Redox biomarkers in dietary interventions and nutritional observation studies - From new insights to old problems

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\textbf{ABSTRACT}

\textbf{Purpose:} The purpose of this review is to give an overview on recently published articles investigating the associations of diet and dietary interventions with biomarkers of oxidative stress with special emphasis on different categories of redox biomarkers.

\textbf{Findings:} Intervention and observational studies both in healthy participants and patients that investigated associations of dietary habits, foodstuffs or isolated nutrients with biomarkers of oxidative stress were included in this review. Recently published observation studies confirm the inverse association between fruit and vegetable intake and oxidative stress markers. Studies investigating the effect of vitamin D and vitamin E, magnesium, zinc, chromium, selenium, probiotic supplementation and several phytochemicals reported consistent changes in redox biomarkers. Of 88 articles included in this review, only seven studies measured biomarkers from the three categories: oxidative damage, endogenous antioxidants, and exogenous antioxidants. Many studies rely on controversial assays for total antioxidant capacity, thus there is potential in many studies to improve biomarker repertoire to cover all three categories of biomarkers and to turn away from such assays.

\section{1. Introduction}

Oxidative stress (OS) is defined as an imbalance between pro- and antioxidants in favor of oxidative compounds such as free radicals and reactive oxygen species (ROS) \cite{1-3}. The interaction of ROS with various biomolecules such as proteins, lipids, carbohydrates and nucleic bases leads to the formation of a variety of substances which are often referred to as biomarkers of OS. Those substances include in general products of enzymatic and non-enzymatic lipid peroxidation such as malondialdehyde (MDA), 4-hydroxyhexenal (4-HNE), and isoprostanes (e.g. 8-isoprostane), DNA adducts like 8-hydroxy-deoxyguanosine (8OHdG), or specific advanced glycation endproducts (AGE) like carbonyllysine (CML). 3-Nitrotyrosine (3NT) and protein carbonyls (PCs) are further prominent biomarkers of OS, resulting from nitration and oxidation of proteins, respectively. Another way to measure redox status is via the activity of antioxidative enzymes like catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPx). Many authors furthermore rely on the measurement of the so-called total antioxidant capacity (TAC). Hence, the possibilities to quantify OS are through the analyses of (1) exogenous antioxidants, (2) endogenous antioxidants, and (3) oxidative damage biomarkers in biological samples.

Even though it has been shown that elevated levels of OS occur in a number of various diseases such as Parkinson’s disease, Alzheimer’s disease \cite{4}, alcoholic and non-alcoholic induced fatty liver disease (AFLD and NAFLD), as well as in patients undergoing hemodialysis (HD), the often-propagated harmful effect of OS is still subject of controversial discussion. Severe OS has been reported to trigger necrosis, but moderate levels of ROS also have a regulatory function in apoptosis and in redox signaling \cite{1}. Multiple studies investigated the influence of nutrition, especially the consumption of fruits and vegetables (F/V) on OS and found beneficial effects in participants with high F/V intake such as reduced levels of MDA and isoprostanes \cite{5,6}. While elevated F/V consumption might modulate OS in a beneficial way, intervention studies focusing on isolated micronutrients often showed controversial results \cite{7,8}. The aim of this review is to summarize the results of observational and intervention studies published over the last three years focusing on the association between diet/nutrition and OS. The substances on which this review will focus thereby range from typical nutritional antioxidants such as carotenoids and polyphenols as well as substances whose role in the modulation of OS is currently

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Abbreviations:

| Abbreviation | Description                                      |
|--------------|--------------------------------------------------|
| AGE          | Advanced glycation endproducts                   |
| AFLD         | Alcoholic induced fatty liver disease           |
| AOPP         | Advanced oxidation protein products             |
| BAP          | Biological antioxidant potential                 |
| CAT          | Catalase                                         |
| CFU          | Colony forming units                            |
| CHD          | Coronary heart disease                          |
| CML          | Carboxymethyllysine                             |
| DB           | Double-blinded                                  |
| DHA          | Docosahexaenoic acid                            |
| dROM         | Derivatives of reactive oxygen metabolites      |
| EPA          | Eicosapentaenoic acid                           |
| FFQ          | Food frequency questionnaire                    |
| FOX2         | Ferrous oxidation-xylenol orange 2              |
| FRAP         | Ferric reducing ability of plasma               |
| F/V          | Fruits and vegetables                           |
| (8-)IsoP     | (8-)isoprostanes                                |
| GPx          | Glutathione peroxidase                          |
| GR           | Glutathione reductase                           |
| GSH          | Glutathione                                     |
| GSSG         | Glutathione dimer                               |
| HD           | Hemodialysis                                    |
| 4-HNE        | 4-hydroxyxynonenal                              |
| IU           | International units                             |
| MDA          | Malondialdehyde                                 |
| MetS         | Metabolic syndrome                              |
| NAFLD        | Non-alcoholic fatty liver disease               |
| NB           | Non-blinded                                     |
| NO           | Nitric oxide                                    |
| 8OHdG        | 8-hydroxy-deoxyguanosine                        |
| ORAC         | Oxygen Radical Absorbance Capacity              |
| OS           | Oxidative stress                                |
| oxLDL        | Oxidized low density lipoprotein                |
| PCs          | Protein carbonyls                               |
| PCOS         | Polycystic ovary syndrome                       |
| PON1         | Paraoxonase and arylesterase 1                  |
| PUFAs        | Polyunsaturated fatty acids                     |
| RFS          | Recommended Food Score                          |
| ROS          | Reactive oxygen species                         |
| SB           | Single-blinded                                  |
| SOD          | Superoxide dismutase                            |
| TAC          | Total antioxidant capacity                      |
| TBARS        | Thiobarbituric acid reactive substances         |
| TRAP         | Total radical-trapping antioxidant parameter    |

