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**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 postprandial lipopolsaccharide (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 phytochemical 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 and their extracts or 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...
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/antioxidative status       | Markers of inflammatory status          | Refs. |
|----------------------------------|--------------------------|-----------------------------------|---------------------------|---------------------------------------------|----------------------------------------|-------|
| Carrot (juice)                   | 16 fl oz                 | Healthy                            | Longitudinal, 3 months   | NEAC↑                                      | CRP and IL-1↔                         | [26]  |
| Tomato (juice)                   | 280 ml                   | Healthy women                      | Longitudinal, 2 months   | MDA↓                                       | Adiponectin↑                           | [27]  |
| Tomato-derived Lyc-O-Mato        | 45 mg lycopene           | Asthmatic                          | Parallel, 14 weeks       | IsoP↔                                      | CRP↑                                  | [28]  |
| Tomato-derived Lyc-O-Mato        | 30 mg lycopene           | Obese                              | Longitudinal, 4 weeks    | Dienes ↔                                   | CRP, TNF-α and IL-6↔                  | [29]  |
| Tomato-derived Lyc-O-Mato        | 250 ml                   | Healthy                            | Crossover, 26 days       | IsoP↔                                      | TNF-α and IFN-γ ex vivo↓               | [30]  |
| Tomato-derived Lyc-O-Mato        | 80 mg lycopene           | Healthy                            | Longitudinal, 1 week; postprandial (3h) | MDA ↔                                   | 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 alpha.

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-2-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].

Craberry 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 of redox/oxidative stress or 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    | 25g (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 ↔ | [41]  |
| Freeze-dried strawberry    | 50g (polyphenols 2.0g)   | Type 2 diabetic 36 | Parallel, 6 weeks | NEAC ↑ MDA ↓ | CRP ↓ | [42]  |
| Freeze-dried whole grape (powder) | 46g (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]  |
| 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 (1.5 g polyphenol) | obese with type 2 diabetes 8 healthy 9 | Longitudinal, 4 weeks     | 4-HNE, MDA ↓ oxLDL ↔               | 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 ↔                              | 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 juice 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 ↓                     | CRP ↔                              | [52]  |
| Red grape (concentrated juice)    | 100ml (polyphenols 0.64 g) | Hemodialysis 16                 | Parallel, 2 weeks         | oxLDL ↓                            | CRP ↔                              | [53]  |
| Rio red grapefruit                | Half 3 times/day          | Obese Metabolic syndrome 74 29 | Parallel, 6 weeks         | IsoP ↔                             | 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; HCV: Hepatitis C Virus; 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 | Crossover, 1 month | NEAC, MDA and IsoP→ | CRP and IL-6 ↔ | [55] |
| Grape seed extract (added in yoghurt) | 2 g | CVD risk factors | Crossover, 4 weeks | oxLDL and IsoP↔ | CRP↔ | [56] |
| Grape seed extract (capsules) | 2 g | Overweight/obese first degree relatives of type 2 diabetic patients | 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 | Crossover, 4 weeks | NEAC ↔ GSH ↑ | CRP ↓ | [58] |
| Monomeric and oligomeric flavanols from grape seeds (capsules) | 200 mg | Male smokers | Parallel, 8 weeks | NEAC, SOD, CAT, GPX and IsoP→ GSH/GSSG ↑ | CRP ↔ TNF-α ↓ | [59] |

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 | 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 | 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 | 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 | 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] |

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 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: oxLDL and TBARS ↔ | CRP ↓ 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 ↓ | IL-8 and TNF-α receptor↓ | [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] |
vitamins, fish oil and polyunsaturated fatty acids (PUFA), containing resveratrol, tomato extract, green tea extract, antioxidant vitamins, fish oil and polyunsaturated fatty acids (PUFA), de-
than 5 and 10 days]

| 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↑                                | 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)↓            | [78]  |

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<sup>a</sup>     | 120 ml                   | Healthy                           | Longitudinal, 12 weeks    | TBARS ↔                             | CRP↔                             | [79]  |
| Citrus-based juice with melanocarpa<sup>a</sup> | 300 ml                  | Metabolic syndrome 33             | Parallel, 6 months       | oxLDL↓                              | CRP↓                             | [80]  |
| Mixed fruit and vegetable beverage<sup>a</sup> | 360 mg/L polyphenols; 170 mg total proanthocyanidins and 9 mg anthocyanins in single dose | Healthy                           | Parallel, acute (0-4h)    | IsoP↓                               | CRP↔                             | [81]  |
| Pineapple, black currant and plum.   | 500 ml (32 mg anthocyanins, 2.5 mg flavan-3-ols and 20 mg flavonols) | Overweight                       | Crossover, acute, post-prandial with high fat and carbohydrates meal (0-8h) | IsoP↔ NEAC↔ | TFN-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; oxLDL: oxidized low density lipoproteins; SOD: superoxide dismutase; TNF-α: tumor necrosis factor alfa.

