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Narrative Review

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Abstract: Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality worldwide, with endothelial dysfunction as a key precursor. Flow-mediated dilation (FMD), the gold-standard measure of endothelial function, is improved by (poly)phenol-rich foods and extracts, with increases of 1% FMD representing 13% reduced cardiovascular risk. This narrative review aims to evaluate the efficacy of various (poly)phenol-rich foods and extracts on endothelial function as measured by flow-mediated dilation (FMD) and assesses the feasibility of a food-first approach. Literature was systematically searched from databases including PubMed and Web of Science, focusing on human clinical trials. While all (poly)phenol-rich food groups demonstrate variable effects, berries (0.9–2.6%), cocoa (0.7–5.9%), and tea (1.2–4.8%) have the most robust evidence, consistently improving FMD, with chronic intake sustaining benefits. A large variance (0.8–8.7%) was observed with grape-derived (poly)phenols, making their effects difficult to substantiate without detailed compositional or metabolomic data; however, a few key studies highlight their potential. Citrus polyphenols also exhibit variable FMD responses (0.2–7.2%). However, strong mechanistic evidence supports their role in vascular health and nitric oxide (NO) bioavailability. Coffee exhibits a variable response, initially impairing FMD, likely due to caffeine, before later improving endothelial function as phenolic metabolites increase. Although estimated (poly)phenol intake in Western populations is high (~1000 - 1200 mg/day), it is primarily derived from tea, coffee, and cocoa, limiting exposure to diverse bioactive compounds. Moreover, the food matrix significantly influences bioavailability, with co-consumed components such as milk or sugar attenuating FMD responses. Interestingly, fortification and enrichment maintain bioactivity and may optimize intake, ensuring consistent and diverse delivery. Future research should refine dietary guidelines, establish intake thresholds, and explore fortification strategies to maximize cardiovascular benefits while considering dose-response relationships and long-term efficacy.

Keywords: (Poly)phenols, FMD, Endothelial Function, Cardiovascular Disease, Berries, Grapes, Citrus fruit, Cocoa, Coffee, Tea



1. Introduction

Cardiovascular disease (CVD) remains a leading cause of mortality worldwide, responsible for approximately 17.9 million deaths annually (WHO 2019), with common cardiovascular risk factors such as hypertension, dyslipidaemia, diabetes, obesity, and smoking playing significant roles in its development ^{1,2}. Increased fruit and vegetable consumption mitigate risk and reduce CVD incidence with consumption of ≥ 8 portions ($>569\text{g/day}$) associated with a reducing risk of cardiovascular mortality by 15% compared to those consuming <3 portions ($<240\text{g/day}$) ³. Similarly, a meta-analysis by Aune and colleagues highlighted a 28% risk reduction in cardiovascular mortality associated with the consumption of 800g/day of fruits and vegetables ⁴. The effects in part are due to the consumption of (poly)phenol-rich foods such as cocoa, coffee, tea, and berries which contain these bioactive compounds that can modulate endothelial function and the inflammatory processes and reduce oxidative stress ^{5,6}. The largest (poly)phenol based randomized intervention study to date, COcoa Supplement and Multivitamin Outcomes Study (COSMOS) also supports these population and experimental observations. The COSMOS study intervened with daily supplementation of 500mg cocoa flavan-3-ols in $n=21,444$ people over ~ 3.6 years reducing cardiovascular mortality by 27% in the study population ⁷. This narrative review aims to evaluate the efficacy of (poly)phenol-rich foods and extracts on endothelial function as measured by flow-mediated dilation (FMD) and explores dietary guidance considerations based on existing evidence. A systematic search was performed using databases including Medline, Scopus and Web of Science. 4,875 manuscripts were screened and 97 were included in the final synthesis (2000-2023). The selection of (poly)phenol-rich foods included in this review was based on their dietary relevance in Western populations, their significant contribution to overall habitual intake, and the availability of robust evidence linking them to improvements in cardiovascular health and endothelial function as measured by FMD.

1.1 Endothelial Function and Its Role in Cardiovascular Disease

Endothelial function is a critical determinant of cardiovascular health, encompassing impaired functionality of the blood vessel inner lining known as the endothelium ⁸. This layer modulates key vascular processes, including blood flow regulation, vasodilation, vasoconstriction, and the release of signalling molecules ⁹. The pathogenesis of endothelial dysfunction is multifaceted ¹⁰. Albeit, at its core, chronic inflammation and oxidative stress are key mediators ^{9,11}, negatively impacting endothelial cells and disrupting their normal functions including, misbalancing vasoconstrictors such as endothelin-1 (ET-1) and angiotensin II (AngII), and reducing the production of nitric oxide (NO), a gaseous signalling molecule and potent vasodilator essential for regulating vascular tone ^{9,12}. Diminished NO availability impairs blood vessel relaxation, leading to vasoconstriction, simultaneously



