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Apples and apple-based products in the modulation of cardiometabolic and functional markers: a systematic review of human intervention studies

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Apple is one of the most widely consumed fruits worldwide, yet its effects on human health remain the subject of ongoing debate. The aim of the present review was to examine evidence from human intervention studies evaluating the impact of apples and apple-based products on functional and metabolic health markers. A total of 38 studies were included: 13 postprandial interventions, 22 medium- or long-term interventions, and 3 assessing both postprandial and chronic effects. Postprandial studies predominantly investigated the effects of apple consumption on blood glucose levels and plasma antioxidant capacity, whereas medium- or long-term interventions assessed a broader range of biomarkers related to cardiometabolic health, oxidative stress, vascular function, inflammation, and gut function. Overall, the findings suggest that apples and apple-based products may beneficially modulate glycaemia, antioxidant capacity, and vascular endothelial function mainly in short-term interventions, while medium/long-term studies reported an apparent improvement in gut microbiota composition. However, the current evidence remains insufficient to draw definitive conclusions. Additionally, substantial heterogeneity in study design, populations, and products tested limits the ability to generalize results. Nonetheless, apple consumption, consistent with fruit intake in general, represents an important component of a healthy and balanced diet, providing valuable nutrients and bioactive compounds whose intake should be encouraged. Therefore, further well-designed intervention studies, particularly in populations with cardiometabolic risk factors, are warranted to better clarify the role of apples and apple-derived products in human health. Future research should also aim to identify the effective amounts and specific bioactive components responsible for the observed effects, as well as to determine whether these benefits may vary according to the health status of the target population.

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1. Introduction

Apple (*Malus domestica*, Rosaceae family) is one of the world's highest appreciated and consumed fruits. Among the wide variety of fruits available on the market, apple is the third most produced fruit worldwide (just after banana and watermelon).[1] According to the Food and Agriculture Organization of the United Nations, more than 96 million tons of apples were produced globally in 2020, with Asia, Europe and America among the major producers.[2] The main apple producers in Europe are Poland, France, and Italy, with more than 7.6 million tons of apples produced in 2020.[3] Regarding consumption, apple represents one of the most consumed fruits, accounting for about 12% of all fruits worldwide.[4] In Europe, the consumption of fresh apples is approximately 22 kg per capita annually[5] while in Italy, according to FAOSTAT, the consumption reached 13.5 kg per capita in 2021.[2]

Apples are widely consumed also due to their ease of use and their long shelf-life compared to other fruits. In addition, they are also consumed in the form of processed foods such as juices, sauces, jams, apple pies, apple snacks (chips), apple cider vinegar, and wine.[3] Among all processed apple products, apple juice represents the most produced (65%).[6] However, apples are also consumed in view of their potential health benefits, with the popular expression "an apple a day can help keep the doctor away" attributed to the nutritional value and the numerous bioactive constituents present in apples. In fact, they are a good source of dietary fibers (*e.g.*, pectins), vitamins, minerals, triterpenic acids and above all phenolic compounds. The fiber content in apples is relatively high compared with other fresh fruits (approximately 2–3%) and is mainly concen-

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trated in the peel (at about 2–3 times compared to the pulp).[7] Apples contain both soluble and insoluble dietary fibers; insoluble fiber accounts for approximately 50% of the total fiber and includes cellulose and hemicellulose, while soluble fiber is mainly constituted by pectin and includes homogalacturonans (the main fraction) and rhamnogalacturonans.[8–10]

Apples also represent a food source of vitamins such as vitamin C (the most abundant), followed by folic acid and vitamin E. Among minerals, potassium, magnesium, nitrogen, phosphorus, and calcium are the most representative macro elements, while among the trace elements, the predominant forms include boron, zinc, iron, manganese, and aluminium.[11] Moreover, apples contain bioactives, including small amounts of carotenoids such as lutein and beta-carotene, but above all polyphenols.[12,13] Vrhovsek and colleagues analysed more than 40 apple samples, representing eight of the most widely cultivated varieties in Western Europe, revealing that the mean content of total polyphenols, measured using the Folin–Ciocalteu method, varied between 66.2 and 211.9 mg per 100 g fresh weight.[14] This variability in the concentration of apple polyphenols could be due to the different cultivars, area of cultivation, maturity, storage, extraction procedures, analytical techniques and pre- or post-harvest factors. The major class of apple polyphenols is represented by flavanols such as catechin and proanthocyanidins (71–90%), followed by hydroxycinnamates (4–18%), flavonols (1–11%), dihydrochalcones (2–6%), and in red apples anthocyanins (1–3%).[14] In this regard, apples may represent an important dietary contributor to the total polyphenol dietary intake (at about 10%), since one Italian serving (150 g) may provide up to 200–250 mg of polyphenols.[15] However, the amount introduced may vary depending on the way of consumption. In fact, despite polyphenols being detected in the whole apple (*e.g.*, flesh, peel, leaf, seed, or root), the major source is the skin which contains above 80% of all the flavonols and anthocyanins (red apples), in addition to an important amount of dihydrochalcones. Phenolic acids are present in the flesh whereas most of the dihydrochalcones are in the core and the seeds.[15] Also, the content in apple-derived products may be different and influenced by the technological procedure.[16] For example, apple juice contains only small amounts of quercetin glycosides and dihydrochalcones since it is obtained by using pulp and excluding peels and seeds. Moreover, the clarification process during the production of clear apple juice and the oxidative conditions may reduce the polyphenol content.[17] In contrast, the anaerobic conditions and the lack of a clarification step during the production of cloudy apple juice seem to retain polyphenols by preventing an important loss in their content.[18] Also, the drying process may affect polyphenol content. In this regard, recent studies documented that the application of advanced drying techniques and/or their combination may prevent nutrient lost.[19–21]

A large body of literature demonstrated the positive effect of fruit consumption in general on human health.[22,23] For example, in an umbrella review of observational studies, Angelino *et al.* found the strongest (probable) evidence for cardiovascular disease protection after fruit and vegetable consumption, while possible evidence for decreased risk of colon cancer, pancreatic diseases and depression was found for fruit intake.[24] In a more recent systematic review and meta-analysis of 12 studies, Liao and coworkers documented that total fruit consumption was associated with a lower risk of gestational diabetes mellitus (GDM), and in a further dose–response analysis of eight studies, the authors found a 3% reduction in the risk of GDM for a 100 g d^{-1} increase in fruit consumption.[25] Finally, in a systematic review of 18 prospective studies, Madsen and colleagues found a reduced risk of hypertension associated with the consumption up to 800 g day^{-1} of fruits and vegetables, and 550 g day^{-1} of fruits, including apples.[26]

When considering the contribution of apples and apple-derived products on health-related conditions, the results are not univocal, especially between observational *versus* interventional studies.[27–30] For example, Guo *et al.* in their meta-analysis of prospective studies found that one serving per week increment of apple and pear consumption was associated with a 3% reduction in type 2 diabetes mellitus (T2DM), documenting significant evidence of an inverse association between apple and pear consumption and T2DM risk.[28] Gayer *et al.* meta-analysed the results derived from 14 prospective observational studies and found that apple or pear intake significantly decreased the risk of cerebrovascular disease, cardiovascular death, T2DM, and all-cause mortality;[30] conversely, when considering the results from 7 randomized controlled trials and 1 non-randomized trial, they found that apple intake significantly decreased BMI, but showed no difference in body weight, serum lipids, blood glucose or blood pressure. Kim *et al.* in a meta-analysis of 18 randomized controlled trials revealed that subjects with high total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) may have more benefits from intervention with apples, while most of the other markers considered (*e.g.*, HDL-C, triglyceride, glucose, insulin, C-reactive protein, and systolic/diastolic blood pressures) were unaffected by the intervention.[29]

Based on these premises, the aim of the present study was to systematically review dietary intervention studies focused on the effects of apples and apple-based products on a wide range of markers of human health. The main markers considered include those related to cardiometabolic health (*e.g.*, lipid and glucose profiles, body weight, and blood pressure), oxidative stress and antioxidant potential (*e.g.*, uric acid and phase two enzymes), inflammation (*e.g.*, interleukins and cytokines) and vascular health (*e.g.*, arterial stiffness and vascular reactivity). In addition, the contribution of apples and apple-based products on additional markers, not yet considered in the previous meta-analyses, was also considered, such as the effect on gut microbiota composition, hunger/satiety sensations and food intake or metabolic response.

2. Methods

2.1. Search strategy

A systematic literature search was conducted using three academic digital databases, PubMed®, Embase and Scopus. The

search was performed in April and updated in May 2025. The following syntax was used: ((apple* OR "Malus domestica" OR "M. domestica" OR "Malus pumila" OR "M. pumila") AND ("lipid profile" OR "lipid distribution" OR lipid* OR cholesterol OR "total cholesterol" OR "TC" OR "low density lipoprotein" OR "LDL" OR "LDL-C" OR "high density lipoprotein" OR "HDL" OR "HDL-C" OR triglyceride* OR triacylglycerol* OR "TG" OR "TAG" OR "lipoprotein" OR "blood pressure" OR "SBP" OR "DBP" OR "insulin" OR "cardiovascular" OR "CVD" OR "diabetes" OR "glucose" OR "glycem*" OR "inflammation" OR "oxidative stress" OR "obesity" OR "overweight" OR "neuroprotection" OR "microbiota") AND ("trial" OR "intervention")).

