Does timing of phytonutrient intake influence the suppression of postprandial oxidative stress? A systematic literature review

Margaret Murray a, b, Sophie Selby-Pham a, Beau-Luke Colton b, Louise Bennett a, Gary Williamson b, Aimee L. Dordevic b, *,

a School of Chemistry, Monash University, Clayton, 3800, Victoria, Australia
b Department of Nutrition, Dietetics & Food, Monash University, Notting Hill, 3168, Victoria, Australia

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ABSTRACT

Background: Postprandial oxidative stress markers in blood are generated transiently from various tissues and cells following high-fat and/or high-carbohydrate (HFHC) meals, and may be suppressed by certain phytonutrients, such as polyphenols and carotenoids. However, the transient presence of phytonutrients in circulation suggests that timing of consumption, relative to the meal, could be important. This systematic review investigates the effect of timing of phytonutrient intake on blood markers of postprandial oxidative processes.

Method: EMBASE, Medline, Scopus and Web of Science were searched up to December 2020. Eligible studies met the criteria: 1) healthy human adults; 2) phytonutrient(s) consumed in solid form within 24 h of a HFHC meal; 3) postprandial measurements of oxidative stress or antioxidants in blood; and 4) controlled study design. Cohen’s d effect sizes were calculated to compare studies.

Results: Nine studies, involving 256 participants, were included. Phytonutrients were consumed either at the same time, 1 h before, or the day (>12 h) before a HFHC meal. Significant decreases in blood markers - plasma lipid hydroperoxides, plasma malondialdehyde, serum sNO2-dp, serum 8-iso-PGF2α, platelet p47phox phosphorylation, and Keap-1 and p47phox protein levels in mononuclear cells (MNCs) - were observed wherever the phytonutrient was consumed together with the challenge meal (n = 4). Lack of any effect on oxidative stress markers was observed where phytonutrients were consumed with (n = 1), 1 h before (n = 1), and the day before (n = 2) the HFHC meal.

Conclusion: Phytonutrients consumed with a HFHC meal significantly suppressed some markers of oxidative stress in blood. Although there were only a limited number of studies, it appears that suppression appeared effective at the time of peak phytonutrient concentration in plasma. However, further studies are required to confirm the observations and systematically optimise the effect of timing.

1. Introduction

Oxidative stress can be generated after consumption of meals high in energy, solid saturated fats and refined carbohydrates, and low in micronutrients [1], for example meals such as a beef burger [2] or cheeseburger [3]. Markers of oxidative stress in the blood are generated from blood cells, the vascular endothelium, intestinal tissues and other organs. For example, treatment of monocytes with fatty acids leads to secretion of myeloperoxidase, which is then taken up by vascular endothelial cells and generates intracellular superoxide [4]. Postprandial oxidative stress is observed experimentally in the blood by increases in, for example, malondialdehyde (MDA), a biomarker of oxidative stress [5] resulting from ingestion of oxidised fats, from oxidation of LDL and other circulating lipids [6], and from hepatocyte membrane oxidation [7]. Modern dietary patterns contribute to persistent postprandial oxidative stress, leading ultimately to chronic elevation, and development of chronic disease [8,9]. This can be through accumulation of oxidised LDL [10], modifications to the endothelium [4] and generation of chronic inflammation [11].

Postprandial oxidative stress can be modulated by antioxidant nutrients, especially in the blood and gastrointestinal tract [1–3,5,12,13]. Postprandial oxidative stress after consumption of energy-dense high-fat meals...

* Corresponding author. Department of Nutrition, Dietetics and Food, Monash University, Level 1, 264 Ferntree Gully Rd, Notting Hill, VIC, 3168, Australia.

E-mail addresses: margaret.murray@monash.edu (M. Murray), sophie.selby-pham@monash.edu (S. Selby-Pham), beau.colton@gmail.com (B.-L. Colton), louise.bennett1@monash.edu (L. Bennett), gary.williamson1@monash.edu (G. Williamson), aimee.dordevic@monash.edu (A.L. Dordevic).

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and/or high carbohydrate (HFHC) meals has been demonstrated in healthy adults as transient increases in biomarkers such as lipid hydroperoxides, MDA and protein 47 phosphorylation (p47-phox) [2,12, 14–17]. Reducing postprandial oxidative stress when dietary antioxidants may protect against chronic disease risk factors typically associated with postprandial hyperlipidaemia and/or hyperglycaemia [18, 19].

The human diet contains naturally-occurring plant secondary metabolites called phytonutrients (including polyphenols and carotenoids), which may activate endogenous antioxidant enzymes such as superoxide dismutase and catalase, and inhibit pro-oxidant enzymes such as NADPH oxidase [20,21]. However, reduction of oxidative stress by intervention with phytonutrients or phytonutrient-rich foods in human trials yields inconsistent results [22,23]. While some human postprandial studies show significant antioxidant effects of phytonutrient intake, in the form of reductions in the biomarkers: soluble NADPH oxidase-derived peptide activity (sNox2-dp), 8-iso-prostaglandin-2a (8-iso-PGF2a), platelet p47-phox phosphorylation, MDA and protein carbonyls [13,24], others indicate no antioxidant effect of phytonutrients [25], or effectiveness against some biomarkers but not others [26].

Due to the transient presence of phytonutrients in circulation, the timing of intake, relative to the meal that causes the oxidative stress, is important for maximising their activity and may explain some of the variability in reported findings [17,27,28]. After ingestion, phytonutrients are absorbed into circulation at relatively low concentrations (in the nM to low μM range) and most have half-lives of less than 6 h [29–32]. Therefore, the time when phytonutrients are at their maximum concentrations in circulation (Tmax) represents a short window where they can exert bioactivity. For example, anthocyanins have been shown to suppress postprandial oxidative stress, but their low concentration (metabolites ranging from 0 to 40 nmol/L) and short Tmax window in circulation (peaking in plasma 1–2 h post-ingestion) suggests that the timing of consumption relative to meal intake, and therefore to the onset of postprandial oxidative stress, may represent an important variable [17,23].