increasing oxidative stress, damaging endothelial cells and further reducing NO bioavailability (the amount of a compound or nutrient that is absorbed, entering systemic circulation where it becomes available to exert a physiological effect), thereby fostering inflammation and stimulating the release of pro-inflammatory cytokines, which contribute to the pathogenesis of atherosclerosis and other cardiovascular conditions^{9,13}. NO, produced by endothelial nitric oxide synthase (eNOS), is crucial for vascular health as it promotes vasodilation, inhibits platelet aggregation, and suppresses smooth muscle cell proliferation¹⁴. Reduced NO bioavailability is a hallmark of endothelial dysfunction and a key contributor to CVD progression¹⁵.

Experimental studies with endothelial cell cultures have provided valuable insights into mechanisms by which various (poly)phenols may mediate endothelial function^{16–18}. For instance, resveratrol in human umbilical vein endothelial cells (HUVECs) significantly upregulate eNOS expression, increasing NO production and improving endothelial function¹⁹. However, phenolic metabolites have been shown to play a more significant role than their parent compounds in modulating endothelial function due to their greater bioavailability and prolonged circulation time. Studies demonstrate direct stimulation of eNOS activity by certain phenolic metabolites including vanillic acid and protocatechuic acid reducing superoxide levels by downregulating NADPH oxidase (NOX) activity, indirectly enhancing NO bioavailability²⁰. Additionally, they have been shown to enhance nitric oxide (NO) bioavailability by activating the Akt-eNOS signalling pathway in endothelial cells²¹. Furthermore, protocatechuic acid has been demonstrated to reduce pro-inflammatory markers such as soluble vascular cellular adhesion molecule-1 (sVCAM-1) through modulation of gene expression in HUVECs, highlighting their role in mitigating endothelial inflammation²². This modulation of endothelial function has also been confirmed in human studies via several mechanisms including upregulation of eNOS activity, and by scavenging reactive oxygen species (ROS), which degrade NO and reduce its bioavailability^{23,24}. Additionally, flavan-3-ols such as epicatechin and catechin have been shown to downregulate endothelial dysfunction markers such as EDN1, reducing the production of the potent vasoconstrictor ET-1, and suppress the expression of angiotensin-converting enzyme (ACE), which decreases Angiotensin II levels^{25,26}. These mechanisms collectively enhance vascular function, contributing to improved cardiovascular outcomes²⁷, however a diverse intake of (poly)phenols is required to attain the collective bioactive effects.

1.2 Flow-mediated dilation (FMD): A Biomarker of Endothelial Function

Flow mediated dilation (FMD) is the gold standard and non-invasive assessment of endothelial function, utilising ultrasound to measure arterial dilation in response to shear stress, mediated by the release of NO, with lower FMD values indicating endothelial dysfunction^{28,29}. The clinical relevance of





FMD has been validated through the establishment of reference values amongst a predominately European population (n=1,579), observing a mean FMD of $6.2\% \pm 2.0\%$, with 0.3–0.4% age-related decreases observed per decade. Importantly, values below 3.1% were identified as pathological, while values above 6.5% were considered optimal³⁰. Moreover, ~26% of healthy individuals with low cardiovascular risk (SCORE <1%) exhibited low FMD values (<5.4%), highlighting the complexity of endothelial health beyond traditional risk factors³⁰. Observational meta-analyses further demonstrate that each 1% increase in FMD is associated with a 13% reduction in future cardiovascular events, reinforcing its predictive utility in both diseased and asymptomatic populations³¹. Furthermore, age- and sex-specific reference values were established from a pooled cohort (n=5,362), confirming that lower FMD values correlate with key cardiovascular risk factors, including hypertension, dyslipidaemia, and diabetes³². Additionally, FMD values below 3.1% exhibit 95% specificity for identifying individuals at high cardiovascular risk, whereas values above 6.5% demonstrate 95% sensitivity for excluding coronary artery disease³⁰. However, the accuracy and reliability of FMD measurements are dependent on the use of standardized protocols. Thijssen and colleagues highlight the importance of controlling for factors such as baseline arterial diameter, occlusion time, and ultrasound techniques to ensure reproducibility and comparability across studies³³. Without such standardization, the variability in FMD results can obscure the true effects of interventions like (poly)phenol supplementation^{33–35}.