Fig. 1. Flowchart of the selection process.
### Table 1

| Focus of Observation | Participants | N (age in years) | Biomarkers | Conclusion | Ref. |
|----------------------|--------------|-----------------|------------|------------|------|
| F/V intake (15-day dietary record and F/V questionnaire) | healthy | 83 (40 ± 10) | TAC, carotenoids, FOX2, oxLDL, PON1, dietary TAC | positive correlation between F/V and plasma carotenoids, negative correlation between F/V and oxLDL as well as between β-carotene and oxLDL | [6] |
| Dietary pattern (annual semi-quantitative FFQ with 160 items) | healthy (obese) | 68: 20 normal (56.4 ± 10.1) 35 overweight (51.7 ± 11.7) 13 obese (47.8 ± 10.2) | MDA | MDA higher in cluster with obese participants, obese had lower F/V intake | [9] |
| Diet quality score (46 foods or food groups) | healthy vs. persons with OS conditions | 1229: 823 healthy (45.3 ± 10.7) 406 OS (51.8 ± 11.2) | carotenoids, MDA (plasma, urine and erythrocytes) | only in the OS group: negative association between Recommended Food Score (RFS) and erythrocyte MDA concentrations but not with plasma MDA association between RFS and plasma carotenoids, especially total and β-carotene, in healthy and OS | [5] |
| Dietary pattern (assessed by diet history questionnaire, 124 food items) | healthy | 269 (59.8 ± 5.5) | 8-isoP | inverse associations between dietary intake of PUFAs, zinc and insoluble fiber with 8-isoP | [10] |
| Seafood intake (3-day dietary record) | healthy | 81: men (39.9–49.3) women (36.6–47.9) | oxLDL, 8-isoP, TBARS | shellfish consumption associated with elevated levels of plasma oxLDL | [11] |
| Vitamin E intake (semi-quantitative FFQ, 146 items) | CHD | 1002 (20–75) | 3NT, GSH/GSSG, GPx | higher GPx activity associated with an inadequate intake of vitamin E | [12] |
| Magnesium intake (3-day food diary) | healthy vs. obese | 83 women: 31 obese (34.7 ± 7.58) 52 control (35.4 ± 8.64) | TBARS | negative correlations between erythrocyte magnesium concentrations and plasma TBARS only in obese group | [13] |
| Dietary intake (dietary habits questionnaire) | healthy but cognitive frail | 815 (68.9 ± 6.1) | MDA | cognitive frail participants had lower intakes of niacin and riboflavin as well as higher plasma MDA | [14] |
| Nutritional status/intake (standardized 24h food record) | HD | 49 (18–65) | TAC, iron, Mn, Se, Zn, MDA, PCs, erythrocyte GPx | carbohydrate intake correlated positively with MDA and PCs, zinc intake correlated negatively with MDA and PCs | [15] |
| Dietary intake (semi-quantitative FFQ) | HD | 85 (62 ± 13.7) | TAC, SOD, MDA, GST, NO | low plasma NO associated with higher intake of nutrients with antioxidant properties (Cu, Mn, ω-3, ω-6, vitamin E) | [16] |

All biomarker measurements in blood (unless otherwise stated); men and women included (unless otherwise stated).
controversially discussed or has not yet been conclusively clarified including ω-3 fatty acids, vitamin D and probiotic supplementation.

We furthermore aimed to evaluate different categories of redox biomarkers.

2. Methods

Literature search using PubMed was conducted on June 11th, 2020. Search terms included “nutrition” AND “oxidative stress” AND “biomarkers”. The search was restricted to articles published between January 1st, 2017 and the search date. A total of 498 articles were screened by two investigators based on abstracts. Inclusion criteria were: evaluation of dietary habits OR a dietary intervention AND measuring at least one OS biomarker of the following categories: (I) exogenous antioxidants, (II) endogenous antioxidants, and (III) oxidative damage biomarkers in biological samples. Articles that did not meet the inclusion criteria were removed. Studies assessing diet/interventions in children, pregnant or lactating women as well as those concerning patients suffering from cancer, HIV or gastrointestinal diseases were excluded. The selection process of articles used in this review is shown in Fig. 1. Studies were grouped into those reporting analyses of (I) exogenous antioxidants, (II) endogenous antioxidants, and (III) oxidative damage biomarkers in biological samples. Articles that did not meet the inclusion criteria were removed. Studies assessing diet/interventions in children, pregnant or lactating women as well as those concerning patients suffering from cancer, HIV or gastrointestinal diseases were excluded.

3. Results

3.1. Observational studies

Ten observational studies focusing on general dietary patterns as well as isolated micronutrients were included in this review (Fig. 3).

Although most studies were conducted with healthy participants two studies included HD patients and one study included patients suffering from coronary heart disease (CHD). The characteristics of each study are summarized in Table 1. Regarding F/V intake one observational study found significant negative correlations between individual plasma values of oxLDL and plasma levels of lutein as well as β-carotene and TAC [6]. These observed dietary habits were significantly sex-related with a higher F/V intake (p < 0.05) and higher plasma β-carotene (p < 0.001) in women compared to men. Additionally, levels of plasma lipid hydroperoxides were significantly lower in women compared to men. Likewise, MDA was higher in the cluster of obese participants and the obese participants had a lower F/V intake [9]. Examination of associations for diet quality and OS reported negative correlations between Recommended Food Score (RFS) and plasma MDA concentrations in participants suffering from “OS conditions” (obesity, hypertension, metabolic syndrome (MetS), diabetes and cancers), while no association between RFS and plasma MDA was found in the healthy control group [5]. One study found inverse associations between dietary intake of polyunsaturated fatty acids (PUFAs) and insoluble fiber with plasma isoprostanes concentrations [10]; a higher shellfish consumption was also reported to be associated with higher levels of plasma oxLDL in a Mediterranean population [11].

Focusing on single micronutrients, one study observed that higher intakes of niacin and riboflavin as well as higher plasma MDA [14]. Concerning patients undergoing HD, Silva et al. [15] found no
### Table 3
Probiotic supplementation in patients.

| Intervention | Disease | N (age in years) | Biomarkers | Effect of intervention | Ref. |
|--------------|---------|------------------|------------|------------------------|------|
| 100 ml Sorghum drink with probiotics, 3-4x/wk, 2pk on day of HD and the day after, 7 wks, SB | CKD/HD | 58: 29 PG (63 ± 10.6) 29 IG (63.2 ± 11.2) | TAC, MDA, SOD, polyphenols | TAC higher (*), MDA lower (*), SOD higher (*) | [27] |
| Probiotic supplements daily (one capsule/day), 12 wks, DB | HD | 60: 30 PG (59.4 ± 16.0) 30 IG (54.0 ± 16.0) | TAC, MDA, NO, GSH | MDA lower (*), TAC lower | [30] |
| 100 mg Lactobacillus casei Lactobacillus tablet, 2 per day, 8 wks, DB | HD | 46 (63 ± 17) | MDA | MDA decreased (#) | [31] |
| Probiotic capsule(s) supplements daily, 12 wks, DB | diabetic nephropathy | 60: 30 PG (60.9 ± 4.4) 30 IG (58.9 ± 8.8) | TAC, MDA, GSH, NO, AGEs | NO increased, GSH increased, MDA reduced, AGEs reduced (*) | [32] |
| 200 ml probiotic soy milk/day, 8 wks (vs. soy milk), SB | diabetic kidney disease | 40: 20 PG (53.6 ± 1.6) 20 IG (56.9 ± 1.8) | TAC, MDA, GPx, GSH/GSSG, GR, 8-isoP | increase in GSH, GPx and GR, decrease in GSSG (+) | [28] |
| 220 g yoghurt or milk per day, 24 wks, NB | NAFLD and MetS | 92 women (36–66) 44 PG 48 IG | SOD, GPx | SOD, GPx increased in yoghurt vs. milk group after 24 wks (+) | [29] |
| Syn-/Probiotic supplements daily, 12 wks, DB | overweight, diabetes and CHD | 60: 30 PG (64.9 ± 11.7) 30 IG (64.2 ± 12.0) | TAC, MDA, NO, GSH | NO increased, MDA decreased (#) | [33] |
| Probiotic supplement capsules daily, 12 wks, DB | Multiple Sclerosis | 60: 30 PG (33.8 ± 8.9) 30 IG (34.4 ± 9.2) | TAC, MDA, NO, GSH | differences in adjusted changes between MDA and NO (*) | [34] |
| Probiotic supplements capsule daily, 12 wks, DB | diabetic foot ulcer | 60: 29 PG (58.5 ± 11.0) 30 IG (62.6 ± 9.7) | TAC, MDA, NO, GSH | higher TAC, NO, lower MDA (*) | [35] |
| Probiotic supplements daily, 12 wks, DB | PCOS | 60: 30 PG (27.7 ± 4.7) 30 IG (27.2 ± 4.6) | TAC, MDA, NO, GSH | TAC, MDA, NO, GSH higher MDA (*) | [36] |

All biomarkers measurements in blood (unless otherwise stated); men and women included (unless otherwise stated); PG (placebo group), IG (intervention group). DB (double-blind), SB (single blind), NB (not blinded); only significant results are mentioned. Significant changes are marked by: (*) vs. PG; (+) vs. baseline; (#) vs. baseline and PG.