The absorption pharmacokinetics of phytonutrients such as carotenoids, anthocyanins, stilbenes and some vitamins that have a passive absorption component in the small intestine can be predicted using a phytonutrient absorption prediction (PCAP) model (35). According to this model, passively absorbed phytonutrients that are administered in a solid form (e.g. a solid supplement) exhibit Tmax fairly consistently, 1.6–3.7 h after ingestion [27]. This is different to phytonutrients dispersed in liquid-form, where the range of Tmax for passive absorption may be up to 12 h after ingestion and varies significantly between different treatments [27]. For example, phytonutrients in a tomato extract are predicted to reach their Tmax 1.6–3.7 h after ingestion when consumed in solid-form, and 0.5–8 h after ingestion when consumed in drink form [27]. Furthermore, Sandhu et al. [33] observed differences in phytonutrient bioavailability when an anthocyanin-rich drink was administered 2 h before, with, and 2 h after a meal [33]. Bioavailability was highest when the anthocyanins were consumed before the meal [33], suggesting that the challenge meal itself, and its composition, may influence the absorption of phytonutrients, in a way that is not predicted by the PCAP model. Passively absorbed phytonutrients, consumed in solid form, display a relatively narrow and consistent window of plasma Tmax. Therefore, to investigate the impact of timing of phytonutrient consumption on postprandial oxidative stress, this review focusses on phytonutrients administered in solid (supplement) form [27].

This systematic review investigates whether the regulation of postprandial oxidative stress by phytonutrients consumed in solid-form is influenced by the timing of intake relative to the meal. The concept of modulation of postprandial oxidative stress by co-consumption of phytonutrients has been proposed (reviewed in Refs. [34,35]), however, this is the first systematic literature review to investigate the relationship of timing of phytonutrient consumption, relative to the meal, on postprandial oxidative stress.

2. Methods

This review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on May 9, 2019 (registration number CRD42019134930). This review is reported in accordance with the PRISMA statement [36].

2.1. Literature search

A literature search was conducted up to December 2020 in EMBASE, MEDLINE, Scopus and Web of Science databases. Search terms described the population (e.g. person), intervention (e.g. polyphenol, supplement) and outcomes of interest (e.g. postprandial, oxidative stress, glutathione). Subject headings and English language limits were also used in EMBASE and MEDLINE. An example search strategy is available in the supplementary material (Appendix 1).

The criteria for inclusion in this review were: 1) controlled intervention study, 2) adult population free from serious illness, 3) postprandial measures taken following a challenge meal, 4) assessment of circulating biomarkers of oxidative stress or antioxidant status, 5) study intervention was a phytonutrient supplement in solid-form.

Following database searches and removal of duplicate articles, first pass screening was completed independently by BLC, MM and SSP. Disagreements were resolved by MM and SSP. Papers were excluded if the supplement was not given in a solid (e.g. tablet or capsule) form, or was not given within 24 h of a meal challenge. The focus on solid supplements was elected, which delivered uniform phytonutrient absorption kinetics [27], permitting a defined timing of the phytonutrient plasma peak. Full-text articles were extracted and assessed for eligibility by BLC, MM and SSP. Disagreements were resolved by MM and SSP and reasons for exclusion were recorded.

2.2. Data extraction

Data extraction was performed by MM, SSP and BLC, using a tool adapted from the Australian National Health and Medical Research Council’s data extraction tool for cohort and randomised controlled trials. Extracted data included: study design, randomisation process, sample size, participant characteristics, intervention and placebo description, challenge meal description, statistical analysis and outcomes measured. An example of data extraction is available in the supplementary material (Appendix 2). For studies that reported data in graphic form only, numeric data were extracted from graphs using the online data extraction toolkit Web Plot Digitizer [37].

2.3. Risk of bias

Risk of bias (ROB) was assessed by MM and SSP. Randomised parallel and crossover trials were assessed using the Revised Cochrane risk of bias tool for randomised trials (RoB 2.0) [38,39]. Briefly, this assesses ROB in five domains: the randomisation process, deviations from intended interventions, missing data, outcome measurement, and selective reporting. Non-randomised trials were assessed using the Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment tool [40]. This assesses ROB in seven domains: confounding, participant selection, intervention classification, deviations from intended interventions, missing data, outcome measurement, and selective reporting. Based on criteria within each domain, papers were given a low, some concerns or high ROB rating for each domain, which was then combined to give an overall ROB rating.

2.4. Data analysis

Due to the variety of outcome markers and time points reported, a meta-analysis was not possible. Instead, Cohen’s d effect sizes and 95% confidence intervals (CI) were calculated [41] to quantitate differences
in the magnitude of phytonutrient-dependent changes in postprandial oxidative stress and antioxidant status. Effect sizes were calculated by comparing the intervention and control groups at the time point where the maximum difference between the groups was observed. This was used to determine whether the treatment effect differed according to when the phytonutrient was administered. Cohen’s $d$ effects sizes were considered significant where the 95% CI did not include zero.

3. Results

Database searches identified 3039 unique articles. Following title and abstract screening, 74 full texts were assessed for eligibility. Of those, nine papers met all the inclusion criteria for review (Fig. 1).