2. Efficacy of (Poly)phenol-Rich Foods and Extracts on FMD

Research has increasingly focused on the efficacy of (poly)phenol-rich foods and their extracts in improving FMD and overall endothelial function. Numerous intervention trials (Table 1), meta-analyses and systematic reviews^{23,25,36,37} have explored the effects of foods such as berries, grapes, citrus fruits, cocoa, coffee and teas, alongside their respective (poly)phenol extracts, on cardiovascular health. Given the sensitivity of FMD to endothelial changes, it is commonly employed as a primary outcome in studies examining the cardiovascular effects of (poly)phenol-rich foods^{38,39}. For instance, (poly)phenols have consistently been shown to improve FMD, reflecting their ability to enhance endothelial function via increased NO bioavailability, modulation of antioxidative pathways, and inflammation reduction, suggesting that these compounds directly enhance endothelial function and reduce CVD risk^{6,40}. However, the bioavailability and bioaccessibility (the amount or proportion of a nutrient or compound that is released from the food matrix during digestion which becomes available for absorption in intestine) of (poly)phenols are critical determinants of their efficacy⁴¹, as ingested (poly)phenols undergo extensive metabolism in the gastrointestinal tract and liver, resulting in a wide range of metabolites with varying biological activity^{5,42,43}. Despite this, studies have consistently

shown that (poly)phenols from various sources (Table 1 & 2, and Figure 1) can improve endothelial function through their action on NO bioavailability and their ability to mitigate oxidative stress and inflammation^{9,12}. However, the perceived effect may be impacted by various factors including, class of (poly)phenol, their bioavailability, additional food component or matrix, health status and individual variability.

2.1 Berries

Blueberries, cranberries, and blackcurrants are rich in (poly)phenols (200-600mg/100 g fresh weight) including anthocyanins, flavan-3-ols, and proanthocyanidins⁴⁴ and significantly contribute to dietary (poly)phenol intake, accounting for approximately 5–20% of total anthocyanin consumption⁴⁵. Multiple studies (Table 3) have investigated their efficacy in modulating endothelial function as measured by FMD, highlighting both acute and chronic improvements with varying ranges of total (poly)phenol content (TPC), dependant on the timing, dosage, and food matrix^{46–51}. Despite this, variability in outcomes—particularly regarding the long-term efficacy of certain berries like cranberries—warrants further analysis.

Blueberries have been the focus of several studies^{46,47,52–56}, indicating their beneficial effects on endothelial function, reporting acute improvements in FMD ranging from 0.9% to 2.4%, typically observed within 1 to 2 hours post-consumption with some studies observing a biphasic response (a second peak) occurring around 6 hours post-ingestion⁵³. Dosages ranging between 300mg and 1,800mg TPC (Figure 2) have been tested, but many findings suggest that benefits plateau at moderate doses (~750mg), with higher doses failing to offer additional vascular improvements⁵³. This plateau effect underscores the importance of optimal dosing. Curtis and colleagues demonstrated a 1.45% increase in FMD with a daily intake of 1 cup (150g) equivalent of freeze-dried blueberries (879mg TPC) over six months in individuals with metabolic syndrome⁴⁷. However, the study also found that a lower dose (approximately 75 g, which aligns closely with the recommended portion size of 80 g) did not elicit significant FMD improvements. These findings suggest that an above average, but more importantly sustained intake of blueberries can provide long-term benefits without requiring excessive consumption. However, an important consideration which warrants further investigation, is the lack of studies investigating blueberries as a whole food. This highlights questions regarding the efficacy of whole blueberries, as processing, such as freeze-drying, can concentrate (poly)phenols, enhancing their bioaccessibility and bioavailability and thus their impact on FMD.

Cranberries, like blueberries, have been studied for their vascular effects, albeit results have shown less consistency, particularly in chronic interventions. Although reports indicate a modest and statistically significant 1% increase in FMD (from $7.7 \pm 2.9\%$ to $8.7 \pm 3.1\%$, $P = 0.01$) four hours after



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acute consumption of cranberry juice (835mg TPC) in an uncontrolled pilot study involving medicated patients with coronary artery disease (CAD), no significant changes were observed following four weeks of daily intake ⁵⁷. Consistent with the previous findings, Rodriguez-Mateos and colleagues demonstrated that cranberry juice (ranging from 409mg to 1,910mg TPC) produced acute dose-dependent improvements in FMD increasing up to 2.6%. Notably, a significant effect detected at 787mg TPC, similar to that of the previous study. Moreover, a plateau effect was again observed at 1,200mg TPC ⁵⁸. Given that acute improvements were observed in both studies, irrespective of health status (healthy vs. CAD patients), the key distinction lies in the chronic response, warranting further investigation. A more recent study ⁵⁹ found significant acute (1.5%) vascular improvements aligning with the previous study but, more importantly, significant ($p<0.05$) chronic (1.1%) improvements in FMD with a daily intake of cranberry extract (525mg TPC), confirming the presence of persistence effects of cranberries, although the mode of delivery (extract) and (poly)phenol composition differs (anthocyanins - 94mg vs 23mg vs 54mg respectively).