### Table 4
Interventions with vitamin E and/or ω-3 supplementation in patients.

| Intervention | Disease | N (age in years) | Biomarkers | Effect of intervention | Ref. |
|--------------|---------|------------------|------------|------------------------|------|
| 1000 mg ω-3 + 400 IU vitamin E, 12 wks, DB | Fibrocystic breast disease | 56: 28 PG (47.6 ± 5.8) 28 IG (45.3 ± 7.2) | TAC, MDA, NO, GSH | NO higher (*) | [37] |
| 1000 mg flaxseed oil/day, 12 wks, DB | diabetic nephropathy | 60: 30 PG (62.4 ± 9.6) 30 IG (62.9 ± 10.5) | TAC, MDA, NO, GSH | no effect | [38] |
| 1000 mg flaxseed oil + 400 IU vitamin E/day, 12 wks, DB | PCOS | 68: 34 PG (26.6 ± 5.6) 34 IG (24.9 ± 5.5) | TAC, MDA, GSH | TAC increased (#), MDA decreased (#) | [39] |
| 2x1000 mg/day flaxseed oil ω-3 supplements, 12 wks, DB | PCOS | 60: 30 PG (27.0 ± 3.2) 30 IG (28.4 ± 6.4) | NO | no effect | [40] |
| 180 mg EPA, 120 mg DHA, 2 mg vitamin E, 3x/day, 8 wks, DB | Type 2 diabetes | 30: 15 PG (50.5 ± 6.1) 15 IG (50.7 ± 6.7) | TBARS, 8-isoP, TRAP, SOD, uric acid | no effect | [41] |
| 400 IU vitamin E, 12 wks, DB | implantation failure | 40: 20 IG (32.2 ± 2.3) 20 PG (31.5 ± 2.3) | MDA | MDA lower (*) | [42] |
| 800 IU vitamin E, 12 wks, DB | diabetic nephropathy | 54: 27 PG (64.5 ± 9.2) 27 IG (62.2 ± 9.8) | TAC, MDA, NO, GSH, vitamin E | GSH higher (*) | [43] |
| (A) 30 g isolated soy protein + flaxseed oil (B) isolated soy protein + corn oil (C) wheat flour + corn oil 12 wks, DB | wound healing of burn patients | 73: | MDA, SOD | no effect | [44] |
statistically significant associations between nutritional status and OS status in HD patients while Epifano et al. [16] found inverse associations between nutrient intake with antioxidant properties (Cu, Zn, Mn, vitamin C and ω-3, vitamin E) and plasma nitric oxide (NO) concentrations in HD patients.

### 3.2. Intervention studies with patients

#### 3.2.1. Vitamin D supplementation

Multiple studies investigated the influence of high-dose vitamin D supplementation on OS status in patients with various diseases. Intervention doses ranged from 50000 IU vitamin D3 every two weeks to 1000 IU daily. Intervention duration ranged from eight weeks to six months. An overview of the study characteristics is shown in Table 2.

Studies investigating the influence of high-dose vitamin D supplementation on OS in patients suffering from polycystic ovary syndrome (PCOS) found consistent results regarding significantly reduced plasma MDA levels compared to the placebo group [17–19]. No effect was found on NO concentrations between placebo and intervention [18,19], while few studies reported positive effects on TAC and GSH levels [17,19]. In diabetic patient’s high-dose vitamin D supplementation showed different effects on OS markers. Even though plasma MDA was significantly reduced in patients with diabetic foot ulcer compared to the placebo group [20], no effect on OS markers were observed in patients with diabetic nephropathy [21]. Consensus results on plasma MDA reduction in the intervention group were found in multiple studies including patients suffering from coronary artery disease, irritable bowel syndrome, multiple sclerosis as well as patients undergoing HD after long-term (three - six months) high-dose vitamin D supplementation [22–25]. Vitamin D intervention in methadone treated patients lead to a significant increase in plasma GSH and TAC levels while plasma MDA levels were not affected compared to the placebo group [26].

#### 3.2.2. Probiotic supplementation

Probiotic supplementation was performed in multiple studies by daily administration of one capsule probiotic supplement containing 2x10^9 colony forming units (CFU) of Lactobacillus species L.casei, L. acidophilus or L.fermentum as well as Bifidobacterium bifidum for twelve weeks (Table 3). Another way of probiotic supplementation was performed by administering probiotic drinks or yoghurt [27–29] for seven–eight weeks.

Three studies investigated the effect of probiotic supplementation in patients undergoing HD and reported consistent results regarding an improved OS status in patients receiving probiotic treatment. Each study reported significantly reduced plasma MDA levels in the intervention group compared to the placebo group [27,30] or compared to baseline [31]. An increase in plasma TAC in the intervention group was found in two studies [27,30], while an additional increase in SOD activity was reported by Lopes et al. [27]. Probiotic supplementation in patients suffering from diabetic kidney disease led to mixed results. Although daily administration of probiotic supplements for twelve weeks showed a significant increase in plasma GSH with simultaneous decrease in plasma MDA [32], no effect on plasma MDA was observed after daily consumption of probiotic soy milk for eight weeks, while plasma GSH as well as GR and GPx activity showed a significant increase [28]. Increased activity of plasma GPx and SOD as well as reduced 8-isoP

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**Table 5**

Supplementation with phytochemicals in patients.