3.1. Description of included studies

Eight studies reported at least one biomarker of postprandial oxidative stress [2,16,24,25,42–45] and seven reported at least one marker of antioxidant status [2,16,24,42,43,45,46]. Measures of plasma concentrations of phytonutrients and their metabolites have been included, although they are only indicative of phytonutrient absorption and not of any physiological antioxidant response.

The measured biomarkers of oxidative stress were serum sNOX2-dp, serum 8-iso-PGF2α, serum lipid hydroperoxides, plasma lipid hydroperoxides, plasma oxidised low-density lipoprotein (LDL), plasma MDA, platelet p47phox phosphorylation, p47phox protein levels in mononuclear cells (MNC), and Keap-1 protein levels in MNC. The measured markers of antioxidant status were nuclear NF-E2-related factor-2 (Nrf-2) DNA binding capacity, NAD(P)H:quinone oxidoreductase-1 (NQO1) protein levels in MNC, plasma nitrate/nitrite, plasma trolox equivalent antioxidant capacity (TEAC), plasma ferric reducing antioxidant power (FRAP), plasma oxygen radical absorbance capacity (ORAC) (hydrophilic and hydrophobic), plasma total radical-trapping antioxidant parameter (TRAP), plasma uric acid, plasma sulhydrily groups, plasma glutathione, plasma ascorbic acid, plasma α-tocopherol, plasma β-carotene, plasma retinol, plasma flavonols, plasma lycopene, plasma hydroxytyrosol, and plasma quercetin.

Seven studies were acute single supplement interventions [2,16,24,25,42,45,46], while two studies consisted of 1–2 week interventions, with supplements taken daily, followed by postprandial testing at the end of the intervention period [43,44]. The supplement doses varied from 20 mg [24] up to 3000 mg [25]. The plant origin of phytonutrients varied across studies and the chemical composition was not always provided (Table 1). Reported sources of phytonutrient extracts included onion skin [46], Misona chinensis [42], tomato [44], grape seed [2,45], grape [16], and Cinnamomum zeylanicum [25].

Individual study populations ranged from 8 to 146 participants (n = 256 participants across all studies), with mixed study populations including: healthy weight, overweight, obese, hypercholesterolaemic and hypertensive participants. The challenge meals ranged in energy content from 2349 to 4757 kJ and included high fat meals [25,43–46], high carbohydrate meals [24,42,43], and HFHC meals [2,16]. Only three studies reported using a power calculation for specific study endpoints: Carnevale et al. [24] were powered to detect a difference in postprandial sNOX2-dp, Deplanque et al. [44] were powered to detect a difference in postprandial LDL oxidation, and Markey et al. [25] were powered to detect differences in the rate of gastric emptying.

3.2. Risk of bias

All six randomised studies received a low ROB rating across all domains and thus an overall low ROB rating [24,25,42,44–46]. Of the non-randomised studies, Ghanim et al. [16] and Natella et al. [2] both received low ROB ratings across all domains, resulting in an overall low

![Fig. 1. PRISMA flow diagram of included studies.](image-url)
Table 1
Description of included studies.

| Author, year, location (reference) | Study design | Population | Intervention description | Meal challenge description | Supplement | Outcome(s) measured |
|-----------------------------------|--------------|------------|--------------------------|---------------------------|------------|---------------------|
| Brull et al., 2017, Germany [44]  | Double-blind, placebo-controlled, randomised crossover trial | n = 22
Male – 11, Female – 11
Age 48.1 (10.9)
BMI 20.9 (3.6)
Pre-hypertension or stage 1 hypertension, dyslipidaemia (elevated TGs or low HDL), and pro-inflammatory state (hs-CRP > 2 mg/L). | Fasting (10–12 h) venous blood sampling was conducted before the test meal (0 h) and at 2 and 4 h after finishing the test meal. The supplement was administered with the test meal. Comparator: placebo | 80 g croissant, 40 g bread roll, 20 g butter 60 g cheese, 25 g jam, and 400 mL lemonade | 132 mg onion skin extract, containing 54 mg quercetin, in hard gelatin capsules | Plasma TEAC, Plasma flavonoids, Plasma quercetin, Plasma α-tocopherol, Plasma retinol, Plasma β-carotene |
| Carnevale et al., 2018, Italy [21] | Double-blind, placebo-controlled, randomised crossover trial | n = 20
Male – 10, Female – 10
Age 33.9 (6.9)
BMI 20.7 (3.7)
Healthy | Wash out: 6 weeks
Blood sampling was conducted before and 2 h after lunch meal. Participants received the supplement immediately before lunch. No mention of whether participants fasted prior to the meal. Comparator: placebo | 100 g pasta, 150 g chicken breast, 80 g salad, 80 g bread, 200 g apple | 20 mg oleuropein in capsules | Serum SNOx2-dp, Serum 8-iso-PGF2α, Platelet p47phox phosphorylation, Plasma hydroxytyrosol |
| Chusak et al., 2014, Thailand [40] | Randomised, controlled crossover trial | n = 11
Male – 11
Mean (SEM)
Age 25.0 (2.3)
BMI 24.7 (1.0)
Healthy | Wash out: 10 days
Fasting (8 h) blood samples were collected prior to the meal. Postprandial blood samples were taken every 30 min for 4 h. Participants consumed the supplement with the meal. Comparator: no treatment | Six tablespoons of Ensure® (230 mL), three slices of white bread with one tablespoon condensed milk | 0.5 g of Misona chinensis extract OR 1 g of Misona chinensis extract | Phenolic content: 212.37 (5.64) mg/g GAE, Plasma MDA, Plasma FRAP, Plasma ORAC |
| Dennis et al., 2008, Canada [41] | Single group, two-phase, controlled trial | n = 18
Male – 18
Age 18–26
BMI 20–30 kg/m²
Healthy | Intervention: Participants restricted lycopene-rich foods for 1 week while also consuming 80 mg lycopene supplements/day. Participants then consumed HF and HC meals (separated by 24 h) following an overnight fast, 12 h after last lycopene supplement. Blood was collected pre-meal and 3 h after meal. Comparator: Same as intervention but without taking a lycopene supplement. Wash out: 2 weeks | 100 g carbohydrates (69% energy)
21 g* protein (15% energy) | 80 mg lycopene in capsules | Plasma MDA, Plasma lycopene, Plasma α-tocopherol, Plasma retinol, Plasma β-carotene, Plasma nitrate/nitrite |
| Deplanque et al., 2016, France [43] | Double-blind, placebo-controlled, randomised parallel trial | n = 146
Male – 66, Female – 80
Moderately elevated LDL cholesterol
Intervention = 75
Age 34.8 (11.7)
BMI: 22.4 (2.2) | Postprandial testing took place before and after a 2-week study where participants consumed a supplement daily with their lunch meal. Results from the end of the study period were | 48 g* fat (50% energy) | Carotenoid-rich tomato extract containing lycopene (15 mg), phytosterols (15 mg), tocopherols (4 mg), phytoene (4 mg), and phytofluene (4 mg), and Plasma oxidised LDL |