The studies on blueberries and cranberries consistently point to the critical role of the food matrix in modulating the bioavailability and efficacy of (poly)phenols. Whole foods and extracts offer varying degrees of (poly)phenol concentrations and absorption kinetics, which directly influence their vascular effects ^{60,61}. The absorption of (poly)phenols is also influenced by the interaction between the (poly)phenol compounds and the food matrix itself ^{62–64}. Complex matrices, such as those found in whole fruits, may impede the release and absorption of (poly)phenols in the digestive tract. In contrast, extracts or purified forms of (poly)phenols, which lack the complex matrix of whole fruits, are absorbed more efficiently, resulting in higher concentrations of (poly)phenols in circulation and potentially more efficacious endothelial improvements. This effect was evident in one study comparing the effects of aronia extract vs whole fruit, demonstrating a significant ($p<0.01$) 1.2% improvement in FMD after 12 weeks of daily extract consumption (TPC 116mg), whereas whole fruit (TPC 12mg) consumption resulted in a lesser (0.9%, $p<0.05$), yet still significant improvement ⁴⁹, confirming what is highlighted when comparing cranberries composition and resulting effects ^{58,59}. These studies highlight that the food matrix and mode of delivery significantly affect the absorption and subsequent vascular benefits of (poly)phenols, with extracts delivering more pronounced effects due to their enhanced bioavailability. While some evidence suggests that extracts and processed forms may enhance (poly)phenol bioavailability and, in some cases, yield greater effects than whole fruits, direct comparisons remain limited and warrant further exploring. Moderate doses (100 to 200 g fresh weight or equivalent) appear to provide meaningful improvements in FMD, typically ranging from 0.9% to 2.5%. However, much of the available research focuses on extract/juice-based

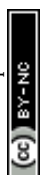
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interventions, warranting further investigation into whether the same bioactivity persists when using whole-berry approaches.

In comparison, other berries, such as raspberries, blackcurrants, and strawberries, have been investigated to a lesser extent. Albeit, available research illustrates promising results regarding their impact on FMD, suggesting potential cardiovascular benefits warranting further exploration. For instance, acute FMD improvements of 1.6% and 1.2% were observed 2 hours post-consumption of raspberry drinks containing 201 mg and 403 mg TPC, respectively, in healthy volunteers. Notably, these improvements persisted at 24 hours post-consumption, correlating with plasma concentrations of urolithin metabolites, highlighting the importance of microbial metabolites in mediating vascular benefits⁶⁵. Blackcurrants also show promising effects on endothelial function, as evidenced by a Khan and colleagues⁵¹ where healthy subjects with habitually low fruit and vegetable intake showed significant increases in FMD from 5.8% to 6.9% following 6 weeks of daily consumption of blackcurrant juice (250 ml x 4 per day), compared to placebo. This improvement was correlated with increased plasma vitamin C concentrations opposed to circulating phenolics, warranting further investigation. Strawberry interventions also demonstrated a significant acute increase in FMD by 1.5% following strawberry intake (50 g freeze-dried powder equivalent to ~500 g fresh strawberries), suggesting that strawberries may enhance vascular health independently of broader metabolic changes, potentially mediated by microbial-derived phenolic metabolites such as 3-(4-methoxyphenyl)propanoic acid-3-O-glucuronide⁶⁶. However, this effect was not retained after 4-weeks consumption, raising questions about the persistence of this benefit, although this may be explained by the observed increase in baseline FMD % which may have attenuated the effect size, which arguably, may be indication of endothelial recovery. Collectively, these preliminary findings underscore the potential for raspberries, blackcurrants, and strawberries to positively impact endothelial function, despite fewer studies compared with blueberries and cranberries. Future research should further characterize their efficacy, optimal dosages, and mechanisms of action, including the roles of microbial metabolites, to fully understand their cardiovascular potential.

2.2 Grape

While many studies have reported vascular benefits from grape (poly)phenol consumption, the effects vary depending on factors such as (poly)phenol type, dosage, and delivery method (whole food vs. extract), as well as the population studied. Notably, a range of FMD improvements has been observed across various grape (poly)phenol interventions^{67–69}. Several studies have examined the impact of grape-derived products, such as grape juice, red wine and grape seed extract (GSE), with results showing FMD increases ranging between 0.8% and 8% over periods of 1 to 8 weeks. However,



comparing these findings across studies reveals significant variation, not attributable to a clear dose response relationship, but rather to differences in intervention duration, food matrix, and population characteristics. For example, moderate grape juice consumption (~400–600 mL/day) as calculated for a 70kg individual, was associated with FMD improvements of 1–2% over 1 to 2 weeks in at-risk populations, such as CAD patients and smokers^{67,70}. These modest improvements suggest that even moderate (poly)phenol consumption may exert beneficial effects on endothelial function, though variability between studies remains. For instance, substantial FMD increases of up to 8% in adolescents with metabolic syndrome were observed after a month of consuming a higher dose of grape juice (~1,260 mL/day)⁷¹. However, the lack of a control group in this study limits the validity of the findings. Moreover, the absence of specific (poly)phenol composition data in the studies of Hashemi and Chou^{70,71} further weakens the ability to draw concrete conclusions about the mechanisms driving FMD enhancements. Siasos and colleagues further elucidate this, noting that consumption of 490ml concord grape juice (965mg TPC) over 2 weeks, led to significant improvements in FMD (1.14%, $p<0.05$) in addition to mitigating the transient decline post smoking. However, no change in plasma lipids or glucose levels were observed and circulating metabolites were unmeasured, raising questions about the direct impact of (poly)phenols.