| Intervention | Disease | N (age in years) | Biomarkers | Effect of intervention | Ref. |
|--------------|---------|-----------------|------------|-----------------------|------|
| 2 capsules 250 mg pomegranate extract/day, 8 wks, DB | rheumatoid arthritis | 55: 30 IG (48.4 ± 11.4) 25 PG (49.1 ± 12.2) | GPx, MDA | GPx higher (*) | [45] |
| 100 ml pomegranate juice, 3x/wk, crossover (8 wks IG/PG, 4 wks wash-out, 8 wks IG/PG), NB | HD | 41 (18–65) 22 IG 19 PG | TAC, MDA, IL-6, blood pressure | TAC increased, MDA decreased (#) | [46] |
| 300 mg mulberry extract/day, 12 wks, DB | diabetic nephropathy | 60: 30 IG (63.7 ± 10.8) 30 PG (63.1 ± 9.6) | TAC, NO, GSH, MDA | IG: NO increased (+), GSH increased (+), MDA decreased (#), PG: MDA increased (#) | [47] |
| 200 ml agraiz (blueberry) nectar daily, crossover (4 wks intervention, 4 wks washout, 4 wks intervention), DB | MetS | 40 women (47 ± 9) | TAC (AC by DPPH), TBARS, urinary 8OHdG, 8-isoP | higher TAC, lower 8OHdG (*) | [48] |
| 3 g (~3 capsules) Melissa officinalis extract/day, 8 wks, DB | chronic stable angina pectoris | 73: 35 IG (58.8 ± 8.3) 38 PG (56.5 ± 8.9) | MDA, PON1 | MDA lower (*) PON1 higher (*) | [49] |
| Genistein supplementation 2 capsules/day (54 mg), 12 wks, DB | Type 2 diabetes | 54 women (47–69) 28 IG 36 PG | TAC, MDA | MDA decreased (+), TAC higher (*) | [50] |
| 2x 500 mg curcumin capsules daily, 12 wks vs. placebo, DB | β-Thalassemia | 61: 31 IG (25.97 ± 6.92) 30 PG (27.61 ± 6.23) | TAC, MDA, CAT, vitamin E | MDA decreased (#), TAC increased (+) | [51] |
| 30 mg crocin/day, 4 wks, DB | Multiple sclerosis | 40: 20 IG (29 ± 5) 20 PG (31.5 ± 5.3) | TAC, MDA, total thiols, DNA damage | MDA decreased in PG (+) and IG (#) DNA damage lower in PG and IG (*) Total thiols lower only in IG (*) TAC increased in Ig (*) | [52] |
| 15 mg/day gallic acid, 1 wk, crossover, DB | type 2 diabetes | 19 (66.6 ± 7.5) | MDA, FRAP, oxLDL | oxLDL reduction in Ig (+) | [53] |
| 2/day, 6 months (303 mg silybin, 10 μg vitamin D, 15 μg vitamin E), 6 months additional follow-up with no intervention vs. healthy control and vs. untreated patients, NB | NAFLD | 90 (18–85) 60 treated, 30 did not, vs. 60 healthy controls | TBARS | TBARS ‘improved’ by 80% in treated group after 6 months (+); significance is not clear | [54] |
levels were observed in patients with MetS and NAFLD after intervention; (#) vs. baseline and PG. Significant changes are marked by: (*) vs. PG; (†) vs. women included (unless otherwise stated); PG (placebo group), IG (intervention group). DB (double-blind), SB (single blind), NB (not blinded); only significant results are mentioned. Significant changes are marked by: (*) vs. PG; (†) vs. baseline; (#) vs. baseline and PG.

### Table 6

| Intervention | Disease | N (age in years) | Biomarkers | Effect of intervention | Ref. |
|-------------|---------|-----------------|------------|------------------------|------|
| 250 mg magnesium oxide + 220 mg ZnSO4 2x/day, 12 wks, DB | PCOS 60 women (18–40) | TAC, GSH, MDA, NO, PCs | GSH higher (*) | [55] |
| 250 mg magnesium vitamin E/day, 12 wks, DB | PCOS 60 women: 30 IG (26 ± 3.7) 30 PG (27.2 ± 7.1) | TAC, GSH, MDA, NO | TAC and NO increased (#) | [56] |
| 100 mg magnesium, 4 mg zinc, 400 mg calcium + 200 IU vitamin D 2x/day, 12 wks, DB | PCOS 60 women: 30 IG (24.8 ± 4.8) 30 PG (23.8 ± 5.7) | TAC, GSH, MDA, NO | MDA lower (*), TAC higher (*) | [57] |
| 200 µg/day chromium, 8 wks, DB | PCOS 40 women (18–40) | TAC, GSH, MDA, NO | TAC higher (*), MDA lower (*) | [58] |
| 200 µg selenium yeast/cardiac bypass, 4 wks, DB | TAC, GSH, MDA, NO | GSH higher (*) | [59] |

All biomarkers measurements in blood (unless otherwise stated); men and women included (unless otherwise stated); PG (placebo group), IG (intervention group). DB (double-blind), SB (single blind), NB (not blinded); only significant results are mentioned. Significant changes are marked by: (*) vs. PG; (†) vs. baseline; (#) vs. baseline and PG.

3.2.3. Vitamin E and ω-3 supplementation

ω-3 supplementation was mainly performed by administration of 1000 mg flaxseed oil, rich in α-linolenic acid, each day for twelve weeks [37–40] whereby two supplements contained additional 400 IU vitamin E [37,39]. Co-supplementation of long-chain PUFA and vitamin E delivering 180 mg eicosapentaenoic acid (EPA), 120 mg docosahexaenoic acid (DHA) and 9 IU vitamin E per day for eight weeks was performed in one study [41] while isolated vitamin E supplementation in high doses of 400 and 800 IU per day for twelve weeks was conducted in two studies [42,43]. Study details are enlisted in Table 4.

Findings on the effect of isolated ω-3-administration on OS status have been mostly consistent. Administration of 1000 mg flaxseed oil/day for twelve weeks neither showed an effect on OS status in women with PCOS nor in patients with diabetic nephropathy [38,40]. The same was observed after even higher dosage of 30 g flaxseed oil/day for three weeks in wound healing patients [44]. The co-supplementation of 1000 mg flaxseed oil and 400 IU vitamin E in patients diagnosed with fibrocystic breast disease on the other hand led to a significant increase in plasma NO in the intervention group, but had no effect on plasma MDA [37]. Contrary, flaxseed oil and vitamin E co-supplementation significantly lowered plasma MDA levels in PCOS patients, but no effect on plasma GSH was observed [39]. Intervention with long-chain PUFA and low-dose vitamin E in type 2 diabetic patients again showed no significant effect on plasma TBARS [41]. High-dose vitamin E supplementation for twelve weeks in implantation failure patients significantly lowered plasma MDA levels [42], while no effect on OS markers were observed in diabetic nephropathy patients with exception of significantly elevated plasma GSH levels [43].

3.2.4. Supplementation with polyphenol-rich plant extracts or single phytochemicals

Extracts from various fruits containing high amounts of polyphenols such as pomegranate, mulberry and blueberry have been evaluated for their influence on the OS status in multiple diseases as well as isolated phytochemicals such as genistein, gallic acid, curcumin (from the curcuma root), crocin (crocus and gardenia flowers) or silybin (from the milk thistle seeds) leading to various improvements in OS markers (see Table 5).

Intervention with 250 mg pomegranate extract twice a day for eight weeks in patients with rheumatoid arthritis showed no effect on plasma MDA in the intervention group while plasma GPx activity was significantly elevated [45]. In contrast, 100 ml pomegranate juice three times a day for three weeks led to significant reduction in plasma MDA compared to the placebo group in patients undergoing HD [46]. Likewise, administration of 300 mg mulberry extract per day for twelve weeks reduced plasma MDA while increasing plasma GSH in diabetic kidney disease patients [47]. Daily administration of 200 ml blueberry nectar for four weeks significantly increased TAC while plasma TBARS and isoprostanes were not affected [48]. 3 g of Melissa officinalis extract per day for eight weeks was reported to significantly reduce plasma MDA levels in patients with chronic stable angina pectoris while increasing PON1 activity [49]. Studies concerning supplementation with isolated phytochemicals reported almost consistent beneficial results. Thus, a reduction of plasma MDA with simultaneous increase in TAC was observed for genistein supplementation in type 2 diabetic patients, after curcumin supplementation in β-thalassemia patients and after crocin supplementation in multiple sclerosis patients [50–52]. In a crossover study, the daily administration of 15 mg gallic acid significantly reduced plasma oxLDL levels while plasma MDA and FRAP levels were unchanged [53]. Intervention with 303 mg silybin-phospholipid twice a day for four weeks significantly reduced plasma TBARS in NAFLD patients [54].