(continued on next page)
Table 1 (continued)

| Author, year, location (reference) | Study design | Population | Intervention description | Meal challenge description | Supplement | Outcome(s) measured |
|-----------------------------------|--------------|------------|--------------------------|---------------------------|------------|-------------------|
| Edirisinghe et al., 2012, U.S.A [43]. | Placebo-controlled, randomised crossover trial | n = 12 Male = 5, Female = 7 Age 45 (15) BMI 35.9 (6.7) Healthy | Comparator: placebo Following an overnight fast, a venous blood sample was collected. Immediately following the initial blood draw (-1 h), subjects were administered the supplement with water. One hour later, a pre-meal blood sample was drawn (0 h) and participants consumed the breakfast meal. Blood was then collected hourly for 5 h after meal consumption. | Bagel 110 g, Cream cheese 14 g, Margarine 5 g, Egg 50 g, Cantaloupe 85 g, Whole milk 240 mL | MegaNatural Gold Grape Seed Extract containing 94.3 GAE (wt/wt) in capsules | Plasma hydrophilic and hydrophobic ORAC Plasma oxidised LDL |
| Ghanim et al., 2011, U.S.A [12]. | Placebo-controlled, intervention study. | n = 10 Male = 4, Female = 6 Age: 37 (4) BMI: 22.6 (0.5) Healthy | Comparator: placebo Wash out: 7–10 days Following a fasting (overnight) blood sample, participants were administered the supplement, followed 10 min later by the meal. Blood samples were collected 1, 3 and 5 h after the meal. | High fat high carbohydrate meal 3906 kJ energy | 75 mg polyphenols from grape extract +100 mg resveratrol as a supplement | In MNCs: Keap-1 protein levels NQO1 protein levels Nuclear Nrf-2 DNA binding capacity |
| Markey et al., 2011, Ireland [23] | Single-blind, placebo-controlled, randomised crossover trial | n = 9 Male = 3, Female = 6 Age: 26.2 (3.0) BMI: 22.4 (2.5) Healthy | Comparator: placebo Wash out: 7 days A fasting (12 h) blood sample was obtained. Then participants consumed the test meal, accompanied by the supplement. Blood was collected hourly for 4 h after the meal. | Three pancakes (36 g flour, 44 g egg, 70 g whole milk, 30 g sunflower oil), 20 g chocolate spread, and 300 mL water | 3000 mg cinnamon powdered spice (Cinnamomum zeylanicum) in capsules | Serum lipid hydroperoxides |
| Natella et al., 2002, Italy [14] | Controlled, crossover trial | n = 8 Male = 8 Age: 25–40 Healthy | Comparator: no treatment Wash out: 2 weeks A fasting (16 h) blood sample was obtained. Then participants consumed the test meal along with the supplement. Blood samples were collected 1 and 3 h after the meal. | “Milanese” meat (beef, egg and breadcrumbs fried in corn oil) and fried potatoes | 300 mg Leucoselect grapes extract containing: 15% catechin and epicatechin 80% EGC, dimers, trimers, tetramers, and their gallates 5% pentamers, hexamers, heptamers and their gallates, in capsules | Plasma lipid hydroperoxides Plasma TRAP Plasma α-tocopherol Plasma sulfhydryl groups Plasma uric acid Plasma glutathione total Plasma glutathione reduced Plasma ascorbic acid total Plasma ascorbic acid reduced |

*a*calculated values; 8-iso-PGF2α, 8-iso-prostaglandin-2α; BMI, body mass index; BMR, basal metabolic rate; EER, estimated energy expenditure; FRAP, ferric reducing antioxidant capacity; LDL, low density lipoprotein; MDA, malondialdehyde; MNC, mononuclear cells; NQO1, NAD(P)H:quinone oxidoreductase-1; NF-κB, nuclear NF-E2-related factor-2; ORAC, oxygen radical absorbance capacity; sNOS2-dp, soluble NADPH oxidase-derived peptide activity; TEAC, trolox equivalent antioxidant capacity; TRAP, plasma total radical-trapping antioxidant capacity.
ROB rating. However, Denniss et al. [43] received ratings of uncertain ROB, due to potential bias in confounding, selection of participants, measurement of outcomes and selection of reported results, and a rating of high ROB due to missing data. Therefore, this study received an overall rating of a high ROB (Fig. 2), and so the interpretation is limited by this characteristic [2].