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↑                                | 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)↓            | [78]  |

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<sup>a</sup>     | 120 ml                   | Healthy                           | Longitudinal, 12 weeks    | TBARS ↔                             | CRP↔                             | [79]  |
| Citrus-based juice with melanocarpa<sup>a</sup> | 300 ml                  | Metabolic syndrome 33             | Parallel, 6 months       | oxLDL↓                              | CRP↓                             | [80]  |
| Mixed fruit and vegetable beverage<sup>a</sup> | 360 mg/L polyphenols; 170 mg total proanthocyanidins and 9 mg anthocyanins in single dose | Healthy                           | Parallel, acute (0-4h)    | IsoP↓                               | CRP↔                             | [81]  |
| Pineapple, black currant and plum.   | 500 ml (32 mg anthocyanins, 2.5 mg flavan-3-ols and 20 mg flavonols) | Overweight                       | Crossover, acute, post-prandial with high fat and carbohydrates meal (0-8h) | IsoP↔ NEAC↔ | TFN-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; oxLDL: oxidized low density lipoproteins; SOD: superoxide dismutase; TNF-α: tumor necrosis factor alfa.

On the other hand, after acute consumption of a polyphenol-rich beverage containing an extremely variegated 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 red-ox/diabetic 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, 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 variegated 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 overweight individuals.
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, α-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                                      | Three twice a day with meal                                                              | Healthy 117                       | Parallel, 60 days           | SOD↑ CRP↔                         | SOD↑ CRP↔                         | [85]  |
| FVB: FV with the addition of mixed berry juice powderb                     |                                                                                         |                                    |                           |                                   |                                |       |
| 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           | oxDL↓                             | CRP ↔                             | [86]  |
| Capsule containing powder concentrate derived from fruits and vegetablesc | 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: Carboxyls and oxDL↓ MDA ↔ Post-exercise: Carboxyls, oxDL and MDA ↔ | 8 weeks: TNF-α and IL-6 ↔ Post-exercise: TNF-α ↓ IL-6 ↔ | [87]  |
| Vitamins, minerals and mixed plant extractsd (Tablets)                    | 2 tablets                                                                                | Healthy 42                        | Longitudinal, 4 weeks       | oxDL↓ 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]  |
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 fibre) 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

| Treatment | Substances | 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 | Carbons ↔ | CRP ↔ and IL-6← | [92] |
| Powder containing green tea extract (1g) + vitamins 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: sulphydryls; SOD: superoxide dismutase; TNF-α: tumor necrosis factor alfa; T2D: Type 2 diabetes; ‡ : capsules blended fruit and vegetable juice powder concentrate derived from acerola cherry, apple, beet, broccoli, cabbage, carrot, cranberry, kala, orange, peach, papaya, parsley, pineapple, spinach, and tomato; †: bilberry, blackberry, black currant, blueberry, cranberry, Concord grape, elderberry, raspberry and red currant; ‡: 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; †: 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 DW 5% infused over 1 hour on the first day, then 8 ml of IMOD in 100 ml/d; †: pancreaticoduodenectomy; ‡: 2 day before the operation and the third day of surgery 3 h before the anaesthesia.
Table 9. Overview of the reviewed intervention studies with cocoa products in humans: characteristics, study design and effect on markers of red-ox, 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 |
|-----------------------------------|--------------------------|-----------------------------------|---------------------------|------------------------------------|-------------------------------|
| 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 washout period | NEAC, IsoP ↔ oxLDL ↓ | CRP ↔ Ex vivo IL-1β, IL-6, TNF-α ↔ |
| Cocoa beverages                   | 180 mg flavanols (low), 400 mg flavanols (medium), 900 mg flavanols (high) | Obese 19                     | Crossover, 5 days | IsoP ↔ oxLDL ↓ | CRP ↔ IL-6 ↑ CRP ↓ IL-6 ↓ CRP ↔ IL-6 ↑ |
| 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 ↓ | CRP and IL-6 ↔ CRP and IL-6 ↔ CRP and IL-6 ↔ |
| Cocoa powder                      | 45.3 mg flavanols / 400 mL semi-skimmed milk | Moderately hyper-cholesterolaemic 20 | Cross-over, 4 wks | NEAC, MDA, Carboxylys ↔ IL-10 ↓ IL-1β, IL-6, IL-8, TNF-α ↔ | NEAC, MDA, Carboxylys ↔ IL-10 ↓ IL-1β, IL-6, IL-8, TNF-α ↔ |

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 alpha.

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 important 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 scelefoleoside, asiatic acid, madecassic acid, phenolic acid avenanthramides and others can affect Nrf2 and/or NF-kB pathways [107-109]. The mechanism suggested for Nrf2 and/or NF-kB modulation by polyphenols, phenolic acids, saponins and triterpenoids is the interaction of electrophiles with cysteine residues of KEAP1-I-kB 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 oxide-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.

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