20	Parallel, acute (0-4h)	IsoP↓ NEAC↑	CRP↔	[81]
Pineapple, black currant and plum.	500 ml (32 mg anthocyanins, 2.5 mg flavan-3-ols and 20 mg flavonols)	Overweight 14	Crossover, acute, post-prandial with high fat and carbohydrates meal (0-8h)	IsoP↔ NEAC↔	TNF- α, IL-6 and IL-17↓	[8, 82]

CRP: C reactive protein; IFN: interferon; IL: interleukin; IsoP: isoprostanes; MDA: malondialdehyde; NEAC: non-enzymatic antioxidant capacity; TBARS: thiobarbituric acid reactive substances; TNF- α: tumor necrosis factor alfa. Mixed fruit beverage[a]: Acai pulp, pomegranate, wolfberry, camu camu, passion fruit, aronia, acerola, bilberry, apricot, purple grape, white grape, lychee, banana, kiwi, pear, cranberry, blueberry and prune. Citrus-based juice[b]. juice citrus (95%) with 5% of A. melanocarpa extract. Mixed fruit and vegetable beverage[c]: Coffee fruit extract, grape seed, North American wild blueberry, quercetin, resveratrol, bilberry, raspberry, cranberry, prune, tart cherry, strawberry, grape seed extract, broccoli sprouts, broccoli, tomato, carrot, spinach, kale, brussels sprout, pomegranate extract and acai pulp) dissolved in a blend of juices (grape, pomegranate, pear, apple, strawberry, chiloensis; acai, yumberry, rubra; cupuacu and camu and a standardized extract of Ashwagandha).

juice with added A. melanocarpa extract for 6 months reduced both oxLDL and CRP in patients with metabolic syndrome [80] (Table **7**).

On the other hand, after acute consumption of a polyphenol-rich beverage containing an extremely variegate variety of mixed fruit and vegetable extracts improve redox markers without affecting CRP levels in healthy subjects [81].

On the contrary, half liter of a mixed fruit-based drink decreased the postprandial inflammatory stress induced by a high fat meal (1361 calories) without affecting redox markers in overweight subjects [8, 82] as displayed in Table **7**.

As described in Table **8**, when supplements with mixed composition were administered as capsules, tablets, powder or by infusion, three studies showed a combined effect on both markers of redox/oxidative and inflammatory status.

In particular, five weeks of supplementation with capsules containing resveratrol, tomato extract, green tea extract, antioxidant vitamins, fish oil and polyunsaturated fatty acids (PUFA), decreased isoprostanes concentration concomitantly with a reduction of IL-18 in overweight subjects [83]. After 8 weeks of consumption of capsules containing powder concentrate derived from acerola cherry, apple, bilberry, blackberry, black currant, blueberry, beetroot, broccoli, cabbage, carrot, Concord grape, cranberry, elderberry, kale, orange, peach, papaya, parsley, pineapple, raspberry, red currant, spinach and tomato, were found a decrease in protein (carbonyls) and lipid (oxLDL) oxidative damage, as well as the exercise-induced increase of TNF-α [87]. Furthermore, 8 weeks of supplementation with capsule containing curcuminoids (1g) + piperine (10 mg) was able to modulate SOD in conjunction with a decrease in lipid peroxidation (MDA) and the inflammatory CRP [91]. In the study from Soare *et al.* [92] providing an extremely variegate composition of functional ingredients, ranging from resveratrol, to fish oil to green, black and white tea etc. for 6 months failed to show any results on redox/oxidative and inflammatory status. Negative results were also obtained by Nieman *et al.* [90], with green tea, blueberry and soy protein extracts, and by Braga *et al.* [93] with green tea extracts and vitamin C and E, in healthy and

Table 8. Overview of the reviewed intervention studies with extracts with mixed composition in humans: characteristics, study design and effect on markers of redox, oxidative and inflammatory status.

Treatment	Dose/day Standardization	Subjects (healthy status and no.)	Study design and Duration	Markers of red-ox/ oxidative status	Markers of inflammatory status	Refs.
Capsule containing antioxidants, plant-food extracts and PUFA	Four capsules (resveratrol 6.3 mg, tomato extract (3.75 mg lycopene), green tea extract 94.5 mg, a-tocopherol 90.7 mg, vitamin C 125 mg, eicosapentaenoic acid (EPA) 380 mg, docosahexaenoic acid(DHA) 260 mg, other PUFA 60 mg)	Overweight 36	Crossover, 5 weeks	IsoP↓	CRP ↔ IL-18 ↓ MPO ↑	[83]
CHOLACTIV (capsule)	Two capsule Leucoselect® Phytosome® 250 mg; policosanol 15 mg; tomato extract (lycopene≥ 10%) 75mg; *Oenothera biennis* oil (cis-γ-linolenic acid≥9%) 250 mg)	Dyslipidemia 60	Parallel, 6 weeks	SOD ↔ GPX ↔ MDA ↔	CRP ↓	[84]
Fruits and vegetables capsules (FV)[a] FVB: FV with the addition of mixed berry juice powder[b]	Three twice a day with meal	Healthy 117	Parallel, 60 days	SOD↑ SOD↑	CRP↔ CRP↔	[85]
Capsule containing: ginseng roots, mulberry leaf water extract and banana leaf water extract.	6 g	Impaired glucose tolerance or mild T2D 94	Parallel, 24 weeks	oxLDL↓	CRP↔	[86]
Capsule containing powder concentrate derived from fruits and vegetables[c]	Three twice a day with meal (6 capsules) (7.5mg β-carotene, 200mg vitamin C, 60 mg α-tocopherol)	Overweight and obese pre-menopausal women 42	Parallel, 8 weeks Pre- and post-30 min exercise	8 weeks: Carbonyls and oxLDL↓ MDA↔ Post-exercise: Carbonyls, oxLDL and MDA↔	8 weeks: TNF- α and IL-6↔ Post-exercise: TNF- α ↓ IL-6↔	[87]
Vitamins, minerals and mixed plant extracts[d] (Tablets)	2 tablets	Healthy 42	Longitudinal, 4 weeks	oxLDL↓ IsoP↔	CRP↔	[88]
Infusion of IMOD (urtica, carotenoids, urea, and selenium)	125 mg of IMOD*	Severe sepsis 16	Parallel, 14 days	NEAC, lipid peroxidation and SH ↔	TNF-α↓ IL-1, IL-2, IL-6↔	[89]
Powder containing: green tea extract, blueberry pomace extract, Soy protein complex	Soy protein complex 40 g. 2, 136 mg GAE.	Healthy 31	Parallel, 2 weeks 2.5-h exercise (3-day exercise period).	NEAC, carbonyls and IsoP↔ NEAC, carbonyls and IsoP↔	CRP, TNF-α IL-6 and IL-8 ↔ CRP, TNF-α IL-6 and IL-8 ↔	[90]

(Table 8) Contd....