Grape-derived products including wine have also demonstrated promising modulation of endothelial function, as measured by FMD⁴⁰. For instance, acute intake of red wine (0.8 g ethanol/kg body weight) significantly improved brachial artery FMD (1.6%, $p<0.01$) in healthy men, 120 minutes post consumption⁷². Nonetheless, consumption of alcohol-free red wine yielded a similar response at 120 minutes (1.8%, $p<0.01$) in addition to substantial improvement at 30 mins (4.8%, $p<0.01$)⁷², indicating that endothelial benefits are largely independent of alcohol and can be attributed primarily to wine-derived (poly)phenols, although it could be hypothesised that the (poly)phenols present in the alcoholised red wine mitigated the transient decline in FMD % as demonstrated with comparison of alcohol (Japanese vodka) intake (2.0%, $p<0.05$) 30 minutes post-intervention⁷². In support of this, one study⁷³ noted that the acute detrimental effects of smoking on FMD were mitigated by consumption of both red wine and dealcoholized red wine (250 mL), maintaining FMD close to baseline levels, with the dealcoholized red wine appearing to have somewhat of a stronger effect⁷³, further supporting a protective role of wine/grape-derived (poly)phenols independent of alcohol. Hampton and colleagues⁷⁴ further explored this alcohol-independent benefit by demonstrating comparable increases in postprandial FMD following consumption of a meal and intake of a grape juice beverage (122.5 mL) with and without alcohol (12% v/v, 21 g alcohol). Both drinks significantly increased FMD compared to water, confirming that the beneficial endothelial response is driven primarily by the grape components opposed to alcohol. Additionally, significant improvements in FMD were demonstrated



in hypercholesterolemic individuals after daily consumption of either red wine (250 mL/day) or grape juice (500 mL/day) for 14 days, significantly ($p < 0.05$) increasing FMD by 5.5% and 6.8% respectively. Interestingly, red wine also enhanced endothelium-independent vasodilation significantly (7% $p < 0.01$), an effect not observed with grape juice, suggesting a possible additional vasodilatory mechanism attributable to red wine's alcohol content. Importantly, neither improvement occurred with significant changes in plasma lipids or platelet function, indicating a different mechanism of action. Nonetheless, the evidence suggests that red wine has potential for improving vascular function as measured by FMD. However, it is important to note the current evidence examining wine and FMD do not provide the (poly)phenol composition of the interventions or the corresponding plasma concentrations of circulating metabolites, limiting the ability to establish an association. Studies investigating (poly)phenol extracts and FMD, generally report more consistent findings with increases typically ranging from 2 - 5%. For example, a 1.1% ($p < 0.05$) improvement in FMD was found after 4 weeks of supplementation with 2 g/day of GSE (1 g of polyphenols) in subjects with elevated vascular risk ⁷⁵. Additionally, Barona and colleagues reported significant improvements in FMD (approximately 1.7%) following daily supplementation (1 month) with 46g grape powder extract (266mg TPC) in subjects with metabolic syndrome. Additionally, a decreased systolic blood pressure correlated with a reduction in inflammatory markers (sVCAM-1) and increased plasma NO metabolites was observed, highlighting anti-inflammatory effects and increased NO bioavailability as potential mechanisms ⁷⁶. Supporting this, significant improvements in FMD (2.14%, $p < 0.01$) were observed following daily intake of 400 mg red grape cell powder over 12 weeks in prehypertensive and mildly hypertensive subjects. Moreover, the researchers noted improvement of plasma lipids although these did not reach significance ⁷⁷. In contrast, Greyling and colleagues reported no statistically significant differences in blood pressure or FMD following eight weeks of high-dose grape and wine polyphenol supplementation (800 mg total polyphenols daily) in hypertensive patients already on antihypertensive medication ⁷⁸. This suggests that the vascular efficacy of grape-derived polyphenols may be attenuated or masked by pharmacological intervention, emphasizing the necessity for further investigation into interactions between dietary polyphenols and existing medication regimens. Additional reports, also found no significant improvement in brachial artery FMD with a muscadine grape seed supplement (83.98 mg TPC) in individuals at high cardiovascular risk, although a significant increase in resting brachial artery diameter was observed suggesting some level of vascular improvement ⁷⁹. Although the consumption of grape-derived (poly)phenols consistently improves FMD across multiple studies, whole foods, such as grape juice, appear to have quite a high degree of variability in response, although this appears to more prevalent in grape juice studies as studies on wine show some degree