3.2.5. Trace and bulk element supplementation

The influence of the bulk element magnesium on OS was the research objective in three intervention studies (Table 6). Magnesium was always co-supplemented with calcium, vitamin E or zinc. Individually performed intervention study on the antioxidative effect of trace elements have been performed for selenium and chromium. Duration of the interventions ranged from four to twelve weeks.

Studies investigating the influence of magnesium co-supplementation on OS markers in women diagnosed with PCOS reported inconsistent changes in different biomarkers [55–57]. While co-supplementation of 250 mg magnesium oxide with 220 mg zinc sulfate twice a day for twelve weeks resulted in a significant reduction in PCs and elevated levels of plasma GSH, no effect on plasma TAC, NO and MDA was observed [55]. Whereas administration with 100 mg magnesium, 4 mg zinc, 400 mg calcium and 200 IU vitamin D3 twice a day for twelve weeks led to significant reductions in plasma MDA and increased plasma TAC, while GSH levels were unchanged [57]. Intervention with 250 mg magnesium oxide and 400 IU vitamin E improved plasma TAC and NO values in the intervention group while plasma MDA and GSH were unaffected [56]. Regarding trace elements, daily supplementation with 200 µg chromium for eight weeks significantly lowered plasma...
Table 7
Interventions with foodstuffs in healthy participants.

| Intervention                                                                 | N (age in years) | Biomarkers                  | Effect of intervention                  | Ref     |
|------------------------------------------------------------------------------|------------------|------------------------------|-----------------------------------------|---------|
| 450 mg/day green tea extract (GTE) or 450 mg/day sour tea extract (STE) vs. placebo | 18 GTE (20.94 ± 1.43) | TAC, MDA                    | MDA decreased (#) and TAC increased (#) in both GTE and STE group | [60]    |
| 10 g matisha powder, single-dose, NB                                          | 17 men (20-40)  | oxLDL                       | oxLDL reduced until 6 h after intake (+) | [61]    |
| Antioxidant ice cream with green tea extract, single-dose, SB                | 14 (38 ± 3)      | FRAP, NOx, H₂O₂, dROM, polyphenols | FRAP increased, H₂O₂, dROM decrease 2 h after antioxidant ice cream consumption (+) | [62]    |
| 200 ml mate tea 3x/day, 7 days vs. control, NB                               | 9 men (25 ± 3)   | GSH/GSSG                    | Lower GSH (*)                           | [63]    |
| 250 mg yerba mate extract 9x/day, 60 d, NB                                   | 14 (age not mentioned) | GSH, Gpx, SOD, CAT, PON1, LOOH, TBARS | Improvement in all markers (+)          | [64]    |
| 3 g cardamom powder intake, 12 days, DB                                      | 40: 20 IG (48.3 ± 10.4) | TAC, MDA, SOD, PCs, GR  | MDA lower (*)                           | [65]    |
| Beetroot juice; 70 ml 2x/day, DB                                             | 20 (60–75)       | 2NT, NOx                    | no effect                              | [66]    |
| 480 ml tart cherry juice/day, 12 days, NB                                    | 37 (65–80)       | 8OHdG, MDA, 8-oxoguanine glycosylate, oxLDL, 4-HNE | no effect                              | [67]    |
| Cranberry extract beverage 450 ml/day, 8 days, DB                            | 78: (43.1 ± 1.1) | GSH/GSSG, Gpx, SOD         | no effect                              | [68]    |
| 500 mg Aronia extract/day, 12 days, DB                                       | 49: 25 IG (32.6 ± 2.6) | oxLDL, CAT, Gpx, SOD       | no effect                              | [69]    |
| 600 ml berry beverage 3x/day, 5 days, NB                                     | 40 (63 ± 1)      | oxLDL, MADA                 | no effect                              | [70]    |
| Prune essence concentrates 100 ml or 50 ml or 50 ml placebo per day, 4 days, NB | 60 (18–53): 20 in each group | TAC, TBARS                 | no effect                              | [71]    |
| 750 ml anthocyanin-rich fruit juice, 8 days, NB                              | 62 men (20–50)   | SOD, CAT, oxLDL, urine anthocyanins | no effect                              | [72]    |
| 500 mL of pomegranate juice once before exercise training, NB               | 9 (21 ± 1)       | MDA, CAT, Gpx               | Lower MDA, higher CAT GPx (*)          | [73]    |
| 200 g of açai pulp/day, 4 weeks, NB                                          | 40 women (24 ± 3) | TAC, oxLDL, PON1, ROS      | oxLDL, MDA decreased, TAC, PON1 increased (+) | [74]    |
| 500 ml of a fermented orange juice beverage a day, 2 days, NB                | 30 (33.9 ± 6.9)  | TAC, ORAC, SOD, Gpx, GR (glutathione reductase), GSH, TBARS, oxLDL. | ORAC higher (*)                        | [75]    |
| Korean black raspberry powder, 30g/day, 2 weeks, NB                          | 102 (30–60)      | MDA, GSH/GSSG, erythrocyte: CAT, SOD, Gpx | Higher GSH/GSSG ratio in erythrocytes, lower plasma MDA (*) | [76]    |
| 22 g freeze-dried highbush blueberry powder/day, 8 days, DB                  | 40 (45–65)       | TBARS, oxLDL, SOD, Gpx, GR, 8-isoP, 8OHdG | short-term effect on 8OHdG, reduction after 4 wks intervention but not 8 wks (+) | [77]    |
| 16.9 g in slowly digestible starch/day, 3 weeks, NB                          | 20 (20–65)       | MDA, GSH, urinary isoP      | MDA increased, GSH decreased (+)       | [78]    |
| 70 g oat porridge/day, 4 weeks, NB                                           | 24 (30–60)       | ORAC, FRAP, MDA             | increased ORAC and FRAP (+)            | [79]    |
| Wine grape beef burger daily, 1 month, NB                                    | 34 men (25–65)   | TRAP, MDA, oxLDL, AOPPs, tocopherols, vitamin C | AOPP, oxLDL lower (*)                  | [80]    |
| 90 g raisins/day, 4 weeks, NB                                                | 36: 14 PG (29.8 ± 1.4)  | MDA, AOPPs, NO             | no effect                              | [81]    |
| 100 mg seaweed/day, 8 weeks, DB, crossover                                   | 80 (30–65)       | TAC, polyphenols             | no effect                              | [82]    |

All biomarkers measurements in blood (unless otherwise stated); men and women included (unless otherwise stated); PG (placebo group), IG (intervention group). DB (double-blind), SB (single blind), NB (not blinded); only significant results are mentioned. Significant changes are marked by: (*) vs. PG; (+) vs. baseline; (#) vs. baseline and PG.