Treatment	Dose/day Standardization	Subjects (healthy status and no.)	Study design and Duration	Markers of red-ox/ oxidative status	Markers of inflammatory status	Refs.
Curcuminoids + piperine (capsules)	curcuminoids (1g) + piperine (10mg)	Metabolic syndrome 100	Parallel, 8 weeks	SOD↑ MDA↓	CRP↓	[91]
Mixed plant extracts and fish oil capsules)	One each supplement/day 100 mg of resveratrol, a complex of 800 mg each of green, black, and white tea extract, 250 mg of pomegranate extract, 650 mg of quercetin, 500 mg of acetyl-l-carnitine, 600 mg of lipoic acid, 900 mg of curcumin, 1 g of sesamin, 1.7 g of cinnamon bark extract, and 1.0 g fish oil	Healthy 54	Parallel, 6 months	Carbonyls ↔	CRP, TNF- α and IL-6↔	[92]
Powder containing green tea extract (1g) + vitamin C and E	Twice/day and one hour before surgery‡	Cancer patients 36	Parallel, three doses†	NEAC ↑ IsoP↔	CRP ↔	[93]

CRP: C reactive protein; GPX: glutathione peroxidase; IL: interleukin; IsoP: isoprostanes; MDA: malondialdehyde; MPO: myeloperoxidase; NEAC: non-enzymatic antioxidant capacity; oxLDL: oxidized low density lipoproteins; PUFA: polyunsaturated fatty acids; SH: sulphydrils; SOD: superoxide dismutase; TNF- α: tumor necrosis factor alfa; T2D: Type 2 diabetes. [a]: capsules blended fruit and vegetable juice powder concentrate derived from acerola cherry, apple, beet, broccoli, cabbage, carrot, cranberry, kale, orange, peach, papaya, parsley, pineapple, spinach, and tomato; [b]: bilberry, blackberry, black currant, blueberry, cranberry, Concord grape, elderberry, raspberry and red currant; [c]: acerola cherry, apple, bilberry, blackberry, black currant, blueberry, beetroot, broccoli, cabbage, carrot, Concord grape, cranberry, elderberry, kale, orange, peach, papaya, parsley, pineapple, raspberry, red currant, spinach and tomato; [d]: Citrus bioflavonoids, green coffee bean extract, pomegranate whole fruit extract, grape seed extract, blueberry fruit extract, green tea leaf extract, bitter melon fruit extract, prune skin extract, watercress herb 4:1 extract, Chinese cinnamon bark powder, Indian gum Arabic tree bark and heart wood extract, rosemary extract and artichoke leaf extract; *: in 100 ml of DW5% infused over 1 hour on the first day, then 8 ml of IMOD in 100 ml/d; ‡ pancreaticoduodenectomy; †: 2 the day before the operation and the third the day of surgery 3 h before the anaesthesia.

cancer patients, where only an effect on plasma NEAC was observed in Braga's study. However, all these three studies suffered from potential bias due to lack or improper placebo. In particular, placebo was prepared from Soy protein isolate containing 1.38 mg/g gallic acid equivalents (GAE) in the study of Nieman *et al.* [90], it was a concentrate orange juice in the study of Braga *et al.* [93] and, in the study from Soare *et al.* [92] placebo was lacking and both groups received a daily multivitamin/mineral supplement. Studies from Gupta *et al.* [84] and Mahmoodpoor *et al.* [89] failed to display any effect on antioxidant status but showing a decrease of levels of CRP in patients with dyslipidaemia and TNF-α in patients with sepsis, respectively. A limited effect on SOD and LDL oxidation was observed after two months of supplementation with capsules containing a wide array of fruit and vegetables [85] or 24 weeks with capsules containing ginseng roots, mulberry and banana extracts [86] in healthy subjects and type 2 diabetes patients, respectively.

8. STUDIES WITH COCOA PRODUCTS

Table **9** describes the reviewed intervention studies with cocoa products, including dark chocolate, beverages and creams. Within these interventions decreases in peroxidation markers were observed in healthy [94], obese [66] and pre-hypertensive or stage-1 hypertensive subjects with high cholesterol [95]. In particular, the consumption of a cocoa beverage with a medium content of flavanols (400mg /day) for 5 days decreased IsoP, CRP and IL-6 levels in obese subjects, whereas beverages with lower (180mg/day) or higher (900mg/day) flavanols content increased IL-6 levels [66]. IL-6 did not decrease [95] after the consumption of a cocoa cream product (78g of cocoa + 30g hazelnuts + 2g phytosterols + 20 g fiber) that decreased levels of oxLDL and CRP [95]. Furthermore, others reported decreased levels of the anti-inflammatory IL-10 after the consumption of a cocoa powder (45.3mg flavanols) with 400 mL of semi-skimmed milk in both normo- and moderate hyper-cholesterolaemic subjects [96, 97].

9. DISCUSSION

In this paper, for the first time, we reviewed available evidence about the effect of supplementation with selected fruits, vegetables, herbs, spices and their extracts or galenic formulations on combined markers of redox and inflammatory status in humans. Overall, 30.7% (27/88) of the interventions did not show any positive effect on any markers, while in the remaining 69.3% (61/88) there was an improvement of at least one of the two category markers. Among the 61 interventions showing an effect on the selected markers, 44.2% (27/61) improved both markers of redox and inflammatory status. More specifically, markers of red-ox and oxidative status change after the interventions as follows: NEAC increased in 48.3% (14/29), GSH in the 50.0% (4/8), antioxidant enzymes in the 31.0% (9/29), whereas marker of protein oxidation and markers of lipid peroxidation decreased in the 33.3% (5/15) and 48.0% (37/77), respectively. For what concerning markers of inflammatory stress, CRP decreased after intervention in 24.6% of the studies (17/69), the 44.9% (22/49) of the interventions reported decreases

Table 9. Overview of the reviewed intervention studies with cocoa products in humans: characteristics, study design and effect on markers of redox, oxidative and inflammatory status.