To ensure completeness, relevant review articles were screened.

The literature identification process was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines and is reported in Fig. 1.

2.2. Study selection

Articles were included if they reported dietary intervention studies that explored the impact of consuming apples or apple-derived products (intervention) compared with meals without apples (control) on health-related parameters in humans. Only articles published from 2010 and written in English were included in the following review. Studies were excluded if carried out exclusively by using apple-rich extracts or mixing apples with other bioactive-rich foods with no possibility to discriminate the contribution of apples. We excluded studies performed on apple cider vinegar as they have recently been the subject of several meta-analyses.[31,32]

Two authors (CDB and AG) screened studies and extracted data from eligible studies. Disagreements between reviewers were resolved through consultation with a third independent reviewer (MR).

The detailed list of eligibility criteria developed following the PICOS (Population, Intervention, Comparison, Outcomes, Study) design is reported in Table 1.

2.3. Data collection

Two authors (AG and MM) independently screened studies and extracted data from eligible studies. Disagreements between reviewers were resolved through consultation with a third independent reviewer (DM) to reach a consensus. Data

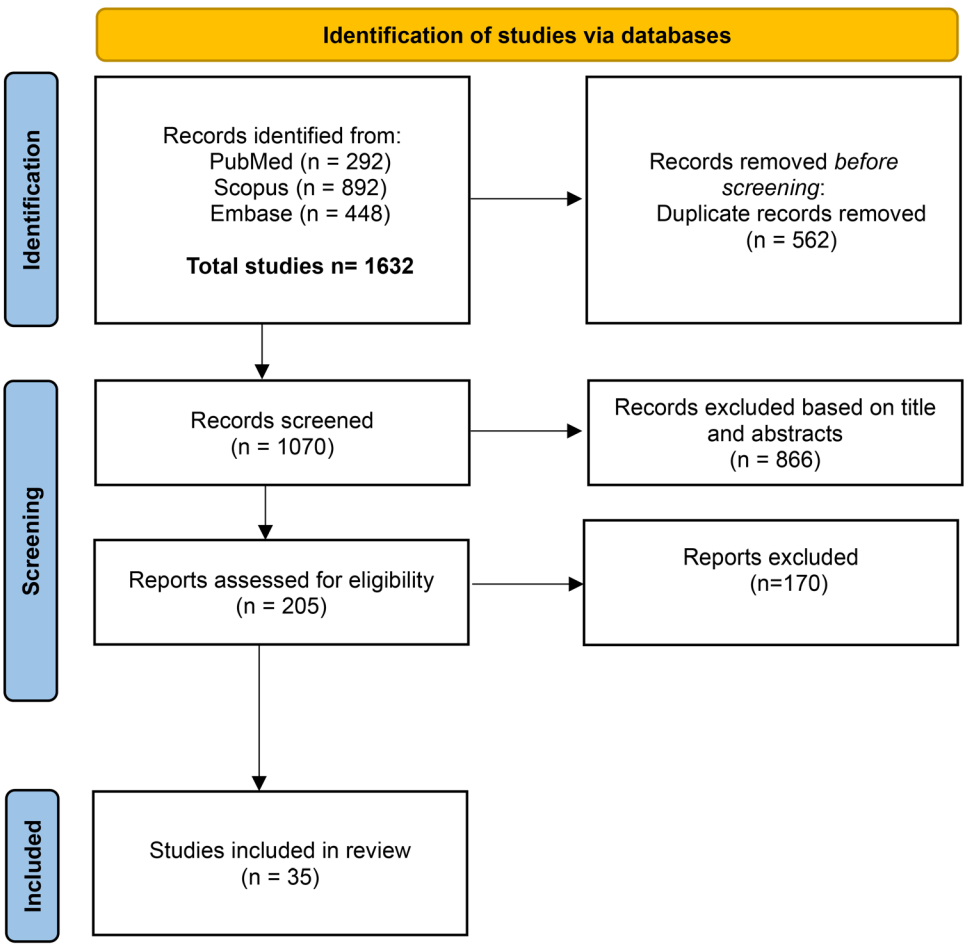

Fig. 1 PRISMA flow diagram illustrating the literature search process and the application of selection criteria.

Table 1 PICOS table for inclusion of studies

Parameters	Inclusion criteria
Population	All ages, healthy and unhealthy
Intervention	Dietary intervention studies involving the consumption of apples or apple-based products, regardless of the form supplied (*e.g.*, raw, dried, juices, purée), not in combination with other foods rich in bioactives that may have overlapping effects
Comparison	Control group (apples totally or partially excluded from the diet, or apples totally or partially substituted with other fruits)
Outcome	Health and disease markers, including nutrients and non-nutrient metabolism
Study design	Human intervention studies (*e.g.*, acute, chronic, randomized, non-randomized, controlled, non-controlled)

extracted included year and country in which the study was performed, number of participants with their respective characteristics (*i.e.*, age, BMI, and health), study design and duration, characteristics of the intervention (including the apple varieties when available) and the control, and the main findings observed.

3. Results

3.1. Study selection

A total of 1632 records were initially identified from the search on PubMed®, Embase and Scopus databases. After removing 562 duplicates, the remaining studies were screened for their title and abstract and 866 were excluded. Among the 205 remaining studies, 170 records were excluded for not reporting results on any health markers, not being in English, and not involving apples or apple-based products but rather derivatives such as apple cider or apple vinegar. Thus, at the end of the selection process, 35 publications were included in this review (Fig. 1). Three of them included short-term and chronic intervention trials.

3.2. Study characteristics

The characteristics of the studies included are reported in SI Tables S1 and S2, while the main results are reported in Tables 2 and 3. The largest number of the studies was carried out in the United States (n = 7) and Ireland (n = 4). The rest of the studies were performed in Iran, United Kingdom, Denmark, Canada, and Brazil. Thirteen studies investigated the effect of a single portion of apples and/or apple-based products,[19,33–45] 19 studies evaluated the effect of a medium/long term intervention,[4,46–63] while 3 studies examined the effects of both acute and chronic consumption.[64–66] The apples were used mainly as raw fruits and juice; some studies used apples in the form of flesh, purée, pomace or dried/lyophilized product. Apples were provided alone or in combination with breakfast[64,66] or a meal.[42]

The amount administered was dependent on the type of product/form considered and varied in the range of 125–550 g for apples and/or apple purée, and 113–1000 mL for apple juice. Regarding dried/lyophilized product, the amount administered was in the range of 20–75 g. The main varieties of apples tested within the studies included Golden Delicious, Cripps Pink, Renetta and Fuji. Four studies administered a mix of apple varieties,[37,51,54,63] one study tested a special crop of apple,[59] while 9 trials did not report the variety of apple tested.[36,39,46,48,50,51,54,57,62]

Most of the studies characterized apples for the content of nutrients and non-nutrients, including (poly)phenols whose content was dependent on both the variety of apple and the amount administered. Specifically, total (poly)phenol content ranged from about 47 mg (contained in 125 g of unfermented apple purée)[58] to about 1 g (contained in 500 mL of unfiltered apple juice)[38] with quercetin, phloretin glycoside, catechin, epicatechin and chlorogenic acid as the main phenolic compounds. Regarding the control treatments selected, most of the short-term (acute) studies provided water, low-flavonoid apple juice, grape juice, or a meal matching the energy and sugar content of the apple product intervention but excluding the bioactive compounds.

The main outcome variables in the short-term studies were glucose response and the antioxidant response/capacity, followed by the evaluation of vascular reactivity, while in the medium-long-term interventions, the main variables analysed included cardiometabolic-related parameters (*e.g.*, cholesterol, triglycerides, blood pressure, and body weight/composition) and inflammatory and oxidative stress markers. The rest of the studies evaluated the impact of apples/apple-based products on gut microbiota composition, satiety-related sensations, and nutrient absorption/metabolism. One study also considered behavioural and psychotic symptoms associated with dementia,[46] while another study considered the contribution to gene interaction.[50]

3.3. Effect of apples and apple-based products on markers related to cardiometabolic health

The effect of apples and apple-based products on markers of cardiometabolic health has been evaluated in 10 short-term term studies[35,37,40–45,65,66] and 18 medium/long-term interventions.[4,47,49–53,55–61,63–66]

Short-term interventions. The main marker analyzed was postprandial glycaemia, followed by insulin response, postprandial lipemia, and heart rate. In an open-label, randomised, pilot, cross-over study, Makarova and colleagues reported that the acute ingestion of a dried and powdered pomace of unripe apples (25 g) significantly reduced the postprandial glucose (50 g) response at 15 to 30 min by approximately two-fold compared to the control in diabetic subjects, while increasing urinary glucose excretion by five-fold during the 2-

Table 2 Characteristics of the short-term interventions investigating the effect of apples and apple-based products on markers of human health