MDA levels in women with PCOS while simultaneously increasing plasma GSH levels [58]. Similar effects were observed after intervention with 200 μg/day selenium as selenium yeast for four weeks in patients undergoing coronary artery bypass grafting which significantly reduced plasma MDA levels while significantly increasing plasma GSH [59].

3.3. Intervention studies in healthy participants

3.3.1. Interventions with foodstuffs

Table 7 shows interventions in healthy participants with foodstuffs. Multiple studies investigating long- and short-term effects on green tea or mate extract consumption in healthy participants found consistent improvements in different markers of OS. Daily consumption of 450 mg green tea extract (Camellia sinensis) or sour tea extract (Hibiscus sabdariffa) for six months significantly reduced plasma MDA and increased TAC in the respective intervention groups compared to the placebo group [60]. Improvements of OS status were also reported in single-dose ingestion of 10 g matisha powder (Camellia sinensis) that resulted in significantly reduced plasma oxLDL until 6 h after intake [61]. After single consumption of ice cream containing green tea extract, increase in plasma FRAP was observed after 2 h of intake while plasma derivatives of reactive oxygen metabolites (dROM) and H₂O₂ were reduced [62]. Administration of 200 ml mate tea (Ilex paraguariensis) three times a day for one week significantly improved the ratio between reduced and plasma FRAP.
oxidized glutathione (GSH:GSSG ratio) [63], the ingestion of 250 mg mate extract nine times a day for 60 days showed beneficial effects on various markers of OS including SOD, CAT, GPX and PON1 activity as well as elevated plasma GSH concentrations [64]. Daily intake of 3 g cardamom powder for twelve weeks was reported to significantly reduce plasma MDA [65].

Studies on the beneficial effects of polyphenol-rich juices and fruit extracts on the OS status in healthy participants came to different results. Interventions with 70 ml beetroot juice for two days [66], 480 ml tart cherry juice a day for twelve weeks [69], 600 ml of a mixed berry beverage three times a day for five weeks [70], 100 ml prune extract per day for four weeks [71] as well as daily intake of 750 ml of an mixed anthocyanin-rich fruit juice for eight weeks [72] showed no effect on the OS status of healthy participants. In contrast, some studies reported improvements. Single-dose administration of 500 ml pomegranate juice after exercise significantly attenuated oxidation of plasma MDA [65].

Table 8 shows interventions in healthy participants with supplements. Several studies investigated the influence of single supplements on the OS status of healthy participants while mainly focusing on supplements rich in antioxidants such as anthocyanins, flavonoids or carotenoids.

Daily supplementation with 60 mg anthocyanins or 6 mg lutein plus 2 mg zeaxanthin/day or both combined was reported to significantly increase plasma MDA and plasma GSH levels decreased after intervention [78]. Administration of 70 g oat porridge per day for four weeks on the other hand was reported to increase plasma ORAC and FRAP, while plasma MDA levels were unchanged [79]. Intake of beef burgers prepared with wine grape pomace flour on a daily basis for one month reduced plasma oxLDL as well as advanced oxidation protein products (AOPP) after intervention [80]. No significant effect on participants redox status was observed in two studies investigating the effect of a daily intake of 90 g raisins for four weeks [81] or 100 mg sea weed for eight weeks [82].

### 3.3.2. Interventions with single supplements or multi-nutrient supplements

Table 8 shows interventions in healthy participants with supplements. Several studies investigated the influence of single supplements on the OS status of healthy participants while mainly focusing on supplements rich in antioxidants such as anthocyanins, flavonoids or carotenoids.

Daily supplementation with 60 mg anthocyanins or 6 mg lutein plus 2 mg zeaxanthin/day or both combined was reported to significantly increase plasma MDA and plasma GSH levels decreased after intervention [78]. Administration of 70 g oat porridge per day for four weeks on the other hand was reported to increase plasma ORAC and FRAP, while plasma MDA levels were unchanged [79]. Intake of beef burgers prepared with wine grape pomace flour on a daily basis for one month reduced plasma oxLDL as well as advanced oxidation protein products (AOPP) after intervention [80]. No significant effect on participants redox status was observed in two studies investigating the effect of a daily intake of 90 g raisins for four weeks [81] or 100 mg sea weed for eight weeks [82].
participants was observed for supplementation with 1720 mg DHA and 600 mg EPA daily for 18 months [90] as well as daily intake of 1500 mg L-carnitine for 24 weeks [91].

Supplementations with multi-nutrient packs showed inconsistent results. While a three-month intervention with daily intake of one multi-micronutrient pack significantly decreased plasma MDA and increasing plasma TAC and GSH levels [92], eight-week intervention with daily consumption of 80 ml Mind Master® containing a mixture of vitamins and trace elements showed no effect on plasma biomarker of OS [93]. A similar observation was made after single administration of an antioxidant supplement containing vitamin C, E and α-linolenic acid where no changes in plasma MDA were observed [94].

4. Discussion

The interplay between dietary factors and lifestyle factors including exercise, sun exposure, diseases and medication and resulting biomarkers is complex. An overview of the study characteristics – diet and supplements, diseases, biomarkers – included in this review is given in Fig. 2. Recent observational studies were able to show inverse association between F/V intake and plasma markers of OS such as oxLDL and MDA. The observed effects were assigned to the antioxidative capacity of F/V’s phytochemicals such as carotenoids as well as their content in insoluble fiber. Interestingly intervention studies supplementing isolated carotenoids were not able to find strong improvements in the redox status of healthy participants showing a possible advantage of consumption of whole F/V compared to isolated phytochemicals.

Intervention studies with patients showed almost uniformly positive effects on the participants redox status by supplementation with vitamin D, independently of the disease. Vitamin D was administered in a dosage of 50,000 IU every two weeks over a timespan of usually 8–12 weeks. Likewise, beneficial effects on patients redox status were reported for intervention with fruit extracts (pomegranate, mulberry), probiotic supplementation with cultures of L.casei, L.acidophilus, L.fermentum and Bifidobacterium bifidum as well as bulk element magnesium and trace elements selenium and chromium.

Consistently no effects on redox biomarkers in patients were observed for intervention studies focusing only on ω-3 fatty acids. It should be noted that the majority of the intervention studies with patients included in this review were conducted by single or collaborating research groups from Iran. One study described their study population as under “OS conditions”. This included MetS, obesity, and diseases such as type 2 diabetes, hypertension, dyslipidemia, cardiovascular/neurovascular diseases, or diet-related cancers (liver, colon, stomach, breast, prostate, and lung) [5]. However, these diseases are heterogeneous and therefore difficult to combine into one group.

Concerning study sample sizes, the majority included 100 participants or less. The largest observational study had 1229 participants [5], while the largest intervention study with healthy subjects had 391 participants [90]. Thus, this is something to keep in mind, especially when interpreting studies.