Treatment	Dose/day Standardization	Subjects (healthy status and no.)	Study design and duration	Markers of red-ox/ oxidative status	Markers of inflammatory status	Refs.
Dark chocolate + Cocoa beverage	36.9 g (Procyanidin 4.56mg/g) + 30.9 g (Procyanidin 15.6mg/g)	Healthy 25	Longitudinal, 6 weeks treatment and 6-weeks wash-out period	NEAC, IsoP ↔ . oxLDL ↓	CRP ↔ *Ex vivo* IL-1β, IL-6, TNF-α ↔	[94]
Cocoa beverages	180 mg flavanols (low), 400 mg flavanols (medium) 900 mg flavanols (high)	Obese 19	Crossover, 5 days	IsoP ↔ . IsoP ↓ IsoP ↔ .	CRP↔, IL-6 ↑ CRP ↓, IL6↓ CRP ↔, IL-6 ↑	[66]
Cocoa cream products	78 g of: A: cocoa; B: cocoa + hazelnut (30 g); C: cocoa + hazelnuts + phytosterols (2 g); D:cocoa+hazelnuts+phytosterols+ fiber (20 g).	Pre-hypertensive or stage-1 hypertensive, high cholesterol 113	Parallel, 4 weeks	oxLDL ↔ oxLDL ↔ oxLDL ↔ oxLDL ↓	CRP and IL-6 ↔ CRP and IL-6 ↔ CRP and IL-6 ↔ CRP ↓, IL-6 ↔	[95]
Cocoa powder	45.3 mg flavanols / 400 mL semi-skimmed milk	Moderately hypercholesterolaemic 20 Healthy 24	Cross-over, 4 wks	NEAC, MDA, Carbonyls ↔ NEAC, MDA, Carbonyls ↔	IL-10 ↓ IL-1β, IL-6, IL-8, TNF-α ↔ IL-10 ↓ IL-1β, IL-6, IL-8, TNF-α ↔	[96, 97]

CRP: C reactive protein; IL: interleukin; IsoP: isoprostanes; MDA: malondialdehyde; NEAC: non-enzymatic antioxidant capacity; oxLDL: oxidized low density lipoproteins; TNF-α: tumor necrosis factor alfa.

in at least one inflammatory cytokines, whereas 40.0% of the interventions (4/10) reported increased in markers of ROS generation [i.e. the oxidative burst, iNOS and MPO].

Some considerations are essential for a more comprehensive evaluation of these findings. First, the high heterogeneity of the reviewed studies should be taken into account, as they involved not only wide and very different sources of food, food extracts and supplements, but also different doses, length of supplementation and characteristics of the subjects. Moreover, identified studies presented different robustness and designs, and sometimes a limited sample size. For what concerns the length of the study, in one-day trial it is possible having a clear experimental window of the investigated phenomenon, free of any interference from diet, physical activity and homeostatic controls. On the other hand, when dealing with long-term intervention studies, all the potential bias due to subjects variability, selection criteria, study design, food/extract/ galenic composition must be taken into account. The choice of the biomarkers and the type of measurements also represent an enormous source of variability: markers of redox status can include assessment of endogenous antioxidant (NEAC, single antioxidants, enzymes etc.), while markers of oxidative stress status might involve lipid peroxidation (oxLDL, MDA, isoprostanes, and others) and markers for inflammatory stress are mainly CRP and cytokines. All these markers respond differently to the different types of supplementation, providing different physiological meanings. In our view, in order to obtain a clearer picture of the phenomenon, it is preferable to assess a battery of biomarkers for three interconnected but different responses. For lipid oxidation, despite isoprostane levels being considered a gold standard, it will be also useful to assess other markers such as LDL oxidation or hydro-peroxides levels in order to obtain more complete information. At the same time, the assessment of antioxidant status should include markers for NEAC [Ferric Reducing Antioxidant Potential (FRAP), Total-radical Trapping Antioxidant Parameter (TRAP) and oxygen radical absorbance capacity (ORAC)], endogenous antioxidants (GSH, uric acid and thiols) and endogenous enzymes, preferably in cellular systems (CAT, SOD, GPX). With respect to the inflammatory response it is crucial to understand the role that every single cytokine plays in the different type of pathology or metabolic conditions, keeping in mind that their supposedly low or undetectable levels in healthy and young people could be raised by specific stressors such as post-prandial stress or strenuous physical exercise.

In long term studies we need to consider the existence of physiological mechanism of homeostatic control for both oxidative and inflammatory stress, aimed to tune the antioxidant network and to optimize inflammatory response to the stress. As we showed in previous works [98, 99], in healthy condition such as the absence of specific risk factors for oxidative stress (smoking, obesity, old age etc.), the body require a minimum dose of nutritional antioxidant to maintain physiological red-ox homeostasis, translating in a lack of effect on markers of antioxidant status following long term supplementation. We showed that 58% of the intervention studies con-

ducted with fruit, vegetables, tea, wine, cocoa-products, olive oil and galenic flavonoids, reported a lack of effect in healthy subjects [99] with an effect size of 0.367 ($p<0.001$;$n=1450$) [98]. On the contrary when the studies were conducted on subjects characterized by different CVD risk factors (smoking, hypercholesterolemia, metabolic syndrome, hypertension etc.) involving the existence of an oxidative/inflammatory stress, the percentage of efficiency rise to 70% of the intervention studies and effect size of 0.937 ($p<0.001$;$n=526$) [98, 99].

A detailed description of the nutritional, antioxidant as well as bioactive ingredient composition of the tested food or extracts is crucial for characterizing the tested matrix and for defining the "effective dose" able to display an antioxidant/anti-inflammatory effect in humans. However, most of the studies lack this information and the majority of the compounds present in the food or in the extracts were not identified. However, between the different ingredients, flavonoids, with their considerable in vitro antioxidant capacity [100-102], might play a role in the modulation of redox-regulated genes as well as in the anti-inflammatory activity of plant foods [103, 104]. Flavonoids, such as catechins from green tea, curcumin from turmeric and grape seed procyanidins [1, 104-106] exert their anti-inflammatory and antioxidant effects through the activation of Nrf2, inducing the antioxidant enzymes transcription, and the inhibition of NF-kB, key transcription factors in inflammatory responses. In this framework, it must be taken into account that not only flavonoids, but also other bioactive phytochemicals like triterpenes, centella saponin, asiaticoside, and sceffoleoside, asiatic acid, madecassic acid, phenolic acid avenanthramides and others can affect Nrf2 and/or NF-κB pathways [107-109]. The mechanism suggested for Nrf2 and/or NF-κB modulation by polyphenols, phenolic acids, saponins and triterpenoids is the interaction of electrophiles with cysteine residues of KEAP1 I-κB and/or I-kappa kinases (IKK) [110-119].

However, due to the extensive metabolic activity during digestion, leading to different metabolites endowed with different bioactive ingredients from parental compounds, it is still unclear which are the bioactive ingredients or metabolites responsible of the effect and their relevance in humans [98, 99, 120].