3.3. Impact on oxidative stress biomarkers

The data were analysed in terms of the reported effects of phytonutrient supplementation on postprandial oxidative stress biomarkers as well as calculated effect sizes (Table 2). The following biomarkers of oxidative stress significantly increased following the challenge meal alone (control): serum sNOx2-dp [24], serum 8-iso-PGF2α [24], lipid hydroperoxides [2,25], platelet p47phox phosphorylation [24], keap-1 protein levels in MNC [16], and p47phox protein levels in MNC [16]. For all of these, except serum lipid hydroperoxides [25], the postprandial increase was significantly suppressed following phytonutrient supplementation. All of these studies administered the phytonutrient supplement with the challenge meal.

The oxidative stress biomarkers MDA [42,43] and oxidised LDL [44,45] did not significantly increase following the challenge meal. However, Edirisinghe et al. [45] reported a reduction in plasma oxidised LDL, compared to control, 5 h after challenge meal consumption and 6 h after phytonutrient supplementation (consumed 1 h before the meal). Deplanque et al. [44] reported a reduction in plasma oxidised LDL, compared with baseline, at three, six and 8 h after challenge meal consumption, but this was not different to the control. Deplanque et al. [44] gave their phytonutrient supplement the day before the challenge meal. Compared with control, a reduction in plasma MDA was observed at 3 and 3.5 h postprandial following the high dose phytonutrient supplement (1.0 g) by Chusak et al. [42], who gave the phytonutrient supplement with the challenge meal. Denniss et al. [43] gave the phytonutrient supplement 12 h before the challenge meal and reported no change in MDA as a result of the meal alone or the meal with the phytonutrient, however they only assessed a single postprandial time point (3 h).

Effect sizes were calculated to evaluate the magnitude of the change in oxidative stress biomarkers following the meal plus phytonutrient (intervention), compared with the meal alone (control), and to determine whether there was an association between change magnitude and the timing of when the phytonutrient supplement was administered. In all instances where significant effect sizes were observed (n = 5), the phytonutrient supplement was consumed at the same time as the challenge meal. Significant effect sizes were observed for the following oxidative stress biomarkers: serum sNOx2-dp [24], serum 8-iso-PGF2α [24], platelet p47phox phosphorylation [24], Keap-1 protein levels in MNC [16] and plasma MDA (high dose only) [42]. Non-significant effect sizes were observed in cases where the phytonutrient was administered with (n = 4), 1 h before (n = 1) and the day before (n = 3) the challenge meal for the following oxidative stress biomarkers: lipid hydroperoxides [2,25], p47phox protein levels in MNCs [16], oxidised LDL [44,45] and MDA [42,43] (Table 2).

3.4. Impact on antioxidants and antioxidant status

Table 3 shows a summary of the reported blood antioxidants along with the calculated effect sizes. This table includes direct compound markers of the administered phytonutrient (e.g. flavonols, hydroxytyrosol, lycopene), antioxidant vitamin concentrations in the blood (e.g. α-tocopherol, β-carotene, ascorbic acid, retinol), chemical measures of plasma “antioxidant capacity” (e.g. TEAC, FRAP, ORAC, TRAP), as well as endogenous antioxidants (e.g. NQO1 protein, Nrf-2 DNA binding capacity, nitrate/nitrite, glutathione). The biomarkers that significantly increased following phytonutrient consumption were plasma hydroxytyrosol [24], nuclear Nrf-2 DNA binding capacity [16], NQO1 protein...
levels in MNC [16], plasma quercetin [46] and plasma flavonols [46]. Similarly, biomarkers for which a postprandial reduction was recovered following phytonutrient consumption were plasma ORAC [42, 45], plasma FRAP [42] and plasma ascorbic acid reduced (% total) [2]. All of these studies administered the phytonutrient supplement with [2, 16, 24, 42, 46] or 1 h before [45] the challenge meal. Plasma TRAP [2], plasma ascorbic acid total [2] and plasma sulfhydryl groups [2] all increased from baseline following phytonutrient consumption, however this was not reported to be different from the control group.

Denniss et al. [43] reported that plasma lycopene, α-tocopherol and β-carotene were each significantly elevated compared with control. However, this was not a postprandial effect, but was elevated as a result of one week of lycopene supplementation compared with a week of lycopene restriction (the supplement was consumed ~12 h prior to meal challenge) [43]. There was no postprandial effect of phytonutrient supplementation on the following markers: plasma nitrate/nitrite [43], plasma uric acid [2], plasma glutathione [2], plasma TEAC [46] and plasma retinol [43, 46].

Significant calculated effect sizes (indicating that markers of antioxidant status increased following phytonutrient supplementation, compared with control) were observed for the following markers: plasma hydroxytyrosol [24], plasma hydrophilic and hydrophobic ORAC [45], plasma FRAP (following the high dose only, 1.0 g) [42], plasma ascorbic acid reduced (% total) [2], plasma flavonols [46] and plasma quercetin [46] (Table 3). In all except for one of these studies, the phytonutrient supplement was consumed at the same time as the meal [2,24,42,46]. In the remaining study, the supplement was given 1 h before the meal [45]. Significant treatment effects were also identified for plasma lycopene and plasma β-carotene in the study by Denniss et al. [43], however these were not in the postprandial phase but associated with an extended course of supplementation over one week.

### 4. Discussion

Based on the data from this systematic review, certain phytonutrient supplements in solid form can lower postprandial oxidative stress or improve antioxidant status when given with, or 1 h before, a challenge meal, but there were exceptions to this observation.