Intervention studies conducted with healthy participants were able to show positive effects on redox status by intake of tea extracts derived from Camelia sinensis and Ilex paraguariensis regardless of the duration. Observations on redox status after intake of polyphenol-rich juices and fruit extracts have been mostly inconsistent because the number of studies showing improvements and those with no effect are balanced. The same applies to multi-nutrient intervention studies with healthy participants included in this review which in general express the overriding problem that observed improvements in participant’s redox status cannot be tracked down to one component and are therefore difficult to interpret.

It is encouraging that the vast majority of the studies included in this review rely on the measurement of multiple biomarkers to determine the redox status of their participants rather than focusing on one isolated
biomarker as OS should not be regarded as a closed system and until now no known biomarker of OS can be viewed as a stand-alone “gold standard” [95–97].

For the determination of the endogenous antioxidative defense multiple studies relied on rather unspecific assays based on simple redox reactions like TRAP, FRAP, TEAC or ORAC which can be regarded as insufficient for capturing the in vivo redox state as they are heavily influenced by plasma uric acid [98] and do not account for the activity of enzymes with antioxidative properties such as SOD, CAT and GPx. While the use of assays like TRAP, FRAP, TEAC and ORAC is appropriate for in vitro applications like determination of the antioxidative potential of beverages or plant extracts they should not be used as a stand-alone marker for in vivo antioxidative capacity and at least be combined with the measurement of CAT, SOD or GPx activities [95].

Only seven studies were identified that analyzed blood biomarkers of every category: exogenous antioxidants, endogenous antioxidants and OS (see Fig. 3). Four of these were intervention studies with healthy participants [62,72,80,84], two were interventions in patients [27,51]. One observation study with healthy participants also used all three categories [6] but again, measurement of endogenous antioxidants was based on TAC, FOX2 (ferrous oxidation-xylenol orange 2) and dietary TAC, thus limiting results. Of the 7 studies four studies did not only rely on TAC/FRAP/ORAC assays as endogenous antioxidant measure [27,51, 62,72].

One should keep in mind, that some biomarkers should only be analyzed in specific specimen, for instance, the GSH:GSSG ratio should be measured in whole blood or red blood cells as GSH is a major intracellular non-protein thiol whose concentration is known to be strongly affected by hemolysis of plasma/serum samples as well as storage time [99] while MDA, due to the autoxidation during agglutination is best measured in plasma. Thus, the sample type must be considered when carrying out and interpreting human studies.

The most commonly used biomarkers in the selected studies were TAC, MDA and GSH. These are relatively easy methods but are limited in informative value and come with limitations. Again, many of the intervention studies came from the same research group from Iran, thus applying similar study protocols and similar sample sizes.

5. Conclusion

Current observational studies strengthen the already known beneficial effects of a sufficient intake of F/V by showing inverse association between F/V intake and markers of OS. Nevertheless, the significance of these findings could be improved by conducting observational studies with larger study populations and using biomarkers of all three categories. Generally, it should be possible when taking a blood sample, to split the sample and use it for different assays. Nutrients which have been reported to modulate the redox status in a positive way include vitamin D and E, magnesium, zinc, chromium and selenium as well as probiotic supplementation and several phytochemicals. Regarding foodstuffs, the intake of extracts derived from Camelia sinensis and Ilex paraguariensis were shown to improve markers of OS. Larger study populations and using biomarkers of all three categories could improve meaningfulness of studies and allow better comparison of studies.

Overall, we recommend that researchers look for alternatives to TAC to analyze endogenous antioxidant status, such as GHS:GSSH ratio. Our recommendations are summarized in an Expert Opinion Box. As we are at the edge of a true demographic explosion, it would be very useful, if scientists were be able to include high-quality studies in future reviews based on these criteria.

Furthermore, biomarkers from all three categories should be used. Ideally, these biomarkers would be measured with standard protocols, in the appropriate sample (serum/plasma/whole blood) and units would be published in comparable manner (i.e. units vs. change % etc.).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.
Human observational studies on redox biomarkers lose interpretability if they:

- do not involve a broad spectrum of both biomarker categories: antioxidants and damage biomarkers
- only use total antioxidant capacity (TAC) measures or general, highly sensitive, unstable or poorly specific biomarkers
- do not include a rigorous assessment of the participants, especially age and gender
- do not include any parameters associated with biomarkers and health condition (lifestyle habits and season for healthy individuals and disease-specific markers for patients)
- do not analyse results in the context of overall lifestyle habits and comorbidities (particularly relevant as the world’s population is rapidly expanding and at disease risk, i.e. persons aged 80 years and older, or multimorbid)

Human intervention studies on redox biomarkers may lose interpretability if they:

- use supplements with single compounds unless there is a specific research question
- use a mixture of substances independent of lifestyle in general and natural nutrition in particular, unless there is a specific biochemical reason