CONCLUSION

In this review, we have shown that some fruits, vegetables, herbs, spices, cocoa and their extracts display a perceived functional activity increasing antioxidant status and at the same time modulating oxidative and inflammatory stress in humans. Interestingly, the modulatory effect of plant foods seems much more efficient in subjects characterized by different risk factors and high level of inflammatory and oxidative stress. In order to fully identify the food items, their functional ingredients as well as the mechanism of action able to display mutual antioxidant/anti-inflammatory activities, more evidence in humans is needed. Meanwhile, it is highly recommended to fully utilize the "functional heritage" of the wide array of different phytochemicals with multi-factorial synergistic interactions contained in fruits, vegetables, herbs and spices and their extracts to efficiently prevent the raise of oxidative and inflammatory stress, major determinants of degenerative diseases.

LIST OF ABBREVIATIONS

4-HNE	=	4-hydroxynonenal
8-OHdG	=	8-hydroxy-2'–deoxyguanosine
ARE	=	Antioxidant responsive elements
CAT	=	catalase
CRP	=	C-reactive protein
CVD	=	cardiovascular disease
FRAP	=	ferric Reducing Antioxidant Potential
GAE	=	gallic acid equivalents
GPX	=	glutathione peroxidase
GSH	=	glutathione
GSH/GSSG	=	ratio of reduced/oxidized glutathione
HSP70	=	heat shock protein 70
IFN	=	interferon
IkB	=	inhibitor of NF-kB
IKK	=	I-kappa kinases
IL	=	interleukin
iNOS	=	inducible nitric oxide synthases
IsoP	=	isoprostanes
KEAP1	=	kelch-like protein-1
LPS	=	lipopolysaccharide
MDA	=	malondialdehyde
MPO	=	myeloperoxidase
NEAC	=	non-enzymatic antioxidant capacity
NF-kB	=	nuclear factor- kappa B
NFR2	=	nuclear factor-erythroid 2-related factor 2
NOX	=	NADPH-oxidase
ORAC	=	oxygen radical absorbance capacity
oxLDL	=	oxidized low density lipoproteins
PAB	=	pro-oxidant- antioxidant balance
PUFA	=	polyunsaturated fatty acids
RNS	=	reactive nitrogen species
ROS	=	reactive oxygen species
SOD	=	superoxide dismutase
TBARS	=	thiobarbituric acid reactive substances
TLR4	=	toll-like receptor-4
TNF-α	=	tumour necrosis factor-alpha
TRAP	=	total-radical trapping antioxidant parameter

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

Editorial assistance was provided by Luca Giacomelli, PhD, on behalf of Content Ed Net; this assistance was funded by PGT Healthcare.

REFERENCES

[1] Serafini M, Del Rio D, Yao DN, Bettuzzi S, Peluso I. Health Benefits of Tea. In: Benzie IFF, Wachtel-Galor S, Eds. Herbal Medicine: Biomolecular and Clinical Aspects. 2nd ed. Boca Raton (FL): CRC Press 2011; Chapter 12.

[2] Hu R, Saw CL, Yu R, Kong AN. Regulation of NF-E2-related factor 2 signaling for cancer chemoprevention: antioxidant coupled with antiinflammatory. Antioxid Redox Signal 2010; 13(11): 1679-98.

[3] Halliwell B, Cross CE. Oxygen-derived species: their relation to human disease and environmental stress. Environ Health Perspect 1994; 102 (Suppl 10): 5-12.

[4] Guarner V, Rubio-Ruiz ME. Low-grade systemic inflammation connects aging, metabolic syndrome and cardiovascular disease. Interdiscip Top Gerontol 2015; 40: 99-106.

[5] Magrone T, Jirillo E. Mechanisms of neutrophil-mediated disease: innovative therapeutic interventions. Curr Pharm Des 2012; 18(12): 1609-19.

[6] Burton-Freeman B. Postprandial metabolic events and fruit-derived phenolics: a review of the science. Br J Nutr 2010; 104 (Suppl 3): S1-14.

[7] Morabito G, Kucan P, Serafini M. Prevention of postprandial metabolic stress in humans: role of fruit-derived products. Endocr Metab Immune Disord Drug Targets 2015; 15(1): 46-53.

[8] Peluso I, Raguzzini A, Villano DV, *et al*. High fat meal increase of IL-17 is prevented by ingestion of fruit juice drink in healthy overweight subjects. Curr Pharm Des 2012; 18(1): 85-90.

[9] Deopurkar R, Ghanim H, Friedman J, *et al*. Differential effects of cream, glucose, and orange juice on inflammation, endotoxin, and the expression of Toll-like receptor-4 and suppressor of cytokine signaling-3. Diabetes Care 2010; 33(5): 991-7.

[10] Trichopoulou A, Bamia C, Trichopoulos D. Anatomy of health effects of Mediterranean diet: Greek EPIC prospective cohort study. BMJ 2009 Jun 23; 338: b2337.

[11] Kumar S, Pandey AK. Free Radicals: Health Implications and their Mitigation by Herbals. Br J Med Med Res 2015; 7: 438-57.

[12] Opara EI, Chohan M. Culinary herbs and spices: their bioactive properties, the contribution of polyphenols and the challenges in deducing their true health benefits. Int J Mol Sci 2014; 15(10): 19183-202.

[13] Bower A, Marquez S, De Mejia EG. The health benefits of selected culinary herbs and spices found in the traditional mediterranean diet. Crit Rev Food Sci Nutr 2016; 56(16): 2728-46.

[14] Mashhadi NS, Ghiasvand R, Askari G, Hariri M, Darvishi L, Mofid MR. Anti-oxidative and anti-inflammatory effects of ginger in health and physical activity: review of current evidence. Int J Prev Med 2013; 4(Suppl 1): S36-42.

[15] Vaid M, Katiyar SK. Molecular mechanisms of inhibition of photocarcinogenesis by silymarin, a phytochemical from milk thistle (Silybum marianum L. Gaertn.) Int J Oncol 2010; 36(5): 1053-60.

[16] Hatipoğlu M, Sağlam M, Köseoğlu S, Köksal E, Keleş A, Esen HH. The Effectiveness of Crataegus orientalis M Bieber. (Hawthorn) Extract Administration in Preventing Alveolar Bone Loss in Rats with Experimental Periodontitis. PLoS One 2015; 10(6): e0128134.

[17] Zhang J, Liang R, Wang L, *et al*. Effects of an aqueous extract of Crataegus pinnatifida Bge. var. major N.E.Br. fruit on experimental atherosclerosis in rats. J Ethnopharmacol 2013; 148(2): 563-9.

[18] Silva RO, Damasceno SR, Brito TV, *et al*. Polysaccharide fraction isolated from Passiflora edulis inhibits the inflammatory response and the oxidative stress in mice. J Pharm Pharmacol 2015; 67(7): 1017-27.