of endothelial improvement across all studies, whether it is improving FMD or mitigating a transient decline. However, it must be noted that the removal of alcohol from these interventions, appears to offer more pronounced effect size likely mediated by the phenolics. In contrast, extracts appear to provide more consistent results, partly because of lack of interacting food components but also the length of the studies allowing sufficient exposure time for the phenolics and their metabolites to have an effect. However, the optimal (poly)phenol dosage to maximize FMD improvements without eliciting a plateau effect remains an area that requires further investigation. Additionally, it is important to note that GSE has a distinct (poly)phenol composition compared to whole grapes or grape juice. While GSE is primarily composed of proanthocyanidins, whole grapes particularly red or purple varieties which contain anthocyanins alongside a broader range of (poly)phenols. These compositional differences may influence their respective vascular effects and mechanisms of action. Moreover, the lack of detailed data on circulating (poly)phenol metabolites presents a significant limitation in our understanding of how these compounds exert their cardiovascular benefits. Therefore, future research should focus on optimizing (poly)phenol bioavailability, understanding long-term effects, and refining dosage recommendations to ensure maximum cardiovascular benefits.

2.3 Citrus Fruits

Citrus fruits contain significant levels of (poly)phenols, primarily flavanones such as hesperidin and narirutin. Although research in this area is limited, several studies have reported potential benefits with respect to endothelial function including effects on FMD^{80–88}. For instance, daily consumption (500 ml) of red orange juice (ROJ) over one week significantly improved FMD from 5.7% ± 1.2% to 7.9% ± 1.4% (p<0.001) in subjects at risk for CVD. This improvement was accompanied by reductions in inflammatory markers, including C-reactive protein (CRP) and interleukin-6 (IL-6)⁸⁰. Similarly, two weeks of blood orange juice (BOJ) consumption led to significant FMD improvements in overweight and obese individuals, with an increase from 8.15% ± 2.92% to 10.2% ± 3.31%⁸¹. Interestingly, flavanone-rich citrus (orange) beverages were found to mitigate (3.6%) the postprandial decline in endothelial function following a high-fat meal⁸⁶. Collectively these results suggest a strong mechanistic role of citrus (poly)phenols including hesperidin and narirutin in modulating endothelial function by increasing NO bioavailability and reducing inflammation^{80,81,86}. However, a null effect observed by Constans and colleagues following a longer 4-week intervention of BOJ in subjects with mild hypercholesterolaemia raises questions about sustained benefits⁸². This contrast may be owed to differences in the health status of the study population. However, the baseline FMD was lower in the aforementioned study (1.1% vs 5.7% and 8.15%) thus a comparable effect would be expected as

the composition and dosages of interventions were somewhat comparable^{80–82,86}, warranting further longer-term studies to elucidate these findings.

Interestingly, daily supplementation (1000mg/day) of lemon and sour orange peel extracts, found notable FMD improvements (5.50 ± 2.12 to 11.99 ± 4.05 and 5.55 ± 2.17 to 12.79 ± 5.47 respectively) after four weeks⁸⁴. The substantially higher FMD increases observed in this study, compared to juice-based interventions, suggest that peel extracts may provide enhanced vascular benefits however the lack of (poly)phenol composition or metabolomics make it difficult to substantiate. Additionally, daily hesperidin (500mg) consumption across 3 weeks, was also found to significantly increase FMD in individuals with metabolic syndrome, from $7.78\% \pm 0.76\%$ to $10.26\% \pm 1.19\%$ ($p=0.02$). The study also reported significant reductions in inflammatory biomarkers, such as CRP and serum amyloid A (SAA), which supports the earlier hypothesis that hesperidin's cardiovascular benefits are mediated by both enhanced NO bioavailability and anti-inflammatory effects⁸⁵. Moreover, in vitro studies demonstrate that hesperitin—a metabolite of hesperidin—stimulates NO production through endothelial nitric oxide synthase (eNOS) activation, further highlighting the mechanistic pathway by which hesperidin enhances vasodilation and improves endothelial function. These results are significant as they provide both in vivo and mechanistic evidence of the role that hesperidin and its metabolites play in vascular health. While these studies strongly support the vascular benefits of citrus (poly)phenols, some research highlights the importance of the food matrix and dosage in determining their efficacy. Purified compounds or peel extracts, as previously mentioned may provide a more concentrated and bioavailable source of (poly)phenols than juices, leading to greater improvements in FMD. This distinction between different food matrices raises important questions about how best to deliver citrus (poly)phenols for optimal cardiovascular benefits.