### 4.1. Effect of supplementation timing on postprandial outcome markers

Phytonutrients appear only transiently in the circulation [27]. The PCAP model indicates that some low molecular weight phytonutrients without a chemically attached sugar (<~1000 Da) and administered in a solid form are passively absorbed in the small intestine and peak in the bloodstream one to 4 h after ingestion [27]. This implicates a limited window of action for these compounds, which is supported by reports that most phytonutrients, delivered in either solid or liquid form, are cleared from circulation within 8 h after intake [28, 47, 48]. All studies included in this review administered a phytonutrient supplement in a solid-form, suggesting that $T_{\text{max}}$ for the passively absorbed phytonutrients was one to 4 h after ingestion [27]. Phytonutrients consumed levels in MNC [16], plasma quercetin [46] and plasma flavonols [46]. Similarly, biomarkers for which a postprandial reduction was recovered following phytonutrient consumption were plasma ORAC [42, 45], plasma FRAP [42] and plasma ascorbic acid reduced (% total) [2]. All of these studies administered the phytonutrient supplement with [2, 16, 24, 42, 46] or 1 h before [45] the challenge meal. Plasma TRAP [2], plasma ascorbic acid total [2] and plasma sulfhydryl groups [2] all increased from baseline following phytonutrient consumption, however this was not reported to be different from the control group.

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Significant calculated effect sizes (indicating that markers of antioxidant status increased following phytonutrient supplementation, compared with control) were observed for the following markers: plasma hydroxytyrosol [24], plasma hydrophilic and hydrophobic ORAC [45], plasma FRAP (following the high dose only, 1.0 g) [42], plasma ascorbic acid reduced (% total) [2], plasma flavonols [46] and plasma quercetin [46] (Table 3). In all except for one of these studies, the phytonutrient supplement was consumed at the same time as the meal [2,24,42,46]. In the remaining study, the supplement was given 1 h before the meal [45]. Significant treatment effects were also identified for plasma lycopene and plasma β-carotene in the study by Denniss et al. [43], however these were not in the postprandial phase but associated with an extended course of supplementation over one week.

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### 4.1. Effect of supplementation timing on postprandial outcome markers

Phytonutrients appear only transiently in the circulation [27]. The PCAP model indicates that some low molecular weight phytonutrients without a chemically attached sugar (<~1000 Da) and administered in a solid form are passively absorbed in the small intestine and peak in the bloodstream one to 4 h after ingestion [27]. This implicates a limited window of action for these compounds, which is supported by reports that most phytonutrients, delivered in either solid or liquid form, are cleared from circulation within 8 h after intake [28, 47, 48]. All studies included in this review administered a phytonutrient supplement in a solid-form, suggesting that $T_{\text{max}}$ for the passively absorbed phytonutrients was one to 4 h after ingestion [27]. Phytonutrients consumed
with or immediately before the challenge meal, producing the phytonutrient $T_{\text{max}}$ during the postprandial period, were somewhat effective at suppressing the oxidative stress response. Suppression of oxidative stress was not observed when the phytonutrient was consumed $>12$ h before the meal and neither observed any postprandial increase in oxidative stress (oxidised LDL [44] or MDA [43]) following the meal alone, which limits the interpretation of this finding.

Phytonutrient supplementation consistently suppressed the postprandial increase of biomarkers related to NADPH oxidase, an enzyme that is responsible for multiple functions including the release of $O_2^-$ from macrophages in response to infection [50]. Significant postprandial increases in serum sNOX2-dp, platelet p47$\text{phox}$ (a regulator of NADPH oxidase activity) phosphorylation, and p47$\text{phox}$ protein levels in mononuclear cells were suppressed following phytonutrient supplementation. Ghanim et al. [16] reported suppression of p47$\text{phox}$ protein level in MNCs three- and 5-h after the challenge meal with phytonutrient supplementation, compared with placebo. While Carnevale et al. [24] reported suppression of p47$\text{phox}$ phosphorylation in platelets and suppression of sNOX2-dp 2 h after the challenge meal with phytonutrient supplementation, compared with control. While a number of factors differed between these studies, such as phytonutrient supplement (oleuropein [24] vs. grape extract and resveratrol [16]) and phytonutrient dose (20 mg [24] vs. 175 mg [16]), a consistent factor was the timing of phytonutrient supplementation with the challenge meals, both of which provided just under 4000 kJ and were high in carbohydrates. This suggests that the phytonutrient $T_{\text{max}}$ window of opportunity for action coincided with the postprandial increase in sNOX2-dp and p47$\text{phox}$ and resulted in effective suppression of the response. This is confirmed by the reported increase in circulating hydroxytyrosol, a metabolite of oleuropein, at the 2 h postprandial time point [24]. These data suggest that timing of phytonutrient administration may have been a critical factor in these results, as supported by Huang et al. who demonstrated differences in effectiveness of phytonutrient treatment on postprandial glucose and inflammation (IL-6), that depended on intake timing [17].

Plasma oxidised LDL was reported by two studies in this review. LDL oxidation is enhanced by oxidants [51], and is a commonly studied biomarker of oxidative stress [52]. Though the challenge meals were reported to have no effects on oxidised LDL, there were effects of phytonutrient consumption. Edirisinghe et al. [45] gave the phytonutrient supplement 1 h before the challenge meal and reported a decrease in oxidised LDL, compared with placebo [45]. Deplanque et al. [44] administered the phytonutrient supplement the day before the challenge meal and, while a decrease in oxidised LDL was observed following treatment, this was not different to control [44]. This suggests that phytonutrients were most effective at reducing levels of oxidised LDL when the $T_{\text{max}}$ occurred during the postprandial measurement period. In further support, polyphenol-enriched olive oil (30 mL, 961 mg polyphenols/kg), with a $T_{\text{max}}$ of 53 min, and half-life of approx. 2.4 h, reduced levels of oxidised LDL in hypertensive patients to below baseline at all postprandial time points (1, 2, 4, and 5 h) [53]. Similarly, in 13 healthy subjects, compared with control, a 5.25 mg dose of hydroxytyrosol delivered via a fortified biscuit, with plasma $T_{\text{max}}$ of 0.5–1 h, reduced oxidised LDL levels in the 6 h following consumption [54]. These results indicate that phytonutrient treatment may be most