Ref. and country	Cardiometabolic markers	Oxidative stress and antioxidant markers	Inflammatory markers	Vascular function markers	Microbiota	Additional markers
Godycki-Cwirko *et al.* (2010) and Poland[33]		↑ FRAP and serum DPPH-scavenging activity at 1 h following the three apple juices ↑ Serum uric acid following the three apple juices				= Plasma total phenolics and quercetin
Bondonno *et al.* (2012) and Australia[34]		= F2-isoprostanes	= 20-hydroxyeicosatetraenoic acid	↑ rRXNO, nitrite and nitric oxidases (for all treatments compared to the control) ↑ FMD (for all treatments compared to the control) ↓ Pulse pressure (for all treatments compared to the control) ↓ SBP (apple and spinach treatment) = DBP, endothelin-1		
Vieira *et al.* (2012) and Brazil[35]	= Glucose response	↑ Serum antioxidant capacity following both apple juices compared to the control ↑ Vitamin C and uric acid following both apple juices compared to the control ↓ Serum LH and TBARS following both apple juices compared to the control				
Hollands *et al.* (2013) and UK[36]				↑ Plasma NO after 30 min following apple and flavanol drink intake ↑ Urinary NO after 2 h following apple and flavanol drink intake. Higher NO excretion following high flavanol apple extract after 24 h		↑ Plasma concentration, AUC (0–24 h), absorption and urinary excretion significantly higher after ingestion of both epicatechin drinks compared with apple purée. Maximum plasma epicatechin concentration post-pone following apple purée compared to drinks ↑ Epicatechin bioavailability higher (>2-fold) after ingestion of the high flavanol drink compared to the low flavanol drink

Table 2 *(Contd.)*

Ref. and country	Cardiometabolic markers	Oxidative stress and antioxidant markers	Inflammatory markers	Vascular function markers	Microbiota	Additional markers
Gasper *et al.* (2014) and UK[64]				↓ Platelet reactivity at 2 and 6 h from HF and LF-apple puree compared to baseline ↓ ADP and epinephrine-induced P-selectin expression at 2 h from LF-apple puree compared to baseline ↓ ADP-induced P-selectin expression at 2 h from ASA (no difference compared to HF-and-LF apple puree) ↑ NO metabolites at 6 h from HF-and LF-apple puree compared to baseline (not treatment effect) ↑ Integrin-ß3 expression at 2 h and ADP-induced integrin-ß3 expression at 6 h from HF-apple puree compared to baseline		↑ Total plasma monomeric catechins at 6 h in HF compared to LF-apple puree ↑ Urinary excretion of epicatechin in HF compared to LF-apple puree
Makarova *et al.* (2015) and Latvia[37]	↓ Blood glucose response after 15–30 min from apple intake compared to the control. In addition, apples delayed the decrease of glucose concentrations below basal levels 2 h after the glucose load = Glucose AUC					↑ Urinary glucose excretion during the 2- to 4 h interval compared to control ↑ Urinary metabolites of phlorizin: phloretin-2′-O-glucuronide, phloretin-O-glucuronide and phloretin following apple intake
Wruss *et al.* (2015) and Austria[38]		↑ Plasma antioxidant potential (ORAC and TEAC) at 1 h and after 6 h				↑ Plasma total phenolic content at 6 h with differences for sex at 1 h ↑ Plasma flavan-3-ols, flavonols, hydroxycinnamic acids and benzoic acids ↑ Polyphenol urinary excretion at 6 h with differences for sex at 2 h

Table 2 *(Contd.)*

Ref. and country	Cardiometabolic markers	Oxidative stress and antioxidant markers	Inflammatory markers	Vascular function markers	Microbiota	Additional markers
Erickson *et al.* (2017) and USA[39]					↑ Hydrogen breath response (marker of bacterial fermentation) within the gastrointestinal tract	= Gastrointestinal symptom response
Bondonno *et al.* (2018) and Australia[65]	= HR			↑ FMD after 1 and 2 h in the HFA group compared to control =SBP, DBP, central DBP, AIx75, PWV, plasma/saliva nitrite and nitrate		↑ Quercetin and isorhamnetin at 3 h in HFA compared to control
Sansone *et al.*, (2018) USA[40]	↓ Glucose concentrations at 30, 45, 60, 120 min after dried apple compared to muffin ↓ Insulin at 15 min after dried apple compared to muffin	= Antioxidant status				↑ Executive function, cognitive flexibility pre-to-post in the muffin group ↑ Psychomotor speed pre-to-post in the dried apple group ↓ Verbal memory pre-to-post in the muffin group = Visual memory, reaction time, = Satiety
White *et al.* (2018) and New Zealand[41]	↑ Blood glucose at 30 min after all the treatments. Large apple servings resulted in a greater increase compared to the small serving. No effect of the juice	↑ Plasma uric acid following small and large apple and juice, and fructose. Large apple servings resulted in a greater increase compared to the small serving. No effect for juice		= SBP, DBP,		= Satiety score (including hunger, fullness, satisfaction, and how much people can eat)
Lu *et al.* (2019) and China[42]	↓ Incremental areas under the curve (iAUC) of postprandial glycemic response, average peak value, and glycemic excursion in 240 min following PA + R. ↓ Peak value and glycemic excursion following PSS + R ↓ Acute postprandial glycaemic response without negative effect on satiety markers following PSS + R compared to rice meal					↑ Higher incremental low satiety sensation at 90 min following A + R compared to R, and at 90 min and 120 min compared to PA + R
Zhao *et al.* (2020) and China[43]	↓ Incremental area under the curve 0–120 min following DA + R and PSS + R compared to rice ↓ Glycemic excursion in 240 minutes following DA + R and PSS + R compared to rice ↓ Incremental area under the curve 0–120 min, peak, and glycemic excursion following VDA + R compared to rice					= Satiety among R, PDA + R, PSS + R, and VDA + R

Table 2 *(Contd.)*

Ref. and country	Cardiometabolic markers	Oxidative stress and antioxidant markers	Inflammatory markers	Vascular function markers	Microbiota	Additional markers
Lin *et al.* (2020) and Canada[44]	↑ Insulin, apoB48 (between 20–180 min) = TG, chylomicron properties, glucose, acetaminophen					
Cheng *et al.* (2022) and China[45]	↑ Serum blood glucose concentration and AUC following apples compared to fructose	↓ Serum uric acid at 30 and 60 min after apple consumption compared to fructose powder. Higher postprandial serum uric acid in men compared to women		= SBP, DBP		
Pushpass *et al.* (2023) and Ireland[66]	*Postprandial response to apples before intervention* ↓ Glucose response between 40–150 min, C_{max} ↓ Insulin response between 40–150 min, AUC and iAUC ↓ C-peptide plasma levels between 40–180 min, AUC, iAUC, and C_{max} ↓ iAUC for PYY ↑ NEFA response between 80 and 240 min ↑ C_{min}, AUC and iAUC = TG, FGF-19, ghrelin, GIP, GLP-1, PP *Postprandial response with apples within chronic intervention* = Glucose, insulin, PYY, C-peptide, NEFA, TG, FGF-19, ghrelin, GIP, GLP-1, PP			*Postprandial response to apples before intervention* = SBP, DBP, PWV *Postprandial response with apples within chronic intervention* = SBP, DBP, PWV		*Postprandial response to apples before intervention* = Total, hydrophobic, hydrophilic, unconjugated bile acid plasma response, secondary bile acids *Postprandial response with apples within chronic intervention* = Total, hydrophobic, hydrophilic, unconjugated bile acid plasma response, secondary bile acids

Legend: A + R, co-ingestion of apple and rice; ADP, adenosine diphosphate; AIx75, augmentation index; ASA, aspirin treatment; AUC, area under the curve; DA + R, dried apple + rice; DBP, diastolic blood pressure; DPPH, 2,2-difenil-1-picrilidrazile; FGF-19, fibroblast growth factor 19; FGF-19, fibroblast growth factor 19; FMD, flow mediated dilation; FRAP, ferric reducing antioxidant power; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; HDL-C, high density lipoprotein-cholesterol; HF, high flavonol; HFA, high flavonol apple; HFA, high flavonol apple; HR, heart rate; LDL-C, low density lipoprotein cholesterol; LF, low flavonol; LH, lipid hydroperoxides, NEFA, nonesterified fatty acid; ORAC, oxygen radical absorbance capacity; PA + R, apple preload and rice; PDA + R, DA preload and rice; PP, pancreatic polypeptide; PSS + R, rice with sugar solution preloaded; PSS + R, rice with sugar solution preload; PWV, pulse wave velocity; PYY, peptide tyrosine tyrosine; PYY, peptide YY; RXNO, S-nitrosothiols + other nitrosylated species; SBP, systolic blood pressure; TBARS, thiobarbituric acid-reactive substances; TC, total cholesterol, TEAC, trolox equivalent antioxidant capacity; TG, triglycerides; VDA + R, co-ingestion of rice with vinegar-soaked.