2.4 Cocoa/Dark Chocolate

The cardiovascular benefits of cocoa (poly)phenols, particularly flavan-3-ols such as epicatechin and catechin, are known to improve NO bioavailability, mitigate oxidative stress, and reduce inflammation; all of which contribute to improved vascular health. Increasing studies have emphasized the potential and limitations of cocoa interventions in various populations. Heiss and colleagues provided early evidence⁸⁹ of these effects in healthy smokers, reporting a significant increase (2.7%, $p<0.05$) in FMD following acute consumption of a high-flavan-3-ol cocoa drink (306mg total flavan-3-ols), compared to a 0.9% decrease in the low-flavan-3-ol control. This is further supported by a follow-up study⁹⁰ involving an acute intervention of 100 ml high-flavan-3-ol cocoa (185mg total flavan-3-ols) which improved FMD by 2.4%, thus confirming previous findings. Furthermore, sustained improvements were observed following daily supplementation of 300 ml for one week, with a plateau (2.7%, $p<0.05$)



observed on the fifth day. These findings reinforce the role of both acute and chronic cocoa flavan-3-ol intake in modulating vascular function, particularly in individuals with elevated endothelial dysfunction risk, though the transient nature of peak effects suggests potential adaptation over time (Figure 3). Interestingly, research has indicated that cocoa flavan-3-ols may offer greater effects in individuals with pre-existing endothelial dysfunction (Figure 4). For instance, daily consumption of flavan-3-ol-rich dark chocolate (~800mg total (poly)phenols) in patients with peripheral artery disease significantly improved FMD by 4.0% ($p < 0.001$). This improvement was accompanied by reductions in oxidative stress markers, including a 37% decrease in sNOX2-dp, a key marker of NADPH oxidase activity. Concurrently, NO bioavailability increased by 57%, as indicated by elevated serum nitrite/nitrate (NOx) levels. These biochemical changes correlated with endothelial function improvements, as evidenced by reductions in vascular adhesion molecule-1 and sE-selectin levels. Notably, the *in vitro* findings align with these results, showing that human umbilical vein endothelial cells (HUVEC) treated with cocoa-derived (poly)phenols (including epicatechin, catechin and epigallocatechin-3-gallate) exhibited increased NO production and reduced expression of adhesion molecules, including E-selectin and VCAM-1. These findings reinforce the role of cocoa flavan-3-ols in modulating endothelial function through oxidative stress reduction and enhanced NO signalling⁹¹. In contrast, the Flaviola Health Study⁹² further explored the vascular impact of cocoa flavan-3-ol supplementation in healthy adults, reporting a modest acute FMD improvement of 0.7% after a single dose of a cocoa flavan-3-ol-rich drink (450mg total flavan-3-ols, 64mg epicatechin). This is likely attributable to the cohorts' lack of endothelial dysfunction or potential variations in dosage. Nonetheless, chronic supplementation over four weeks induced a 1.2% increase in FMD ($p < 0.05$), aligning with earlier reports^{93,94}, which observed between 1.0-1.3% increases in FMD following consumption of high-flavan-3-ol chocolate and cocoa supplementation for 2-4 weeks respectively. Faridi and colleagues⁹⁵ expanded on these findings by evaluating cocoa-based interventions in overweight individuals, revealing that solid dark chocolate (3282mg total (poly)phenols) increased FMD by 4.3%, while sugar-free cocoa resulted in a 5.7% improvement. The addition of sugar mitigated the response to 2.0%. Moreover, Rodrigues-Mateos's research group highlighted the importance of the degree of polymerisation (DP) of cocoa flavan-3-ols, demonstrating that lower-degree polymerized flavan-3-ols (DP1-10) yielded a more substantial endothelial function improvement (1.7% vs -0.2%), in contrast to higher polymerized fractions (DP2-10)⁹⁶. Together, these observations emphasize the importance of flavan-3-ol composition and formulation, as well as dietary context, in optimizing cocoa's vascular benefits, indicating that both whole-food products and refined cocoa extracts can serve as effective interventions for enhancing vascular health.



Additionally, cocoa (poly)phenols, particularly their metabolites, have been shown to modulate the production of reactive oxygen species (ROS) through activation of AKT/AMPK/eNOS pathways³⁸. This activation may mitigate NO loss from oxidative stress and protect endothelial cells from damage contributing to the long-term improvement of vascular function. Moreover, the anti-inflammatory effects of cocoa (poly)phenols, demonstrated by their ability to lower CRP and IL-6 levels, further support their role in preventing the progression of endothelial dysfunction and atherosclerosis⁹⁷. These mechanisms, combined with theobromine potential to enhance NO production and inhibit phosphodiesterase activity, suggest that the cardiovascular benefits of cocoa are multifactorial and extend beyond the simple enhancement of NO bioavailability⁹⁸. Notably, evidence from Sansone and colleagues demonstrated that co-administration of cocoa flavan-3-ols with methylxanthines significantly enhanced FMD responses compared to flavan-3-ols alone (2.5% vs 1.4%, $p < 0.05$). This effect was associated with an increased plasma concentration of epicatechin metabolites, suggesting that methylxanthines enhance flavan-3-ol bioavailability, leading to greater improvements in endothelial function. These findings underscore the complex interactions between cocoa flavan-3-ols and methylxanthines, highlighting the importance of considering the full cocoa matrix when evaluating its vascular effects⁹⁹.