| Biomarker | Time of PC relative to meal | Reported value | Outcome | Time-point relative to the meal (hours) | Cohen’s d* (95% CI) | Study |
|----------|----------------------------|---------------|---------|----------------------------------------|---------------------|-------|
| Plasma hydroxystearin | With mean (SD) 20 | Control No change 0.99 (0.03) | | -1 | 0.35 (0.03) | 1.0 (0.10) | Murray et al. [2018] [43] |
| Nuchal NOS-2 DNA binding capacity (Yokogawa) | With | Change from baseline | PC Significant increase 14.8 (0.10) | | -1 | 11.5 (0.03) | 24.7 (0.6) | Glazunov et al. [2011] [44] |
| NOQ1 protein levels in MNC (Yokogawa) | With | Change from baseline | PC No change 11.2 (0.10) | | -1 | 11.7 (0.03) | 24.7 (0.6) | Glazunov et al. [2011] [44] |
| Plasma hydroxy SCOCO (nmol/L) | With mean (SD) 12 | Control No change 31.5 (0.7) | | -1 | 34.1 (0.4) | 2.75 (0.37) | Ellis et al. [2013] [44] |
| Plasma hydroxy SCOCO (nmol/L) | With mean (SD) 12 | Control No change 6.4 (1.0) | | -1 | 6.1 (0.3) | 0.8 (0.13) | Ellis et al. [2013] [44] |
| Plasma SCOCO (nmol/L) | With | difference from baseline mean (SD) 24 | Control No change 3.0 (0.2) | | -1 | 3.0 (0.2) | 0.2 (0.14) | Nuttall et al. [2014] [44] |
| Plasma TRAP (mil) | With mean (SD) 8 | Control No change 1.2 (0.11) | | -1 | 1.14 (0.16) | 1.2 (0.14) | Nuttall et al. [2014] [44] |
| Plasma acetoxy acid reduced (% total) | With mean (SD) 8 | Control No change 0.0 (0.0) | | -1 | 0.0 (0.0) | 0.0 (0.0) | Nuttall et al. [2014] [44] |
| Plasma acetoxy acid (umol) | With mean (SD) 8 | Control No change 8.7 (2.7) | | -1 | 8.0 (2.4) | 7.1 (0.5) | Nuttall et al. [2014] [44] |
| Plasma total flavonoids (mg) | With mean (SD) 22 | Control No change 43.7 (24.5) | | -1 | 51.3 (21.5) | 4.6 (2.4) | Ellis et al. [2014] [44] |
| Plasma total polyphenols (mg) | With mean (SD) 8 | Control No change 463 (26) | | -1 | 543 (20) | 0.8 (0.1) | Nuttall et al. [2014] [44] |
| Plasma pentane (mill) | With mean (SD) 22 | Control No change 3.0 (0.7) | | -1 | 3.4 (0.4) | 0.2 (0.0) | Nuttall et al. [2014] [44] |

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Table 3 Summary of measurements of postprandial markers of antioxidant status.

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effective at reducing oxidised LDL when the phytonutrient \( T_{\text{max}} \) occurs during the postprandial measurement period. However, limited comparison was possible as only one study was identified in which the timing of phytonutrient supplementation was different from this (the day before the meal [44]).

Lipid oxidation has been linked to the pathogenesis of several diseases [2,25,55–58]. Therefore, products derived from oxidation of plasma lipids such as MDA [42, 43], and lipid hydroperoxides [2, 25] were used as markers for oxidative stress in more than one study in this review. The two included studies that measured MDA observed no change in plasma MDA following the challenge meals [42, 43], so the effect of phytonutrient supplementation timing on MDA suppression cannot be determined. Plasma lipid hydroperoxides increased following the challenge meals [2, 25], supporting that plasma lipid hydroperoxides is a more sensitive biomarker of postprandial oxidative stress. However, the effects of phytonutrient supplementation on postprandial lipid hydroperoxides are conflicting. Natella et al. [2] observed a significant suppression of the postprandial increase following phytonutrient consumption, with a significant difference from control at 1 h. On the other hand, Markey et al. [25] observed no effect of phytonutrient consumption. While phytonutrient timing was consistent between these studies, differences in phytonutrient sources and doses may have contributed to the difference in findings. For example, Markey et al. [25] gave a 3000 mg dose of powdered cinnamon containing various phenolic acids, and Natella et al. [2] used a 300 mg grape extract containing phytonutrients from the catechin family with likely differences in the molecular mass profile and relatively capacity for upper gut absorption. There were also inconsistencies around the effects of phytonutrients on postprandial lipid hydroperoxides in the broader literature as well. In 10 overweight/obese men who consumed a high-fat, high-fructose meal (sausage and egg muffins with sugar-sweetened beverage) with fish oil and soy isoflavones (with isoflavones observed in the blood at 4 h postprandial), compared with control, there was no effect of the challenge meal or treatment on lipid hydroperoxides [59]. However, when 12 healthy volunteers consumed a test meal high in oxidised and oxidisable lipids (cheeseburger), compared with control, there was no effect of the challenge meal or treatment on lipid hydroperoxides. In 10 overweight/obese men who consumed a high-fat, high-fructose meal (sausage and egg muffins with sugar-sweetened beverage) with fish oil and soy isoflavones (with isoflavones observed in the blood at 4 h postprandial), compared with control, there was no effect of the challenge meal or treatment on lipid hydroperoxides.
of water or red wine (561 mg phenolics), significant increases in plasma lipid hydroperoxides were observed following the meal, which were completely prevented by the wine [3]. Of course, based on the PCAP model, the expected $T_{\text{max}}$ window of red wine phenolics is likely to be broader than for phytonutrients administered in solid-form [27].