Table 3 Characteristics of the medium–long-term interventions investigating the effect of apples and apple-based products on markers of human health

Ref. and Country	Cardiometabolic markers	Oxidative stress and antioxidant markers	Inflammatory markers	Vascular function markers	Microbiota	Additional markers
Remington *et al.* (2010) and USA[46]						↑ Behavioral and psychotic symptoms associated with dementia
Auclair *et al.* (2010) and France[47]	= Homocysteine, TC, TG, LDL-C, HDL-C, APOA1, APOB, PP, glucose, APOB/APOA1	= Iron, FRAP, ORAC, Vitamin E, uric acid	= CRP	= FMD, glyceryl trinitrate, NOx, SBP, DBP		↑ Phloretin, plasma Vitamin C, (compared to baseline in both the treatments)
Shinohara *et al.* (2010) and Japon[48]					↑ Bifidobacterium ↓Clostridium Lecithinase-positive, Enterobacteriaceae, short-chain fatty acid ammonia, sulphide = Other fecal bacteria, fecal short chain fatty acids, water content, pH	
Vafa *et al.* (2011) and Iran[49]	↓ VLDL and TG in the control group = TC, HDL, LDL, LDL/HDL ratio, apolipoprotein B, lipoprotein a					
Barth *et al.* (2012) and Germany[50]	↑ Lean body fat ↑ TG in both groups ↓ Total body fat, in subjects with IL-6–174 C/C single-nucleotide polymorphism = Body weight, BMI, WC, TC, LDL-C, HDL-C, NEFA, adiponectin, leptin, resistin		= a-FABP, RBP4, CRP, IL-6, TNFa,	= ICAM-1, VCAM-1		
Chai *et al.* (2012) and USA[51]	↓ Serum TC (compared to baseline; at 6 months compared to the control) ↓ Serum LDL-C (compared to baseline) ↓ TC/HDL-C (compared to baseline) ↓ LDL-C/HDL-C (compared to baseline) = Serum HDL-C, serum TG, HDL-C/LDL-C	↓ Serum lipid hydroperoxide (compared to baseline in both the treatments)	↓ Serum CRP			
Zhao *et al.* (2013) and USA[52]	↓ Beta2-glycoprotein I following apples and apple polyphenol extract	↓ Oxidized LDL following apples and apple polyphenol extract = Erythrocyte SOD activity				
Ravn-Haren *et al.* (2013) and Denmark[53]	↑ TC and LDL-C following clear apple juice compared to apples and pomace = HDL-C, TC/HDL-C ratio, TG, weight, waist-to-hip ratio, bile acid concentration, bile acid excretion, HR, ALAT, insulin, IGF1 and IGFBP3	= TEAC, FRAP, ORAC, GPX, GR, SOD, CAT, LIPIDOX	= hs-CRP	= SBP, DBP,	= Gut microbiota composition	
Gasper *et al.* (2014) and UK[64]	= TC, HDL-C, LDL-C, TG,		= CRP	= ET-1, nitric oxide metabolites		↑ Urinary excretion of epicatechin in HF compared to LF-apple puree ↑ Plasma vitamin C in all the treatments after 4 weeks

Table 3 *(Contd.)*

Ref. and Country	Cardiometabolic markers	Oxidative stress and antioxidant markers	Inflammatory markers	Vascular function markers	Microbiota	Additional markers
Mehrabani *et al.* (2014) and Iran[54]						= Energy intake
Soriano-Maldonado *et al.* (2014) and Spain[55]	↑ HOMA-index (time effect for both the treatments) ↑ Insulin (time effect in the PR group) = Glucose, TC, HDL-C, LDL-C, TC/HDL-C, LDL-C/HDL-C, iron, ferritin	↓ GSH (compared to baseline in the PR group) = FRAP, DPPH, DMACA	= hs-CRP, C3, C4, IL-8, IL-6, IL-10	↓ VCAM-1 and ICAM-1 (compared to baseline in the VCR group) = MCP-1, tPAI-1, E-selectin		↑ Plasma Vitamin C (VCR compared to PR group) ↑ Urine polyphenol metabolites
Rago *et al.* (2015) and Denmark[56]	↑ Improvement cholesterol homeostasis	↑ Uric acid				↑ Branched-chain amino acids and aromatic amino acids degradation ↓ Use of lipid fuels ↓ Plasma bile acids ↓ Lysophosphatidylcholines and a steroid hormone precursor
Bondonno *et al.* (2018) and Australia[65]	= Glucose, TC, HDL-C, LDL-C, creatinine, urinary potassium and sodium, heme, bilirubin, biliverdin	= Urinary F2-isoprostanes,		↑ FMD in the HFA group compared to the control = SBP, DBP, HR, PP, AIx75, PWV, plasma/saliva nitrite and nitrate		↑ Quercetin and isorhamnetin in HFA group compared to the control
Eisner *et al.* (2020) and USA[57]	↑ Body weight, FFM, HDL-C in the control = BMI, waist circumference, body composition parameters, TC, TG, LDL-C, TC/HDL-C, HDL-C/LDL-C, glucose, insulin, proinsulin, HOMA-IR index, adiponectin	= Total antioxidant capacity, GPx	= CRP			
Tenore *et al.* (2019) and Italy[58]	↑ HDL-C following the three treatments respect to baseline. Higher effect following lfAAP = TC, LDL-C, glucose, TG	↓ TMAO following the three treatments respect to baseline. Higher effect following lfAAP			↑ Bifidobacterium, Lactobacillus following the three treatments respect to baseline. Higher effect following AAP and LAB ↓ Bacteroides, Enterococcus following the three treatments respect to baseline. Higher effect for Bacteroides following AAP, while for Enterococcus following LAB treatment	
Giaretta *et al.* (2019) and Brazil[59]	= Phosphorus, potassium, glucose and fructosamine	↑ TOS, SOD, GPx, AA ↓ TAS, CAT = GSH, uric acid				= Bowel habits
Koutsos *et al.* (2020) and UK[4]	↓ TC, LDL-C, TG = BMI, waist, HDL-C, nonesterified fatty acidss, glucose, insulin, albumin, adiponectin, bile acids	↑ Uric acid compared to the control	= TNF-α	↓ ICAM-1, endothelium-dependent microvascular vasodilation compared to the control = Endothelin, P-selectin, E-selectin, VCAM-1, ambulatory blood pressure monitor, pulse wave analysis		

Table 3 *(Contd.)*

Ref. and Country	Cardiometabolic markers	Oxidative stress and antioxidant markers	Inflammatory markers	Vascular function markers	Microbiota	Additional markers
Barnett *et al.* (2021) and New Zealand[60]	= TC, LDL-C, HDL-C, TC/HDL-C, TG		= CRP		↓ Streptococcus, Ruminococcus, Blautia and Roseburia ↑ Sutterella, Butyricicoccus, and Lactobacillus = Alpha diversity	↑ Genes related to immunoglobulin
Liddle *et al.* (2021) and Canada[61]	= Weight, BMI, waist circumference, TC, LDL-C, HDL-C, TG, NEFA, glucose, insulin, HOMA-IR	↑ TAC	↓ Serum CRP, IL-6, IL-6 and IL-17 secreted from PBMCs ↓ IFN-γ, MCP-1, TNF-a, secreted from PBMCs only compared to baseline = IL-1β	= SBP, DBP		
Pushpass *et al.* (2023) and Ireland[66]	= Plasma and fecal bile acids, TC, LDL-C, HDL-C, non-HDL-C, LDL-C/HDL-C, TC/HDL-C, TG, NEFA, apoB, glucose, insulin, C-peptide, ghrelin, GLP-1, GIP, PP, PYY, FGF-19, lipid, glucose, insulin		= IL-18, IL-6, CRP, TNF-a		= Alpha diversity	
Alexander *et al.* (2023) and United States[62]					↑ Faecalibacterium and Negativibacillus (pre- to post-intervention) but no longer significant after false discovery rate correction	= Bowel movement frequency
Alzoufairi *et al.* (2025) and Ireland[63]	Gene related to bile acide synthesis: = GPBAR1; CYP27AI Gene related to lipid regulation: = LDL-R; HMGCR; SREBF1; PPARD; ACAT1		Gene related to inflammation: ↓ TLR4; = TNFSF14; NR1H3			Gene related to gastrointestinal hormones: = GIPR

Legend: AA, ascorbic acid; ABTS, 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid); apoA1, apolipoprotein A1; apoB, apolipoprotein B; ACAT1, acetyl-CoA acetyltransferase 1; Aix, augementation index; AIx75, augmentation index standardised to a heart rate of 75 bpm; ALAT, alanine aminotransferase activity; BMI: body mass index; C3, complement factor 3; C4, complement factor 4; CAT, catalase; CRP, C-reactive protein; CYP27A1, cytochrome P450 family 27 subfamily A member 1;DBP, diastolic blood pressure; DMACA, p-dimethylaminocinnamaldehyde; DPPH, 2,2-diphenyl-1-picrylhydrazyl; ET-1, endothelin-1; a-FABP, Fatty acid binding protein; FGF-19, fibroblast growth factor 19; FFM, fat-free mass; FMD, flow mediated dilation; FRAP, ferric ion reducing antioxidant power; GIP, gastric inhibitory polypeptide; GIPR, glucose-dependent insulinotropic polypeptide receptor; GLP-1, glucagon-like peptide-1; GPBAR1, G protein-coupled bile acid receptor 1; GPx, glutathione peroxidase; GR, glutathione reductase; GSH, reduced glutathione; HDL-C, high density lipoprotein cholesterol; HMGCR, 3-hydroxy-3-methylglutaryl coenzyme A reductase; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; HR, heart rate; hs-CRP, high-sensitivity C-reactive protein; ICAM, Intercellular Adhesion Molecule 1; IGF1, insulin-like growth factor 1; IGF1BP3, binding protein 3; IFN-γ, Interferon gamma; IL-1β, interleukin-1beta, IL-6, interleukin-6, IL-8, interleukin-8; IL-10, interleukin-10; IL-17, interleukin-17; IL-18, interleukin-18; LDL-C, low density lipoprotein cholesterol; LDL-R, low-density lipoprotein receptor; LF, low-flavonoid; lfAAP, lactofermented Annurca apple puree; LH, lipid hydroperoxides; MCP-1, Monocyte chemoattractant protein-1; NEFA; nonesterified fatty acid; NOx, nitric oxide metabolites; NR1H3, nuclear receptor subfamily 1 group H member 3; ORAC, Oxygen radical absorbance capacity; PAI-1, plasminogen activator inhibitor-1; PBMCs, peripheral blood mononuclear cells; PP, pulse pressure; PPARD, peroxisome proliferator activated receptor d; PR-group, polyphenol-rich group; PWV, pulse wave velocity; PYY, peptide YY; RBP4, Retinol-binding protein 4; rRXNO, *S*-nitrosothiols + other nitrosylated species; SBP: systolic blood pressure; SOD, superoxide dismutase; SREBF1, sterol regulatory element binding transcription factor 1; TAC, total antioxidant capacity; TAS, total antioxidant status; TBARS, thiobarbituric acid-reactive substances; TC, total cholesterol; TEAC, Trolox equivalent antioxidant capacity; TG, triacylglycerol; TLR4, toll-like receptor 4; TNFSF14, tumour necrosis factor (ligand) superfamily member 14TMAO, trimethylamine N-oxide; TNFα, tumor necrosis factor α; TOS, total oxidant status; VCAM, Vascular cell adhesion protein 1; VCR-group, vitamin C-rich group; VLDL, very low-density lipoprotein; WC, waist circumference.