[19] Drummond EM, Harbourne N, Marete E, Jacquier JC, O'Riordan D, Gibney ER. An *in vivo* study examining the antiinflammatory effects of chamomile, meadowsweet, and willow bark in a novel functional beverage. J Diet Suppl 2013; 10(4): 370-80.

[20] Kolodziejczyk-Czepas J, Bijak M Saluk J, *et al*. Radical scavenging and antioxidant effects of Matricaria chamomilla polyphenolic-polysaccharide conjugates. Int J Biol Macromol 2015; 72: 1152-8.

[21] Georgiev V, Ananga A, Tsolova V. Recent advances and uses of grape flavonoids as nutraceuticals. Nutrients 2014; 6(1): 391-415.

[22] Serban C, Sahebkar A, Antal D, Ursoniu S, Banach M. Effects of supplementation with green tea catechins on plasma C-reactive protein concentrations: A systematic review and meta-analysis of randomized controlled trials. Nutrition 2015; 31(9): 1061-71.

[23] Ghosh S, Banerjee S, Sil PC. The beneficial role of curcumin on inflammation, diabetes and neurodegenerative disease: A recent update. Food Chem Toxicol 2015; 83: 111-24.

[24] Goya L, Martín MÁ, Sarriá B, Ramos S, Mateos R, Bravo L. Effect of cocoa and its flavonoids on biomarkers of inflammation: studies of cell culture, animals and humans. Nutrients 2016; 8(4): 212.

[25] Magrone T, Perez de Heredia F, Jirillo E, Morabito G, Marcos A, Serafini M. Functional foods and nutraceuticals as therapeutic tools for the treatment of diet-related diseases. Can J Physiol Pharmacol 2013; 91(6): 387-96.

[26] Potter AS, Foroudi S, Stamatikos A, Patil BS, Deyhim F. Drinking carrot juice increases total antioxidant status and decreases lipid peroxidation in adults. Nutr J 2011; 10: 96.

[27] Li YF, Chang YY, Huang HC, Wu YC, Yang MD, Chao PM. Tomato juice supplementation in young women reduces inflammatory adipokine levels independently of body fat reduction. Nutrition 2015; 31(5): 691-6.

[28] Wood LG, Garg ML, Smart JM, Scott HA, Barker D, Gibson PG. Manipulating antioxidant intake in asthma: a randomized controlled trial. Am J Clin Nutr 2012; 96(3): 534-43.

[29] Markovits N, Ben Amotz A, Levy Y. The effect of tomato-derived lycopene on low carotenoids and enhanced systemic inflammation and oxidation in severe obesity. Isr Med Assoc J 2009; 11(10): 598-601.

[30] Riso P, Visioli F, Grande S, *et al*. Effect of a tomato-based drink on markers of inflammation, immunomodulation, and oxidative stress. J Agric Food Chem 2006; 54(7): 2563-6.

[31] Denniss SG, Haffner TD, Kroetsch JT, Davidson SR, Rush JW, Hughson RL. Effect of short-term lycopene supplementation and postprandial dyslipidemia on plasma antioxidants and biomarkers of endothelial health in young, healthy individuals. Vasc Health Risk Manag 2008; 4(1): 213-22.

[32] Karlsen A, Paur I, Bøhn SK, *et al*. Bilberry juice modulates plasma concentration of NF-kappaB related inflammatory markers in subjects at increased risk of CVD. Eur J Nutr 2010; 49(6): 345-55.

[33] Vidlar A, Vostalova J, Ulrichova J, *et al*. The effectiveness of dried cranberries (Vaccinium macrocarpon) in men with lower urinary tract symptoms. Br J Nutr 2010; 104(8): 1181-9.

[34] Basu A, Betts NM, Ortiz J, Simmons B, Wu M, Lyons TJ. Low-energy cranberry juice decreases lipid oxidation and increases plasma antioxidant capacity in women with metabolic syndrome. Nutr Res 2011; 31(3): 190-6.

[35] Simão TN, Lozovoy MA, Simão AN, *et al*. Reduced-energy cranberry juice increases folic acid and adiponectin and reduces homocysteine and oxidative stress in patients with the metabolic syndrome. Br J Nutr 2013; 110(10): 1885-94.

[36] Dickerson R, Banerjee J, Rauckhorst A, *et al*. Does oral supplementation of a fermented papaya preparation correct respiratory burst function of innate immune cells in type 2 diabetes mellitus patients? Antioxid Redox Signal 2015; 22(4): 339-45.

[37] Marotta F, Koike K, Lorenzetti A, *et al*. Nutraceutical strategy in aging: targeting heat shock protein and inflammatory profile through understanding interleukin-6 polymorphism. Ann N Y Acad Sci 2007; 1119: 196-202.

[38] Marotta F, Yoshida C, Barreto R, Naito Y, Packer L. Oxidative-inflammatory damage in cirrhosis: effect of vitamin E and a fermented papaya preparation. J Gastroenterol Hepatol 2007; 22(5): 697-703.

[39] Marotta F, Chui DH, Jain S, *et al*. Effect of a fermented nutraceutical on thioredoxin level and TNF-alpha signalling in cirrhotic patients. J Biol Regul Homeost Agents 2011; 25(1): 37-45.

[40] Basu A, Wilkinson M, Penugonda K, Simmons B, Betts NM, Lyons TJ. Freeze-dried strawberry powder improves lipid profile and lipid peroxidation in women with metabolic syndrome: baseline and post intervention effects. Nutr J 2009; 8: 43.

[41] Basu A, Betts NM, Nguyen A, Newman ED, Fu D, Lyons TJ. Freeze-dried strawberries lower serum cholesterol and lipid peroxidation in adults with abdominal adiposity and elevated serum lipids. J Nutr 2014; 144(6): 830-7.

[42] Moazen S, Amani R, Homayouni Rad A, *et al*. Effects of freeze-dried strawberry supplementation on metabolic biomarkers of atherosclerosis in subjects with type 2 diabetes: a randomized double-blind controlled trial. Ann Nutr Metab 2013; 63(3): 256-64.

[43] Barona J, Blesso CN, Andersen CJ, Park Y, Lee J, Fernandez ML. Grape consumption increases anti-inflammatory markers and upregulates peripheral nitric oxide synthase in the absence of dyslipidemias in men with metabolic syndrome. Nutrients 2012; 4(12): 1945-57.

[44] Shishehbor F, Mohammad Shahi M, Zarei M, *et al*. Effects of concentrated pomegranate juice on subclinical inflammation and cardiometabolic risk factors for type 2 diabetes: a quasi-experimental study. Int J Endocrinol Metab 2016; 14(1): e33835.