References

[1] H. Sies, C. Berndt, D.P. Jones, Oxidative stress, Annu. Rev. Biochem. 86 (2017) 715-746.
[2] H. Sies, Biochemistry of oxidative stress, Angew Chem. Int. Ed. Engl. 25 (12) (1986) 1058-1071.
[3] H. Sies, D.P. Jones, Reactive oxygen species (ROS) as pleiotropic physiological signalling agents, Nat. Rev. Mol. Cell Biol. 21 (7) (2020) 363-383.
[4] A. Sharma, et al., Advanced glycation end products and protein carbonyls in plasma reveal sex-specific differences in Parkinson’s and Alzheimer’s disease, Redox Biol. 34 (2020) 101546.
[5] Y. Kim, et al., Combination of diet quality Score, plasma carotenoids, and lipid peroxidation to monitor oxidative stress, Oxid. Med. Cell Longev. 2018 (2018) 960128.
[6] T. Bacchetti, et al., Relationship of fruit and vegetable intake to dietary antioxidant capacity and markers of oxidative stress: a sex-related study, Nutrition 61 (2019) 164-172.
[7] P. Zhang, S.T. Omaye, Antioxidant and prooxidant roles for beta-carotene, alphatocopherol and ascorbic acid in human lung cells, Toxicol. Vitro 15 (1) (2001) 13-24.
[8] G. Block, et al., The effect of vitamins C and E on biomarkers of oxidative stress depends on baseline level, Free Radic. Biol. Med. 45 (4) (2008) 377-384.
[9] T. Fernandez-Navarro, et al., Different intestinal microbial profile in overweight and obese subjects consuming a diet with low content of fiber and antioxidants, Nutrients 9 (6) (2017).
[10] A.Y. Arikawa, et al., Plasma F2-isoprostanes are positively associated with cardiovascular disease: the CORIDIOPREV study, J. Gerontol. A Biol. Sci. Med. Sci. 74 (6) (2019) 770-777.
[11] J.B.S. Morais, et al., Magnesium status and its association with oxidative stress in obese women, Biol. Trace Elem. Res. 175 (2) (2017) 306–311.
[12] N. Aranda, et al., Consumption of seafood and its estimated heavy metals are associated with lipid profile and oxidative lipid damage on healthy adults from a Spanish Mediterranean area: a cross-sectional study, Environ. Res. 156 (2017) 644-651.
[13] A. Corina, et al., Low intake of vitamin E accelerates cellular aging in patients with established cardiovascular disease: the CORIDIOPREV study, J. Gerontol. A Biol. Sci. Med. Sci. 74 (6) (2019) 770-777.
[14] N. F. Malek Rivan, et al., Clinical trial of the effects of vitamin D supplementation on lipid profiles and biomarkers of oxidative stress in vitamin D-deficient women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial, Endocr. Res. 43 (3) (2018) 1–10.
[15] M. Maktabi, M. Chamani, Z. Asemi, The effects of vitamin D supplementation on metabolic status of patients with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial, Horm. Metab. Res. 49 (7) (2017) 499-496.
[16] M. Jamilian, et al., The influences of vitamin D and omega-3 co-supplementation on clinical, metabolic and genetic parameters in women with polycystic ovary syndrome, J. Affect. Disord. 238 (2018) 32–38.
[17] R. Razaghi, et al., The effects of vitamin D supplementation on wound healing and metabolic status in patients with diabetic foot ulcer: a randomized, double-blind, placebo-controlled trial, J. Diabet. Complicat. 31 (4) (2017) 766-772.
[18] M. Barzegari, et al., The effects of vitamin D supplementation on lipid profiles and oxidative indices among diabetic nephropathy patients with marginal vitamin D status, Diabetes Metab. Syndr. 13 (1) (2019) 542-547.
[19] R. Amani, et al., Vitamin D3 induced decrease in IL-17 and malondialdehyde, and increase in IL-10 and total antioxidant capacity levels in patients with irritable bowel syndrome, Iran J. Immunol. 15 (3) (2018) 186–196.
[20] A. Arfokhian, et al., Long-term vitamin D supplementation affects metabolic status in vitamin D-deficient type 2 diabetic patients with coronary artery disease, J. Nutr. 147 (3) (2017) 384-389.
[21] M.R. Tamadon, et al., Clinical trial on the effects of vitamin D supplementation on metabolic profiles in diabetic hemodialysis, Horm. Metab. Res. 50 (1) (2018) 50-55.
[22] E. Koushaki, et al., High-dose omega-3 fatty acid plus vitamin D3 supplementation affects clinical symptoms and metabolic status of patients with multiple sclerosis: a randomized controlled clinical trial, J. Nutr. 148 (8) (2018) 1380–1386.
[23] A. Ghaderi, et al., Clinical trial of the effects of vitamin D supplementation on psychological symptoms and metabolic profiles in maintenance methadone treatment patients, Prog. Neuro-Psychopharmacol. Biol. Psychiatry 79 (Pt B) (2017) 84-89.
[24] R. Lopes, et al., Evaluation of the health benefits consumption of extruded tannin sorghum with unfermented probiotic milk in individuals with chronic kidney disease, Food Res. Int. 107 (2018) 629-638.
[25] M. Miraghaian, et al., The impact of probiotic soy milk consumption on oxidative stress among type 2 diabetic kidney disease patients: a randomized controlled clinical trial, J. Ren. Nutr. 27 (5) (2017) 317-324.
[26] Y. Chen, et al., Yogurt improves insulin resistance and liver fat in obese women with nonalcoholic fatty liver disease and metabolic syndrome: a randomized controlled trial, Am. J. Clin. Nutr. 109 (6) (2019) 1611–1619.
[27] A. Soleimani, et al., Probiotic supplementation in diabetic hemodialysis patients has beneficial metabolic effects, Kidney Int. 91 (2) (2017) 435-442.
[28] A. Kooshki, T. Tofighiyan, M. Mirti, A synthetic biopsy for inflammation and oxidative stress and lipid abnormalities in hemodialysis patients, Hemodial. Int. 23 (2) (2019) 254–260.
[29] A. Maft, et al., Metabolic and genetic response to probiotics supplementation in patients with diabetic nephropathy: a randomized, double-blind, placebo-controlled trial, Food Funct. 9 (9) (2018) 4763-4779.
[30] A. Arfokhian, et al., The effects of synthetic supplementation on carotid intima-media thickness, biomarkers of inflammation, and oxidative stress in people with overweight, diabetes, and coronary heart disease: a randomized, double-blind, placebo-controlled trial, Probiotics Antimicrob. Proteins 11 (1) (2019) 133–142.
[31] E. Koushaki, et al., Clinical and metabolic response to probiotic supplementation in patients with multiple sclerosis: a randomized, double-blind, placebo-controlled trial, Clin. Nutr. 36 (5) (2017) 1245–1249.
[32] S. Mohseni, et al., The beneficial effects of probiotic administration on wound healing and metabolic status in patients with diabetic foot ulcer: a randomized, double-blind, placebo-controlled trial, Diabetes Metab. Res. Rev. 34 (3) (2018).
[33] M. Karamali, et al., Effects of probiotic supplementation on hormonal profiles, biomarkers of inflammation and oxidative stress in women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial, Arch. Iran. Med. 21 (1) (2018) 1–7.
[34] S.M. Mirhashemi, et al., Metabolic response to omega-3 fatty acids and vitamin E co-supplementation in patients with fibrocystic breast disease: a randomized, double-blind, placebo-controlled trial, Arch. Iran. Med. 20 (8) (2017) 466–473.
[35] A. Soleimani, et al., Metabolic response to omega-3 fatty acid supplementation in patients with diabetic nephropathy: a randomized, double-blind, placebo-controlled trial, Clin. Nutr. 36 (1) (2017) 79–84.
[36] E. Rahmani, et al., The effects of omega-3 fatty acids and vitamin E co-supplementation on gene expression of lipoprotein(a) and oxidized low-density lipoprotein, lipid profiles and biomarkers of oxidative stress in patients with polycystic ovary syndrome, Mol. Cell. Endocrinol. 439 (2017) 247–255.
[92] Q. Ren, et al., Effect of micronutrient pack on micronutrient status and antioxidant capacities among institutional older adults in Shanghai, China, Asia Pac. J. Clin. Nutr. 28 (3) (2019) 457–466.

[93] E. Fragopoulou, et al., Suppression of DNA/RNA and protein oxidation by dietary supplement which contains plant extracts and vitamins: a randomized, double-blind, placebo-controlled trial, Lipids Health Dis. 17 (1) (2018) 187.

[94] R.M. Kappun, et al., No evidence of racial differences in endothelial function and exercise blood flow in young, healthy males following acute antioxidant supplementation, Int. J. Sports Med. 38 (3) (2017) 193–200.

[95] H. Sies, Total antioxidant capacity: appraisal of a concept, J. Nutr. 137 (6) (2007) 1493–1495.

[96] J. Frijhoff, et al., Clinical relevance of biomarkers of oxidative stress, Antioxidants Redox Signal. 23 (14) (2015) 1144–1170.

[97] B. Kochlak, T. Grune, D. Weber, New findings of oxidative stress biomarkers in nutritional research, Curr. Opin. Clin. Nutr. Metab. Care 20 (5) (2017) 349–359.

[98] S.B. Lotito, B. Frei, Consumption of flavonoid-rich foods and increased plasma antioxidant capacity in humans: cause, consequence, or epiphenomenon? Free Radic. Biol. Med. 41 (12) (2006) 1727–1746.

[99] D. Giustarini, et al., Interference of plasmatic reduced glutathione and hemolysis on glutathione disulfide levels in human blood, Free Radic. Res. 38 (10) (2004) 1101–1106.