to 4 h interval of the oral glucose tolerance test.[37] In another randomized, crossover study, Sansone and colleagues reported that the consumption of dried apple (equivalent to 55 g of carbohydrates) positively affected acute blood glucose and insulin response compared to muffins as the control (providing the same amount of carbohydrates), in a group of healthy, normal-weight subjects.[40] Specifically, the intervention with dried apples lowered glucose concentrations at 30-, 45-, 60- and 120 min from the intake, while significantly decreasing insulin concentrations after 15 min. In a randomized crossover trial, Lu and coworkers tested the acute postprandial glycaemic responses of co-ingestion of apple and rice (A + R) or apple preload and rice (PA + R), *versus* a condition that included the consumption of rice or rice with sugar solution preload (same sugar profile as in the apple) (PSS + R).[42] The study was carried out in a group of healthy young subjects. Compared with the rice reference, PA + R showed 50% reduction of glucose response (reported as iAUC 0–120 minutes), 51.4% reduction of the average peak value, and 52.6% reduction of glycemic excursion in 240 min, while PSS + R showed 29.7% and 31.6% reduction of the peak value and glycemic excursion, respectively. In a randomized crossover trial, Zhao *et al.* tested the effects of 5 different treatments on acute postprandial glycemic response in a group of healthy female subjects as follows: (1) rice, (2) co-ingestion of dried apples and rice (DA + R), (3) DA preload and rice (PDA + R), (4) rice with sugar solution (same sugar profile as in DA) preloaded (PSS + R), or (5) co-ingestion of rice with vinegar-soaked DA (VDA + R).[43] Overall, compared with the rice reference, PA + R and PSS + R produced 31.4% and 36.3% reduction of glucose response (reported as iAUC 0–120 minutes), 24.3% and 27.0% decrease in the average glucose peak, and 21.6% and 27% decrease in glycemic excursion in 240 minutes, whereas VDA + R resulted in 42.4%, 27.0%, and 29.7% reduction of glucose response (reported as iAUC 0–120 minutes), peak, and glycemic excursion, respectively. In a 4-arm parallel dietary intervention design, healthy subjects were randomly assigned to consume 40 g cornflakes (control), 40 g oats or 2 Renetta Canada apples (amount not reported), each with 2 placebo capsules per day or 40 g cornflakes with 2 *Lactobacillus reuteri* capsules (>5 × 109 CFU) for 8 weeks.[66] The acute effect of apples was tested before and after the long-term intervention. When the consumption was carried out before the intervention, apples significantly decreased the postprandial glucose (40–150 min), serum insulin, iAUC, and C-peptide (40–150 min) response, while increasing circulating non-esterified fatty acids compared to the control. No effect was observed on the levels of triglycerides, glucagon-like peptide-1, pancreatic polypeptide, ghrelin, and fibroblast growth factor 19. When the long-term intervention was followed by an acute intervention, no significant effect was observed on the marker under study. No significant finding on blood glucose response was also documented by Vieira *et al.* following the consumption of 300 mL of two apple juices, compared to water as the control, in a pilot study carried out in a group of 9 healthy subjects.[35] Differently, White and colleagues, in a randomized, controlled trial, showed an increase in blood glucose response at 30 min after the consumption of small and large servings of apple fruit (205 g and 410 g, respectively) and juice (170 mL and 340 mL, respectively) in a group of healthy volunteers.[41] Specifically, the administration of a large apple serving, but not juice, resulted in a greater glucose response compared to the small serving size. Similarly, Cheng *et al.* reported a significant increase in serum blood glucose concentration and AUC following the consumption of 220 g of apple flesh compared to the same amount of fructose as the control, in a group of healthy subjects.[45]

Medium–long-term interventions. The main markers considered included lipid profile, glucose, insulin, BMI and/or body composition. Only three studies revealed a positive effect of intervention on the lipid profile; two trials were conducted in healthy participants, and one study was carried out in subjects with mild hypercholesterolemia. Chai *et al.* found that the consumption of 75 g of dried apples, compared to dried plum as the control, significantly reduced serum total cholesterol (TC) levels after 6 months, but not 12 months, of intervention.[51] A significant decrease was observed after the 12-month intervention with respect to the levels of serum LDL-C and the ratios TC/HDL-C and LDL/HDL-C but only in comparison to baseline values but not *versus* the control group.[51] Rago *et al.* documented that 4-week consumption of apples (550 g) and dried apple pomace (22 g), compared to cloudy and clear apple juice (500 ml), significantly improved cholesterol homeostasis in healthy subjects.[56] Specifically, the authors observed a decreased use of lipid fuels and a reduced level of plasma bile acids as well as of some lysoPCs and steroid hormone precursors, indicating a reduced outbound cholesterol transport from the liver and less use of cholesterol for steroid synthesis. Koutsos *et al.* reported a significant reduction in serum TC, LDL-C and triglycerides in a group of subjects with mild hypercholesterolemia following an 8-week intervention with 340 g of Renetta apples compared to water with sugars as the control.[4] No effect was observed for the levels of HDL-C, glucose, insulin, albumin, and bile acids as well as BMI and waist circumference.[4]

3.4. Effect of apples and apple-based products on markers of oxidative stress and antioxidant potential

The effect of apples and apple-based products on markers of oxidative stress and antioxidant potential has been evaluated in 7 short-term studies[33–35,38,40,41,45] and 12 chronic intervention studies.[4,47,51–53,55–59,61,65]

Short-term interventions. Serum/plasma antioxidant potential or capacity and serum levels of uric acid were the main markers analyzed. Four studies have shown an increase in the plasma antioxidant potential/capacity and uric acid. Godycki-Cwirko and co-authors showed an increase in ferric reducing antioxidant power (FRAP), serum 2,2-diphenyl-1-picrylhydrazyl (DPPH) scavenging activity and serum uric acid following the postprandial intake of 1 L of clear, cloudy apple juice, and apple without polyphenols as the control, in a group of young healthy individuals. However, this effect was not accompanied by a sig-

nificant increase in total phenolics and quercetin plasma levels.[33] Vieira *et al.* found a reduction in free radical initiated lipid (LH) and thiobarbituric acid reactive substance (TBARS) levels, and an increase in serum antioxidant capacity, uric acid and vitamin C, following the postprandial consumption of two apple juices (300 mL) in a group of healthy subjects.[35] In a non-randomized, non-controlled study, Wruss *et al.* observed a significant increase in plasma antioxidant potential at 1 and 6 h after the intake of 500 mL of unfiltered apple juice in healthy volunteers.[38] In parallel, an increase in plasma total phenolic content, flavan-3-ols, flavonols, hydroxycinnamic and benzoic acids, and polyphenol urinary excretion was also documented.[38] White *et al.* showed a significant increase in plasma uric acid following the postprandial intake of small and large servings of apple fruit (205 g and 410 g, respectively), juice (170 mL and 340 mL, respectively) and soda water containing a comparable amount of fructose, but not glucose, as the control, in healthy volunteers.[41] The increase was greater following the administration of a large apple fruit, but not juice serving. Conversely, a significant reduction in serum uric acid was documented at 30 and 60 min after the intake of 222 g of apple flesh compared to pure fructose powder as the control, in healthy subjects. The effect was higher in men compared to women. Sansone and co-workers reported no effect on antioxidant status following the consumption of dried apple with water when compared to a comparable amount of carbohydrates from muffins in a group of healthy subjects.[40] Bondonno and coworkers failed to detect changes in F2-isoprostanes in healthy individuals following the intake of flavonoid-rich apples and nitrate-rich spinach.[34] Finally, Cheng and co-authors[45] detected a decrease in serum uric acid levels following apple flesh consumption (220 g) in healthy subjects.