[45] Basu A, Newman ED, Bryant AL, Lyons TJ, Betts NM. Pomegranate polyphenols lower lipid peroxidation in adults with type 2 diabetes but have no effects in healthy volunteers: a pilot study. J Nutr Metab 2013; 2013: 708381.

[46] Wu PT, Fitschen PJ, Kistler BM, *et al*. Effects of pomegranate extract supplementation on cardiovascular risk factors and physical function in hemodialysis patients. J Med Food 2015; 18(9): 941-9.

[47] Ghavipour M, Sotoudeh G, Tavakoli E, Mowla K, Hasanzadeh J, Mazloom Z. Pomegranate extract alleviates disease activity and some blood biomarkers of inflammation and oxidative stress in Rheumatoid Arthritis patients. Eur J Clin Nutr 2016; doi: 10.1038/ejcn.2016.151.

[48] Hosseini B, Saedisomeolia A, Wood LG, Yaseri M, Tavasoli S. Effects of pomegranate extract supplementation on inflammation in overweight and obese individuals: A randomized controlled clinical trial. Complement Ther Clin Pract 2016; 22: 44-50.

[49] Rivara MB, Mehrotra R, Linke L, Ruzinski J, Ikizler TA, Himmelfarb J. A pilot randomized crossover trial assessing the safety and short-term effects of pomegranate supplementation in hemodialysis patients. J Ren Nutr 2015; 25(1): 40-9.

[50] Shema-Didi L, Kristal B, Ore L, Shapiro G, Geron R, Sela S. Pomegranate juice intake attenuates the increase in oxidative stress induced by intravenous iron during hemodialysis. Nutr Res 2013; 33(6): 442-6.

[51] Shema-Didi L, Sela S, Ore L, *et al*. One year of pomegranate juice intake decreases oxidative stress, inflammation, and incidence of infections in hemodialysis patients: a randomized placebo-controlled trial. Free Radic Biol Med 2012; 53(2): 297-304.

[52] Castilla P, Echarri R, Dávalos A, *et al*. Concentrated red grape juice exerts antioxidant, hypolipidemic, and antiinflammatory effects in both hemodialysis patients and healthy subjects. Am J Clin Nutr 2006; 84(1): 252-62.

[53] Castilla P, Dávalos A, Teruel JL, *et al*. Comparative effects of dietary supplementation with red grape juice and vitamin E on production of superoxide by circulating neutrophil NADPH oxidase in hemodialysis patients. Am J Clin Nutr 2008; 87(4): 1053-61.

[54] Dow CA, Wertheim BC, Patil BS, Thomson CA. Daily consumption of grapefruit for 6 weeks reduces urine F2-isoprostanes in overweight adults with high baseline values but has no effect on plasma high-sensitivity C-reactive protein or soluble vascular cellular adhesion molecule 1. J Nutr 2013; 143(10): 1586-92.

[55] Mellen PB, Daniel KR, Brosnihan KB, Hansen KJ, Herrington DM. Effect of muscadine grape seed supplementation on vascular function in subjects with or at risk for cardiovascular disease: a randomized crossover trial. J Am Coll Nutr 2010; 29(5): 469-75.

[56] Clifton PM. Effect of grape seed extract and quercetin on cardiovascular and endothelial parameters in high-risk subjects. J Biomed Biotechnol 2004; (5): 272-8.

[57] Hokayem M, Blond E, Vidal H, *et al*. Grape polyphenols prevent fructose-induced oxidative stress and insulin resistance in first-degree relatives of type 2 diabetic patients. Diabetes Care 2013; 36(6): 1454-61.

[58] Kar P, Laight D, Rooprai HK, Shaw KM, Cummings M. Effects of grape seed extract in Type 2 diabetic subjects at high cardiovascular risk: a double blind randomized placebo controlled trial examining metabolic markers, vascular tone, inflammation, oxidative stress and insulin sensitivity. Diabet Med 2009; 26(5): 526-31.

[59] Weseler AR, Ruijters EJ, Drittij-Reijnders MJ, Reesink KD, Haenen GR, Bast A. Pleiotropic benefit of monomeric and oligomeric flavanols on vascular health--a randomized controlled clinical pilot study. PLoS One 2011; 6(12): e28460.

[60] Hou CW, Lee SD, Kao CL, *et al*. Improved inflammatory balance of human skeletal muscle during exercise after supplementations of the ginseng-based steroid Rg1. PLoS One 2015; 10(1): e0116387.

[61] Delui MH, Fatehi H, Manavifar M, *et al*. The effects of panax ginseng on lipid profile, pro-oxidant: antioxidant status and high-sensitivity C reactive protein levels in hyperlipidemic patients in iran. Int J Prev Med 2013; 4(9): 1045-51.

[62] Xia ZY, Liu XY, Zhan LY, He YH, Luo T, Xia Z. Ginsenosides compound (shen-fu) attenuates gastrointestinal injury and inhibits inflammatory response after cardiopulmonary bypass in patients with congenital heart disease. J Thorac Cardiovasc Surg 2005; 130(2): 258-64.

[63] Ebrahimpour Koujan S, Gargari BP, Mobasseri M, Valizadeh H, Asghari-Jafarabadi M. Effects of Silybum marianum (L.) Gaertn. (silymarin) extract supplementation on antioxidant status and hs-CRP in patients with type 2 diabetes mellitus: a randomized, triple-blind, placebo-controlled clinical trial. Phytomedicine 2015; 22(2): 290-6.

[64] Namazi N, Tarighat A, Bahrami A. The effect of hydro alcoholic nettle (Urtica dioica) extract on oxidative stress in patients with type 2 diabetes: a randomized double-blind clinical trial. Pak J Biol Sci 2012; 15(2): 98-102.

[65] Namazi N, Esfanjani AT, Heshmati J, Bahrami A. The effect of hydro alcoholic Nettle (Urtica dioica) extracts on insulin sensitivity and some inflammatory indicators in patients with type 2 diabetes: a randomized double-blind control trial. Pak J Biol Sci 2011; 14(15): 775-9.

[66] Stote KS, Clevidence BA, Novotny JA, Henderson T, Radecki SV, Baer DJ. Effect of cocoa and green tea on biomarkers of glucose regulation, oxidative stress, inflammation and hemostasis in obese adults at risk for insulin resistance. Eur J Clin Nutr 2012; 66(10): 1153-9.

[67] Eichenberger P, Mettler S, Arnold M, Colombani PC. No effects of three-week consumption of a green tea extract on time trial performance in endurance-trained men. Int J Vitam Nutr Res 2010; 80(1): 54-64.

[68] Bogdanski P, Suliburska J, Szulinska M, Stepien M, Pupek-Musialik D, Jablecka A. Green tea extract reduces blood pressure, inflammatory biomarkers, and oxidative stress and improves parameters associated with insulin resistance in obese, hypertensive patients. Nutr Res 2012; 32(6): 421-7.