The heterogeneity of studies in this field and identified in this review (e.g. biomarkers measured, challenge meal composition, time points of postprandial sampling) highlight that further exploration of the timing of solid and liquid state phytonutrient supplementation is needed to achieve optimal postprandial oxidative stress reduction by phytonutrients. There are currently very few studies that systematically examine this by giving a consistent, defined phytonutrient dose at different time points before and after a meal [17]. We also need to understand the onset and cascade of biomarkers expressed in response to postprandial stress to identify relevant, sensitive and reliable biomarkers to assess within clinical efficacy studies.

4.2. Understanding the postprandial oxidative stress response

An important finding identified in this review is the lack of consistent biomarkers used for measuring postprandial oxidative stress and antioxidant status, along with, often, a lack of sufficient postprandial time points to observe the temporal changes in these markers over the postprandial period. A previous review observed that measures of postprandial oxidative stress vary, are limited by lack of standardisation, and that standardisation of methodology, including biomarkers of postprandial oxidative stress is needed [18]. There is also debate over the specificity, reliability and clinical relevance of analytical methods currently used to measure oxidative stress and antioxidant status [49, 56]. In order to progress the premise of this review, validation of suitable biomarkers of postprandial oxidative stress is required.

While the scope of this review was intentionally narrow and not intended to identify the optimal biomarkers of postprandial oxidative stress, analysis of the data enabled identification of the following biomarkers that were responsive to both the challenge meal and phytonutrient treatment: lipid hydroperoxides, serum sNOx2-dp, serum 8-iso-PGF2α, platelet p47phox phosphorylation, p47phox protein levels in MNC, Keap-1 protein levels in MNC, and nuclear Nrf-2 DNA binding capacity. These may be promising markers for investigation in future studies.

A postprandial increase in antioxidant status represents an alternative mechanism for regulation of oxidative stress [60]. However, measurement of general markers of antioxidant status, such as ORAC, TRAP, FRAP and TEAC are inappropriate methods for clinical studies because of the broad range of compounds (e.g. uric acid, albumin) that may interfere with the results of these analyses [49,61]. More suitable markers may include nuclear Nrf-2 DNA binding capacity and NQO1 protein levels, which were observed to increase following phytonutrient treatment and not following a challenge meal alone [16]. It is also useful to measure plasma levels of the administered phytonutrient and its metabolites to confirm its presence and $T_{\text{max}}$ in the blood, although this is not a biomarker of protection as such.

If suitable biomarkers of postprandial oxidative stress and antioxidant status can be identified, it will be possible to study their fluctuations and relationships over the postprandial period, before seeking to validate consistency across different populations. This will permit the optimisation of phytochemical intake timing for managing postprandial oxidative stress.

4.3. Strengths and limitations

A strength of this review is the specific criteria that were chosen (i.e. phytonutrient supplements administered in solid-form). Intake of the phytonutrient in solid form imposes a relatively narrow $T_{\text{max}}$ of 1.6–3.7 h [27], which allows for a targeted investigation of the effects of timing and conclusive results to inform future research. The study also excluded other non-phytonutrient treatments with antioxidant properties such as vitamins and fish oils because of the differing pharmacokinetics of these compounds compared with phytonutrients [52–64].

Some limitations of this review are that the included studies presented a limited variety of phytonutrient supplementation timing relative to the meal (with, 1 h before, or the day before (>12 h)), reflecting a lack of consideration of supplement timing in the literature to date. Furthermore, the observed postprandial responses were limited by the study design, sometimes involving <2 postprandial time points. There was also little commonality in the measured biomarkers among studies, therefore limiting comparison across studies and reflecting the current lack of agreed valid and reliable biomarkers. There was considerable methodological heterogeneity across the studies, in aspects such as meal formulation, phytonutrient or plant extract species and dose, as well as postprandial time points and biomarkers assessed. All of these factors require consideration and standardisation in order to evaluate and optimise the benefits of phytonutrients for regulating postprandial OS.

5. Conclusion

This systematic literature review indicates that a solid-form phytonutrient supplement consumed with or immediately before a challenge meal was effective at moderating some biomarkers of postprandial oxidative stress and antioxidant status. This review highlights gaps in the current literature and confirms the need for future, well-designed postprandial phytonutrient efficacy research that uses consistent meal challenges, assesses multiple postprandial time points, and considers the effect of timing of phytonutrient consumption on postprandial oxidative stress. Indeed, the understanding that phytonutrients, especially from solid supplements, have a narrow window of time in circulation, should influence the design of clinical studies in relation to blood sampling and supplementation timing. This understanding also undermines the conclusiveness of research where timing of postprandial sampling is limited.

Further work is also required to identify clinically relevant biomarkers of oxidative stress that are consistently and significantly influenced by a meal (i.e. compared to baseline) and to characterise their postprandial response. A better understanding of the time course of postprandial changes in oxidative stress biomarkers will allow for better evaluation of the impact of timing on phytonutrient treatment efficacy. Foods that promote oxidative stress are common in Western-style diets and can lead to chronic disease. The optimised use of phytonutrients for regulation of postprandial oxidative stress represents a potentially effective, convenient and safe approach to personal risk management associated with Western dietary patterns.

Conflicts of interest

None to declare.

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Declaration of competing interest

The authors declare no conflicting interests.

Appendix A. Supplementary data

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