Medium–long-term interventions. The main biomarkers evaluated included serum/plasma antioxidant capacity, antioxidant enzyme activity (*e.g.*, SOD and CAT), glutathione (GSH) levels, and lipid peroxidation products (*e.g.*, isoprostanes and ox-LDL). Overall, the findings across studies were largely conflicting and strictly dependent on the type of marker analyzed. Auclair *et al.* have shown that 4-week consumption of 135 g of low or high polyphenol-rich apples increased phloretin and plasma vitamin C levels but did not affect FRAP, oxygen radical absorbance capacity (ORAC) and the levels of iron, uric acid and vitamin E in hypercolesterolemic subjects.[47] Zhao *et al.* documented that 4-week consumption of 1 apple or an apple polyphenol-extract per day (similar content of polyphenols) improved the levels of oxidized-LDL-beta2-glycoprotein 1, but not superoxide dismutase, in a group of healthy subjects.[52] Similar findings were reported by Chai *et al.*, documenting a reduction in serum lipid hydroperoxide following 12-month consumption of 75 g of dried apples in postmenopausal women.[51] However, the same effect was also reported in the control group consuming 100 g of dried plums. In another study, Soriano-Maldonado *et al.* showed that the intake of 500 mL of a vitamin C apple juice for 4 weeks improved plasma levels of the vitamin and urinary polyphenol metabolites, but reduced glutathione levels and did not affect FRAP and DPPH in healthy individuals.[55] Rago and colleagues have shown that the consumption of 550 g of apples, or 22 mg of apple pomace, for 4 weeks reduced uric acid in healthy volunteers.[56] No effect was observed following the intake of 500 mL of cloudy or clear apple juice. Tenore *et al.* have reported that 90-day consumption of an unfermented and lactofermented apple puree (125 g) decreased trimethylamine N-oxide (TMAO) levels and the effect was higher in the lactofermented product in subjects with cardiovascular risk.[58] However, the authors also found a similar effect in the placebo group consuming 1 capsule per day of probiotic alone. Giaretta *et al.* in a non-randomized and non-controlled trial documented that the administration of about 360 g of apples increased total oxidant status (TOS), superoxide dismutase (SOD), glutathione peroxidase (GPx) and ascorbic acid (AA), while reducing the total antioxidant status (TAS) and catalase (CAT) in haemodialysis subjects.[59] Conversely, no effect was observed in the levels of glutathione (GSH) and uric acid. Differently, Koutsos *et al.* have reported an increase in uric acid levels following an 8-week intake of 340 g of apples in hypercholesterolemic individuals.[4] Liddle *et al.* showed an increased TAC in overweight and obese individuals consuming about 200 g of apples for 6 weeks.[61] Finally, Gasper and colleagues did not directly analyze markers of oxidative stress but showed that the consumption of 230 g of a high or low flavanol apple puree for 4 weeks increased plasma vitamin C levels and urinary excretion of epicatechin in healthy volunteers.[64] Conversely, Ravn-Haren *et al.*,[53] Bondonno *et al.*[65] and Eisner *et al.*[57] reported no effect.

3.5. Effect of apples and apple-based products on markers of inflammation

The effect of apples and apple-based products on markers of inflammation was evaluated in 1 postprandial study[65] and 12 chronic intervention studies.[4,47,50,51,53,55,57,60,61,63,64,66]

Short-term interventions. The only study investigating the postprandial consumption of a high-flavonoid apple intervention (apple flesh plus skin) in healthy adults did not report the modulation of 20-hydroxyeicosatetraenoic acid, an inflammatory marker related to the eicosanoid pathway.[65]

Medium–long-term interventions. The main inflammatory markers analyzed were C-reactive protein (CRP), followed by cytokines and interleukins, particularly tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6). Only three out of twelve medium–long-term interventions have reported a significant positive modulation of inflammatory markers following apple consumption.[51,61,63] Chai *et al.*[51] showed a decrease in serum CRP levels following 12 months of intervention with dried apples (75 g per die) in healthy post-menopausal women. However, the effects were also reported in the control group consuming dried plum. Alzoufairi and colleagues showed that the daily consumption of 2 Renetta apples for 8 weeks was able to attenuate the upregulation in PBMC of toll-like receptor 4 (TLR4) mRNA expression, thus contributing to the control of the inflammatory response.[63] Furthermore, this observation was also confirmed by the correlations observed between the fold change in gene expression of membrane G protein-

coupled bile acid receptor-1 (GPBAR1), sterol regulatory element binding transcription factor 1 (SREBF1), glucose-dependent insulinotropic polypeptide receptor (GIPR), TLR4 and tumour necrosis factor (ligand) superfamily member 14 (TNFSF14) and change in cardiometabolic disease risk markers following the intervention. Finally, Liddle and co-workers found a reduction in several markers of inflammation secreted from peripheral blood mononuclear cells (PBMCs) such as CRP, IL-6, IL-17, and TNF-α following 6-week consumption of 200 g of apples in overweight/obese subjects.[61] However, two studies conducted in overweight/obese individuals[50,57] and two performed in hypercolesterolemic subjects[4,47] reported no significant effect, particularly in terms of serum CRP levels, consistent with the findings of five studies carried out in healthy subjects.

3.6. Effect of apples and apple-based products on markers of vascular function

The effect of apples and apple-based products on vascular function was evaluated in 7 postprandial studies[34,36,41,45,64–66] and 8 chronic intervention trials.[4,47,50,53,55,61,64,65]

Short-term interventions. The principal markers evaluated included blood pressure, nitric oxide and its derivatives, and flow mediated dilation (FMD). Bondonno and coworkers investigated the independent and additive effects of flavonoid-rich apples and nitrate-rich spinach (four energy-matched treatments: control, apple, spinach, and apple + spinach), on nitric oxide status, flow mediated dilation, and blood pressure, as markers of vascular function in a group of healthy individuals.[34] The authors documented an improvement in nitrosylated species (RXNO), nitrite and nitric oxidase, and FMD, while a decrease in pulse and systolic blood pressure following the treatments with apples and spinach compared to the control. Conversely, no effect was reported on the diastolic blood pressure and endothelin-1. Holland *et al.* tested the effect of four different dietary treatments (1-apple purée; 2-water containing low flavonol apple extract; 3-water containing high flavonol apple extract; and 4-control treatment) on plasma and urinary nitric oxide bioavailability, as a marker of vascular function, in healthy subjects.[36] The results demonstrated that the consumption of 300 g of apple purée and apple flavonol containing beverages increased nitric oxide (NO) bioavailability, as evidenced by the enhanced excretion of NO metabolites. The effect was higher following the intake of high flavonol (140 mg) apple extract beverage. Successively, the same authors hypothesised that the postprandial consumption of flavanol-containing apple puree (230 g) could modulate platelet activity and NO metabolism, and the effects could be dependent on flavonol content.[64] The authors found that the consumption of a low (25 mg) and high (100 mg) flavonol apple purees transiently attenuated *ex vivo* integrin-β3 and P-selectin expression and increased the plasma nitric oxide metabolite in healthy subjects, but the effect was not flavanol-dependent. In this randomized, controlled cross-over trial, Bondonno and colleagues (2018) investigated the effect of acute consumption of apples with skin (high flavonoid apple) compared to intake of apple flesh only (low flavonoid apple) on endothelial function, blood pressure, and arterial stiffness in participants with cardiovascular risk. The results have shown that acute intake of high flavonoid apples increased FMD at 1 and 2 h after consumption while failing to modify arterial stiffness, blood pressure, plasma and saliva nitrate/nitrite. A lack of effects on blood pressure was also reported by White *et al.*[41] Cheng *et al.*[45] and Pushpass *et al.*[66] in healthy individuals.

Medium–long-term interventions. The main markers considered included blood pressure, FMD and vascular adhesion molecules (*e.g.*, VCAM-1 and ICAM-1). Only three out of nine studies reported a positive effect of consumption of apples and/or apple-based products on vascular function markers. In a randomized crossover study, Soriano-Maldonado *et al.*[55] showed that 4-week intervention with 500 ml of vitamin C-rich apple juice (60 mg L^{-1} vitamin C and 510 mg catechin equivalent per L), but not 500 ml of polyphenol-rich juice (22 mg L^{-1} vitamin C and 993 mg catechin equivalent per L), reduced vascular cell adhesion molecules 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1) levels in a group of healthy subjects. No effect was observed for monocyte chemoattractant protein 1 (MCP-1), tissue plasminogen activator and plasminogen activator inhibitor 1 (tPAI-1), and E selectin. Bondonno and coworkers reported that the intake of apples with skin (high flavonoid apple) for 4 weeks increased FMD, but not blood pressure, arterial stiffness and plasma/saliva nitrite and nitrate, in healthy subjects with cardiovascular risk.[65] Finally, Koutsos *et al.* documented an increase in endothelium-dependent microvascular vasodilation and a reduction in ICAM-1 levels following 8 weeks of intervention with 340 g of apples in hypercholesteremic subjects.[4] No effect was observed on arterial stiffness, blood pressure, and vascular adhesion molecules such as endothelin, P-selectin, E-selectin and VCAM-1. The rest of the studies included in the present analysis failed to document any effect both in healthy subjects and in those with cardiovascular risks.[47,50,53,61,64]

3.7. Effect of apples and apple-based products on gut microbiota composition

The role of apples and apple-based products on gut microbiota composition was evaluated in very few human intervention trials: 1 postprandial study[39] and 6 medium–long-term intervention studies.[48,53,58,60,62,66]

Short-term interventions. The only acute intervention study, conducted by Erickson and colleagues documented an increase in hydrogen breath response (a marker of bacterial fermentation) following the consumption of 12 oz of apple juice in healthy volunteers.[39]