[69] Calo LA, Vertolli U, Davis PA, *et al*. Molecular biology based assessment of green tea effects on oxidative stress and cardiac remodelling in dialysis patients. Clin Nutr 2014; 33(3): 437-42.

[70] Hsu SP, Wu MS, Yang CC, *et al*. Chronic green tea extract supplementation reduces hemodialysis-enhanced production of hydrogen peroxide and hypochlorous acid, atherosclerotic factors, and proinflammatory cytokines. Am J Clin Nutr 2007; 86(5): 1539-47.

[71] Drobnic F, Riera J, Appendino G, *et al*. Reduction of delayed onset muscle soreness by a novel curcumin delivery system (Meriva®): a randomised, placebo-controlled trial. J Int Soc Sports Nutr 2014; 11: 31.

[72] Di Silvestro RA, Joseph E, Zhao S, Bomser J. Diverse effects of a low dose supplement of lipidated curcumin in healthy middle aged people. Nutr J 2012; 11: 79.

[73] Wongcharoen W, Jai-Aue S, Phrommintikul A, *et al*. Effects of curcuminoids on frequency of acute myocardial infarction after coronary artery bypass grafting. Am J Cardiol 2012; 110(1): 40-4.

[74] Maithili Karpaga Selvi N, Sridhar MG, Swaminathan RP, Sripradha R. Efficacy of turmeric as adjuvant therapy in type 2 diabetic patients. Indian J Clin Biochem 2015; 30(2): 180-6.

[75] Nieman DC, Cialdella-Kam L, Knab AM, Shanely RA. Influence of red pepper spice and turmeric on inflammation and oxidative stress biomarkers in overweight females: a metabolomics approach. Plant Foods Hum Nutr 2012; 67(4): 415-21.

[76] Imani H, Tabibi H, Najafi I, Atabak S, Hedayati M, Rahmani L. Effects of ginger on serum glucose, advanced glycation end products, and inflammation in peritoneal dialysis patients. Nutrition 2015; 31(5): 703-7.

[77] Shidfar F, Rajab A, Rahideh T, Khandouzi N, Hosseini S, Shidfar S. The effect of ginger (Zingiber officinale) on glycemic markers in patients with type 2 diabetes. J Complement Integr Med 2015; 12(2): 165-70.

[78] Vahdat Shariatpanahi Z, Mokhtari M, Taleban FA, *et al*. Effect of enteral feeding with ginger extract in acute respiratory distress syndrome. J Crit Care 2013; 28(2): 217.e1-6.

[79] Jensen GS, Ager DM, Redman KA, Mitzner MA, Benson KF, Schauss AG. Pain reduction and improvement in range of motion after daily consumption of an açai (Euterpe oleracea Mart.) pulp-fortified polyphenolic-rich fruit and berry juice blend. J Med Food 2011; 14(7-8): 702-11.

[80] Mulero J, Bernabé J, Cerdá B, *et al*. Variations on cardiovascular risk factors in metabolic syndrome after consume of a citrus-based juice. Clin Nutr 2012; 31(3): 372-7.

[81] Nemzer BV, Rodriguez LC, Hammond L, Disilvestro R, Hunter JM, Pietrzkowski Z. Acute reduction of serum 8-iso-PGF2-alpha and advanced oxidation protein products in vivo by a polyphenol-rich beverage; a pilot clinical study with phytochemical and *in vitro* antioxidant characterization. Nutr J 2011; 10: 67.

[82] Miglio C, Peluso I, Raguzzini A, *et al*. Fruit juice drinks prevent endogenous antioxidant response to high-fat meal ingestion. Br J Nutr 2014; 111(2): 294-300.

[83] Bakker GC, van Erk MJ, Pellis L, *et al*. An antiinflammatory dietary mix modulates inflammation and oxidative and metabolic stress in overweight men: a nutrigenomics approach. Am J Clin Nutr 2010; 91(4): 1044-59.

[84] Gupta H, Pawar D, Riva A, Bombardelli E, Morazzoni P. A randomized, double-blind, placebo-controlled trial to evaluate efficacy and tolerability of an optimized botanical combination in the management of patients with primary hypercholesterolemia and mixed dyslipidemia. Phytother Res 2012; 26(2): 265-72.

[85] Jin Y, Cui X, Singh UP, *et al*. Systemic inflammatory load in humans is suppressed by consumption of two formulations of dried, encapsulated juice concentrate. Mol Nutr Food Res 2010; 54(10): 1506-14.

[86] Kim HJ, Yoon KH, Kang MJ, *et al*. A six-month supplementation of mulberry, korean red ginseng, and banaba decreases biomarkers of systemic low-grade inflammation in subjects with impaired glucose tolerance and type 2 diabetes. Evid Based Compl Altern Med 2012; 2012: 735191.

[87] Lamprecht M, Obermayer G, Steinbauer K, *et al*. Supplementation with a juice powder concentrate and exercise decrease oxidation and inflammation, and improve the microcirculation in obese women: randomised controlled trial data. Br J Nutr 2013; 110(9): 1685-95.

[88] Lerman RH, Desai A, Lamb JJ, Chang JL, Darland G, Konda VR. A phytochemical-rich multivitamin-multimineral supplement is bioavailable and reduces serum oxidized low-density lipoprotein, myeloperoxidase, and plasminogen activator inhibitor-1 in a four-week pilot trial of healthy individuals. Glob Adv Health Med 2014; 3(2): 34-9.

[89] Mahmoodpoor A, Eslami K, Mojtahedzadeh M, *et al*. Examination of Setarud (IMOD™) in the management of patients with severe sepsis. Daru 2010; 18(1): 23-8.

[90] Nieman DC, Gillitt ND, Knab AM, *et al*. Influence of a polyphenol-enriched protein powder on exercise-induced inflammation and oxidative stress in athletes: a randomized trial using a metabolomics approach. PLoS One 2013; 8(8): e72215.

[91] Panahi Y, Hosseini MS, Khalili N, Naimi E, Majeed M, Sahebkar A. Antioxidant and anti-inflammatory effects of curcuminoid-piperine combination in subjects with metabolic syndrome: A randomized controlled trial and an updated meta-analysis. Clin Nutr 2015; 34(6): 1101-8.

[92] Soare A, Weiss EP, Holloszy JO, Fontana L. Multiple dietary supplements do not affect metabolic and cardiovascular health. Aging (Albany NY) 2013; [Epub ahead of print].

[93] Braga M, Bissolati M, Rocchetti S, Beneduce A, Pecorelli N, Di Carlo V. Oral preoperative antioxidants in pancreatic surgery: a double-blind, randomized, clinical trial. Nutrition 2012; 28(2): 160-4.