Medium–long-term interventions. The main analyses included gut microbiota composition in terms of bacterial strains and, in one study, the assessment of short-chain fatty acids. Overall, four out of six studies reported a positive modulation.[48,58,60,62] In a 2-week pilot dietary intervention study, Shinohara *et al.* have shown that the consumption of 2 apples per day for 2 weeks improved microbiota composition

by increasing *Bifidobacterium* and by reducing *Clostridium* and *Lecithinase*-positive bacteria, Enterobacteriaceae and short chain fatty acid ammonia in healthy male subjects.[48] In a 3-arm, randomized trial, the consumption of unfermented and lactofermented apple puree (125 g) for 90 days increased the abundance of fecal *Bifidobacterium* and *Lactobacillus*, while decreasing *Bacteroides* and *Enterococcus* in subjects with cardiovascular risk. However, the effect was also observed in the control group after the administration of probiotic alone and the significance was reported only when compared within and not between groups.[58] In a 2-week, randomized, controlled, crossover intervention study, Barnett and coworkers have shown a significant reduction in relative abundances of *Streptococcus*, *Ruminococcus*, *Blautia*, and *Roseburia*, and an increase in the relative abundances of *Sutterella*, *Butyricicoccus*, and *Lactobacillus* after consuming a red-fleshed apple compared with a white-fleshed control apple in healthy subjects. No effect was observed on the alpha diversity.[60] Alexander *et al.* investigated the effects of 4-week consumption of apple juice (16 oz, not providing fiber) or apple juice + pomace (16 oz + 10 g, providing 10 g fiber) on faecal microbiota and faecal bile acid composition in healthy volunteers.[62] Overall, *Faecalibacterium* and *Negativibacillus* were differential abundance between pre- and post-interventions periods following apple consumption; however, these differences were no longer significant after false discovery rate correction. In addition, apple pomace supplementation was insufficient to elicit changes in microbiota diversity and bile acids. No significant effects on gut microbiota composition were observed by Ravn-Haren and coworkers following 4-week consumption of 550 g of apples in a group of healthy individuals.[53] Similarly, Pushpass *et al.* did not report significant differences in the gut bacteria taxa at the genus level or change in microbial alpha diversity between 0 and 8 weeks of intervention with 2 Renetta apple per day compared to the control, probiotics or oat groups in healthy subjects.[66]

3.8. Effect of apples and apple-based products on additional markers

Additional markers analyzed within the studies included those related to the bioavailability of bioactive compounds (*i.e.*, vitamins and polyphenols),[33,35,36] the excretion and metabolism of bioactives[36,37,64] and bile acids,[4,56,63,66] the evaluation of markers related to satiety sensations[40–42,52] and bowel habits.[59,62] Most of the studies (both short and medium/long term) reported a significant increase in the bioavailability of vitamins (*e.g.*, vitamin C), polyphenols and their derivates, also in combination with a change in gut microbiota composition, while no significant changes were detected in gastrointestinal symptom response and bowel habits.[59,62] One study was carried out focusing on the potential role of apples in the modulation of cognitive function, documenting that consumption of 2 4-oz glasses of apple juice daily for 1 month attenuated the cognitive decline in institutionalized individuals with moderate-to-severe dementia.[46]

4. Discussion

The present systematic review analyzed the effects of human intervention studies with apples and apple-based products on cardiometabolic and functional markers. Among cardiometabolic markers, those related to glucose and lipid metabolism are the most extensively investigated, whereas among functional markers, the most frequently analyzed are those associated with oxidative stress, inflammation, and vascular function. Overall, differences between postprandial *versus* medium/long-term interventions emerged. Postprandial studies reported improvements in glycaemic response followed by FMD and NO (as markers of vascular function), and antioxidant potential, whereas medium- to long-term interventions showed a potential effect on the gut microbiota composition.

4.1. Effect on glucose metabolism

Regarding glucose metabolism, most of the postprandial studies have shown that consumption of a meal with apples has an overall beneficial effect on reducing glycaemic and insulin response. Several mechanisms have been hypothesized to be involved in such modulation. First, apples contain soluble fibre such as pectin that may exert a direct effect by increasing the viscosity and by reducing the intestinal absorption of glucose.[67]

In addition, the increased viscosity, together with delayed gastric emptying, could play a crucial role in the regulation of food intake and, consequently, in enhancing satiety-related sensations.[68,69] However, although four studies evaluated satiety-related sensations when analyzing glycemic response, only one reported a concomitant positive effect, whereas the remaining studies did not observe any modulation of satiety. Furthermore, pectin may exert an indirect effect on the control and reduction of starch digestion due to the rheological properties of the fiber by limiting the contact between amylase and starch and thereby slowing starch digestion. This mechanism may contribute to a lower glycaemic response and reduced insulin stimulation. These observations are consistent with some of the reported findings, in which a reduction in insulin response was documented following apple consumption, particularly when consumed together with a carbohydrate-rich meal.

Finally, pectin can be fermented in the gut by producing short-chain fatty acids (SCFAs). These compounds have been shown to reduce the amount of glucose produced by the liver, thus playing a role in the regulation of blood glucose levels and improving insulin sensitivity.[70]

Some preclinical models reported the potential contribution of fermented apple pectin in suppressing the activity of alpha-amylase. For example, fermented apple pectin exhibited a capacity to reduce the concentration of glucose in the blood of diabetic rats by up to 24%.[71] Together with pectin apple polyphenols may also contribute to reducing the glucose uptake by inhibiting intestinal enzymes α-amylases and α-glucosidases as well as the activity of intestinal glucose transporters SGLT1 and GLUT2.[72] In particular, phlorizin (hydro-

lyzed to phloretin in the gut) is expected to lower the rate of intestinal glucose absorption through the inhibition of SGLT1.[73] Furthermore, phloretin, has shown to inhibit GLUT transporters that mediate glucose transport into pancreatic β-cells *in vitro*, and reduces glucose dependent insulin secretion. However, the effects were documented at non-physiological doses (24–40 μM).[74]

4.2. Effect on lipid metabolism

A few studies have shown a positive modulation of markers related to lipid metabolism, particularly following medium/long-term intervention. This paucity of evidence could be attributed to several factors including differences in study population, study design, duration of intervention and the amount of apples/apple constituents administered. However, several preclinical models documented that apple components may play a beneficial role in the modulation of lipid metabolism. In this regard, pectin probably represents the component responsible for the hypocholesterolemic effect. Rivas *et al.* have shown that apple pectin depressed liver cholesterol and can inhibit cholesterol absorption, especially in cholesterol-fed animals.[75] In addition, the fermentation of apple dietary fiber in the large intestine, and the subsequent production of SCFA by bacteria, in particular propionate could inhibit the endogenous synthesis of cholesterol in the liver.[76] Furthermore, pectin can also interfere with the bile acid reabsorption, thereby promoting greater utilization of cholesterol for their ex-novo synthesis.[77] Other potential mechanisms may include some synergistic effects with other constituents of apple, for example, polyphenols. In this regard, preclinical studies showed that polyphenols could exert an effect on cholesterol and triglyceride metabolism through regulating hepatic cholesterol metabolism and increasing fatty acid oxidation and decreasing fatty acid uptake and *de novo* synthesis.[78]

4.3. Effect on oxidative stress and antioxidant status

Apple and apple-based products have also been studied for their potential effects on markers of oxidative stress and antioxidant potential. In the present systematic review, 7 acute and 12 chronic intervention studies have been considered and analysed. Most of them have reported only a mild effect on oxidative stress markers while exhibiting a major increase in plasma antioxidant potential/capacity and plasma/serum uric acid concentration. These results could be explained by the presence of numerous bioactive compounds in apples, like polyphenols and vitamin C, whose levels in plasma or urine samples were shown to increase following the intervention and may have contributed to the antioxidant effect and improvement of oxidative stress markers. However, it is unclear whether this is the result of a single compound or a synergistic/additive effect as well as whether the effect is direct, indirect, or a combination of both. In fact, while vitamin C can directly exert an antioxidant effect *in vivo* and contribute to the increase in the antioxidant activity (*e.g.*, FRAP, TEAC or ORAC) in the short term, polyphenols seem to exhibit more indirect antioxidant activity *in vitro* through the upregulation of the NRF-2 pathway and consequently lead to activation of phase II enzymes and xenobiotic route.[79] However, it should be noted that most of the studies included in the present review did not report an improvement in the activity of phase II enzymes.

Another important contributor to the rise of plasma antioxidant activity is uric acid. Apples and apple-based products, and in general all fruits, represent an important source of fructose, the amount of which is strictly dependent on the dose/portion consumed. In humans, after absorption, fructose is metabolized in the liver leading to a potential increase in uric acid production that acts as an antioxidant in the bloodstream.[80] Some of the included studies have reported that the consumption of apple-based products, in particular juice, increased plasma antioxidant activity in healthy subjects and this was caused by the fructose-induced temporary rise of serum uric acid levels. This rise was probably attributed to a food matrix effect; juice is poor in fiber thus the absorption of sugar is more facilitated. Conversely, human studies reported that the contribution of polyphenols and other bioactive compounds to the overall increase in the antioxidant potential should be excluded due to their low bioavailability, absorption and blood concentration.[81] Although uric acid acts as an antioxidant in the bloodstream by favouring the increase of the antioxidant potential, it should be underlined that this compound can be also a pro-oxidant in several contexts, such as within cells.[82] Furthermore, prolonged high plasma levels of uric acid may represent a risk of hyperuricemia and the development of kidney diseases as evidenced by mechanistic studies.[83]

4.4. Effect on the inflammatory status

Apple and apple-based products have also been studied for their potential role in the modulation of inflammation. In the present systematic review, only two medium–long-term intervention studies reported a positive result following consumption of apple and apple-based products. One study was conducted in healthy individuals showing a reduction in the CRP marker, while another study documented a reduction in CRP, TNF-alpha and other cytokines in overweight and obese subjects. This latter result could be explained by the fact that excess visceral fat promotes the release of inflammatory mediators and immune cells, thereby contributing to a chronic low-grade inflammatory state,[51,61] whereas apples and their bioactive components may help attenuate the inflammatory response. In particular, the presence of polyphenols, fiber and vitamin C may contribute to the reduction of chronic low-grade systemic inflammation. In this regard, mechanistic studies have shown that polyphenols may exert anti-inflammatory effects through the modulation of cell signalling cascades involved in the production of inflammatory cytokines. Particularly, they may prevent the activation of, or inhibit, nuclear factor-κB (NF-κB), a key pathway involved in the regulation of inflammatory cytokine production. Proanthocyanidins appear to be the compounds most effective at inhibiting NF-κB,[84] whereas quercetin seems to inhibit LPS-

induced inflammatory responses mediated by the phosphoinositide 3-kinase (PI3K)/AKT pathway.[85] Phloretin is known to scavenge methylglyoxal to block advanced glycosylation end products, and it has been shown to exert its anti-inflammatory effects *via* inhibiting the RAGE/p38 MAPK/NF-κB signalling pathway.[86] In addition, phloretin was found to decrease the expression of proangiogenic factors (such as IL-1β, IL-6, and MCP-1) in adipocytes stimulated with LPS and CoCl2.[87] Additional compounds include triterpenes, which are able to repress the promoter activity of the tumor necrosis factor-alpha (TNFα) gene[88] and dietary fiber, particularly pectin, which can reduce chronic inflammation by preventing the activation of innate and adaptive immune responses. Finally, some mechanistic studies have reported that pectin can bind to 'toll-like receptors' in the gut, thereby preventing the upregulation of the pro-inflammatory genes involved in the activation of immune responses.

Overall, although findings regarding the effects of apples on inflammatory markers are inconsistent, a potential beneficial contribution cannot be excluded *a priori*, particularly in light of the heterogeneity among studies in terms of intervention duration, type and dose of product administered, and population characteristics. Further research is needed, especially in subjects with cardiometabolic risk factors, including those presenting with low-grade inflammation.

4.5. Effect on vascular function

The short- and medium- to long-term effects of apples and apple-based products on markers of vascular health have also been investigated. While findings regarding arterial stiffness, blood pressure, and adhesion molecules were inconsistent across study populations, some studies (particularly short-term investigations) reported an apparent improvement in FMD and NO production/metabolism in both healthy individuals and subjects with CVD risk factors. Several mechanisms can be postulated in which polyphenols seem to play a pivotal role in exerting endothelial protection. Evidence from *in vitro* and *in vivo* studies has shown that polyphenols can enhance the production of NO, a molecule that relaxes blood vessels and improves blood flow, as well as inhibit the production of vasoconstrictor agents like endothelin-1, monocyte chemotactic protein-1, ICAM-1 and VCAM-1.[89,90] Another possible activity of polyphenols includes the activation of intermediate conductance calcium-activated potassium channel (IKCa) in endothelial cells, potentially contributing to the endothelium-dependent relaxation.[91] In addition, polyphenols can modulate platelet aggregation by interfering with the clotting mechanisms and molecules related to activation and aggregation, including those related to ADP, collagen, and thrombin. Specifically, polyphenols seem to have the capacity to mimic the antiplatelet activity of specific drugs (*e.g.*, aspirin) that target the glycoprotein VI (GPVI), collagen and cyclooxygenase-1 (COX-1), and thromboxane platelet activation pathways, respectively, including the release of platelet microparticles.[92] However, there are numerous gaps in the literature and limitations that need to be addressed with appropriated studies.

Polyphenols can interact with various signalling pathways, such as the PI3K/Akt pathway and the MAPK pathway by positively influencing cellular processes related to vascular health. Specifically, polyphenols could directly inhibit PI3K or AKT, preventing the activation of downstream targets or alternatively influence the expression of genes and proteins involved in the pathway, leading to changes in its activity.[93] Furthermore, polyphenols have also been shown to modulate the expression of microRNAs (miRNAs) that regulate the PI3K/AKT/mTOR pathway, impacting vascularization, cell growth and proliferation.[93] Finally, polyphenols can exert their vascular effect by reducing inflammation and oxidative stress through pathways like ERK/Nrf2, thus preventing NO peroxidation and the production of pro-inflammatory cytokines and interleukins that may damage and alter the endothelium. In the present systematic review, three studies reported an increase in NO and its derivatives following intervention with apples and/or apple-based products, accompanied by improvements in FMD or reductions in platelet activation, in line with the hypothesized mechanisms of action.

4.6. Effect on gut function

Apples and apple-based products seem to play a role in the composition of gut microbiota. Five out of seven studies reported a significant modulation in terms of hydrogen breath response or gut microbiota composition (*Bifidobacterium* and *Lactobacillus*). The main effects were observed in healthy subjects, primarily following the consumption of whole apples rather than apple-derived products. Mechanistic studies reported that this effect is likely attributed to the presence of dietary fiber such as pectin and its capacity to increase the abundance of certain beneficial bacteria, like *Bifidobacterium* and *Lactobacillus*, and reduce the levels of some potentially harmful bacteria.[94] This observation appears to be consistent with the findings reported in the dietary intervention studies considered. Furthermore, pectin and other fibers can be fermented by gut bacteria with the production of SCFAs, which are crucial for maintaining gut health.[95] In addition, the SCFA butyrate is particularly important for nourishing colon cells and regulating local and systemic inflammation.[96] Moreover, chlorogenic acid, phloretin and oligomeric procyanidins can be converted by gut bacteria into metabolites that influence the composition and function of the gut microbial community, potentially impacting human health.[97] Concurrently, the gut microbiota can also influence the bioavailability and metabolism of apple polyphenols. Among the studies analyzed, only one reported that the increase in *Bifidobacterium* and *Lactobacillus* was accompanied by improvements in HDL cholesterol levels and reduction in TMAO concentrations in subjects with CVD risk.

4.7. Effects according to health status

Overall, beneficial effects were more frequently observed in healthy individuals than in subjects with cardiometabolic risk factors or established metabolic disorders. This discrepancy may be explained by several factors, including differences in the baseline cardiometabolic status of participants (*e.g.*, overweight/obesity, hypercholesterolemia, hypertension, or impaired

glucose metabolism), which may influence the responsiveness to dietary interventions. Moreover, substantial heterogeneity among studies in terms of study design, intervention duration, type and dose of apples or apple-derived products administered may have further contributed to the variability in findings. Additional variability may also stem from the broad range of biomarkers evaluated, as cardiometabolic health, inflammation, oxidative stress, and vascular function encompass numerous markers with distinct physiological roles and clinical relevance. Notably, improvements in glucose response and some vascular and oxidative stress markers were more consistently reported in healthy individuals, whereas conflicting or less pronounced effects were observed for markers related to lipid metabolism, body composition, glycemic control, and inflammation, particularly in populations with cardiometabolic risk factors. It is also possible that individuals with more compromised metabolic conditions may require longer intervention periods or higher apple intake to achieve measurable effects.

5. Conclusion

In conclusion, the consumption of apples and apple-based products was associated with a general improvement of cardiometabolic and functional markers. However, differences emerged when comparing short-term with medium- and long-term studies in terms of the observed effects. Postprandial studies reported an overall improvement in glycaemic response, FMD, nitric oxide, and antioxidant potential, while medium–long-term interventions reported an overall improvement in the gut microbiota composition. These findings were documented mainly in healthy individuals, although they were derived from a limited number of studies. The remaining markers showed conflicting findings. This variability limits the ability to support the popular notion of "an apple a day keeps the doctor away". However, the consumption of apples, and fruits in general, should be supported and advised as part of a balanced diet. In fact, all national and international dietary guidelines support and recommend the consumption of at least 400 g per day of fruit and vegetables, in which apple could represent a valuable snack for children and adults to be consumed during mid-morning or in the afternoon, as well as a special treat at the end of the meal.

Therefore, further well-designed studies specifically targeting at-risk populations are warranted to better clarify the potential role of apples and apple-derived products in cardiometabolic health. In particular, future research should aim to better elucidate the effective doses of apples and apple-derived bioactive compounds required to elicit beneficial effects, while also taking into account the variability among different apple cultivars.

Author contributions

Cristian Del Bo' and Patrizia Riso conceptualised the study and designed the experimental protocol; Cristian Del Bo' and Anna Giancristofaro performed the literature review and screened the studies; Anna Giancristofaro and Mirko Marino performed data collection; Marco Rendine and Daniela Martini acted as third independent reviewers; Cristian Del Bo' and Patrizia Riso interpreted the data; Cristian Del Bo' and Daniela Martini drafted the first version of the manuscript. Maria Cristina Casiraghi revised the manuscript. All authors have read and critically revised the manuscript and approved the final version.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information: Tables S1 and S2. See DOI: https://doi.org/10.1039/d5fo05460e.

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