[94] Mathur S, Devaraj S, Grundy SM, Jialal I. Cocoa products decrease low density lipoprotein oxidative susceptibility but do not affect biomarkers of inflammation in humans. J Nutr 2002; 132(12): 3663-7.

[95] Solà R, Valls RM, Godàs G, *et al*. Cocoa, hazelnuts, sterols and soluble fiber cream reduces lipids and inflammation biomarkers in hypertensive patients: a randomized controlled trial. PLoS One 2012; 7(2): e31103.

[96] Martínez-López S, Sarriá B, Sierra-Cinos JL, Goya L, Mateos R, Bravo L. Realistic intake of a flavanol-rich soluble cocoa product increases HDL-cholesterol without inducing anthropometric changes in healthy and moderately hypercholesterolemic subjects. Food Funct 2014; 5(2): 364-74

[97] Sarriá B, Martínez-López S, Sierra-Cinos JL, García-Diz L, Mateos R, Bravo L. Regular consumption of a cocoa product improves the cardiometabolic profile in healthy and moderately hypercholesterolaemic adults. Br J Nutr 2014; 111(1): 122-34.

[98] Lettieri-Barbato D, Tomei F, Sancini A, Morabito G, Serafini M. Effect of plant foods and beverages on plasma non-enzymatic antioxidant capacity in human subjects: a meta-analysis. Br J Nutr 2013; 109(9): 1544-56.

[99] Serafini M, Miglio C, Peluso I, Petrosino T. Modulation of plasma non enzimatic antioxidant capacity (NEAC) by plant foods: the role of polyphenols. Curr Top Med Chem 2011; 11(14): 1821-46.

[100] Pellegrini N, Serafini M, Salvatore S, Del Rio D, Bianchi M, Brighenti F. Total antioxidant capacity of spices, dried fruits, nuts, pulses, cereals and sweets consumed in Italy assessed by three different in vitro assays. Mol Nutr Food Res 2006; 50(11): 1030-8.

[101] Song FL, Gan RY, Zhang Y, Xiao Q, Kuang L, Li HB. Total phenolic contents and antioxidant capacities of selected chinese medicinal plants. Int J Mol Sci 2010; 11(6): 2362-72.

[102] Pellegrini N, Serafini M, Colombi B, *et al*. Total antioxidant capacity of plant foods, beverages and oils consumed in Italy assessed by three different *in vitro* assays. J Nutr 2003; 133(9): 2812-9.

[103] Peluso I, Miglio C, Morabito G, Ioannone F, Serafini M. Flavonoids and immune function in human: a systematic review. Crit Rev Food Sci Nutr 2015; 55(3): 383-95.

[104] Serafini M, Peluso I, Raguzzini A. Flavonoids as anti-inflammatory agents. Proc Nutr Soc 2010; 69(3): 273-8.

[105] Su ZY, Shu L, Khor TO, Lee JH, Fuentes F, Kong AN. A perspective on dietary phytochemicals and cancer chemoprevention: oxidative stress, nrf2, and epigenomics. Top Curr Chem 2013; 329: 133-62.

[106] Upadhyay S, Dixit M. Role of polyphenols and other phytochemicals on molecular signaling. Oxid Med Cell Longev 2015; 2015: 504253.

[107] Shukla SD, Bhatnagar M, Khurana S. Critical evaluation of ayurvedic plants for stimulating intrinsic antioxidant response. Front Neurosci 2012 Jul 26; 6: 112.

[108] Jantan I, Ahmad W, Bukhari SN. Plant-derived immunomodulators: an insight on their preclinical evaluation and clinical trials. Front Plant Sci 2015; 6: 655.

[109] Yadav VR, Prasad S, Sung B, Kannappan R, Aggarwal BB. Targeting inflammatory pathways by triterpenoids for prevention and treatment of cancer. Toxins (Basel) 2010; 2(10): 2428-66.

[110] Han KH, Hashimoto N, Fukushima M. Relationships among alcoholic liver disease, antioxidants, and antioxidant enzymes. World J Gastroenterol 2016; 22(1): 37-49.

[111] Wang L, Gao S, Jiang W, *et al*. Antioxidative dietary compounds modulate gene expression associated with apoptosis, DNA repair, inhibition of cell proliferation and migration. Int J Mol Sci 2014; 15(9): 16226-45.

[112] Copple IM, Shelton LM, Walsh J, *et al*. Chemical tuning enhances both potency toward nrf2 and in vitro therapeutic index of triterpenoids. Toxicol Sci 2014; 140(2): 462-9.

[113] Sirota R, Gibson D, Kohen R. The role of the catecholic and the electrophilic moieties of caffeic acid in Nrf2/Keap1 pathway activation in ovarian carcinoma cell lines. Redox Biol 2015; 4: 48-59.

[114] Son PS, Park SA, Na HK, Jue DM, Kim S, Surh YJ. Piceatannol, a catechol-type polyphenol, inhibits phorbol ester-induced NF-{kappa}B activation and cyclooxygenase-2 expression in human breast epithelial cells: cysteine 179 of IKK{beta} as a potential target. Carcinogenesis 2010; 31(8): 1442-9.

[115] Wu RP, Hayashi T, Cottam HB, *et al*. Nrf2 responses and the therapeutic selectivity of electrophilic compounds in chronic lymphocytic leukemia. Proc Natl Acad Sci USA 2010; 107(16): 7479-84.

[116] Cichocki M, Blumczyńska J, Baer-Dubowska W. Naturally occurring phenolic acids inhibit 12-O-tetradecanoylphorbol-13-acetate induced NF-kappaB, iNOS and COX-2 activation in mouse epidermis. Toxicology 2010; 268(1-2): 118-24.

[117] Ishii T, Ishikawa M, Miyoshi N, *et al*. Catechol type polyphenol is a potential modifier of protein sulfhydryls: development and application of a new probe for understanding the dietary polyphenol actions. Chem Res Toxicol 2009; 22(10): 1689-98.

[118] Nair S, Li W, Kong AN. Natural dietary anti-cancer chemopreventive compounds: redox-mediated differential signaling mechanisms in cytoprotection of normal cells versus cytotoxicity in tumor cells. Acta Pharmacol Sin 2007; 28(4): 459-72.

[119] Balogun E, Hoque M, Gong P, *et al*. Curcumin activates the haem oxygenase-1 gene via regulation of Nrf2 and the antioxidant-responsive element. Biochem J 2003; 371(Pt 3): 887-95.

[120] Petrosino T, Serafini M. Antioxidant modulation of F2-isoprostanes in humans: a systematic review. Crit Rev Food Sci Nutr 2014; 54(9): 1202-21.