To summarise, cocoa (poly)phenols, particularly flavan-3-ols such as epicatechin, offer significant potential for improving endothelial function, as evidenced by the robust increases in FMD observed across multiple studies. The dose-dependent nature of these effects, as well as the influence of food matrices and the correlation between circulating metabolites and FMD, underscores the complexity of cocoa's impact on vascular health. While NO bioavailability remains a central mechanism, the antioxidant and anti-inflammatory properties of cocoa (poly)phenols are equally important in contributing to their cardiovascular benefits. Future research should focus on optimizing the delivery and establishing dosages and dietary recommendation of cocoa (poly)phenols to maximize their therapeutic potential, particularly in populations at high-risk for endothelial dysfunction.

2.5 Caffeinated and decaffeinated coffee

Coffee, one of the most widely consumed beverages globally, contains bioactive compounds such as caffeine, and chlorogenic acids (CGAs), all of which have been linked to effects on cardiometabolic health. The impact of coffee consumption on endothelial function, has been extensively investigated, though the findings remain ambiguous. The variability in results likely arises from factors such as coffee type (ground, instant, espresso), caffeine content, (poly)phenol concentration, and individual tolerances. In particular, studies comparing caffeinated coffee (CC) and decaffeinated coffee (DC) have revealed conflicting results. While some studies suggest that DC yields a more favourable response in



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terms of FMD, CC has been associated with detrimental or static effects, likely due to caffeine's influence on endothelial function.

Early reports examined the acute effects of caffeinated and decaffeinated instant coffee on FMD in healthy subjects, finding CC (80mg caffeine) significantly reduced FMD from 7.78% to 2.12% at 60 minutes post-ingestion ($p<0.001$), indicating acute endothelial impairment¹⁰⁰. Similarly, a study investigating the acute consumption of caffeinated espresso (130mg caffeine) reported a reduction in FMD from 7.7% to 6.0% ($p<0.001$)¹⁰¹. Interestingly, in both studies, DC had a more favourable outcome. Caffeine increases sympathetic nervous system activity, elevating circulating adrenaline and noradrenaline levels^{102–105}, leading to increased vascular tone and peripheral vasoconstriction^{104–107}. This acute vasoconstriction reduces arterial responsiveness, reflected as impaired FMD. Thus, the initial endothelial dysfunction observed following caffeinated coffee intake is potentially driven by caffeine-induced vasoconstrictive effects rather than (poly)phenol content. In the study by Papamichael and colleagues, the reduction in FMD for DC was smaller (7.07% to 5.20%) and non-significant, while Buscemi's research group noted a modest improvement in FMD (6.9% to 8.5%) with DC, though this did not reach statistical significance. However, when investigating dose-dependent effects in earlier research, they found that FMD improved significantly following the consumption of 1 cup (6.9% to 8.5%) and 2 cups (7.4% to 10.8%, $p<0.001$) of DC, likely due to its higher (poly)phenol and lower caffeine content compared to instant coffee¹⁰⁸. These findings suggest that caffeine may acutely impair endothelial function (Figure 3), while DC, with its lower caffeine content and higher (poly)phenol concentration, may offer protective benefits. Decaffeinated coffee's (poly)phenol profile and the potential endothelial improvements may be impacted by the decaffeination method used¹⁰⁹. Processes such as the Swiss Water Process, solvent-based chemical decaffeination, and carbon dioxide extraction differ substantially in their efficiency at retaining chlorogenic acids and other bioactive (poly)phenols^{109,110} potentially altering decaffeinated coffee's vascular benefits. Consequently, the specific decaffeination method may critically influence the cardiovascular outcomes associated with decaffeinated coffee consumption. However, as highlighted by Boon and colleagues the variability in responses may be influenced by other factors such as brewing method, frequency of consumption/individual tolerances, and baseline endothelial health¹¹¹. Additives commonly consumed with coffee, such as milk and sugar, significantly modulate its cardiovascular effects. For instance, the inclusion of sugars can negatively impact endothelial function through increased oxidative stress and impaired glycaemic control, potentially counteracting the benefits of coffee (poly)phenols¹¹². Milk proteins can form complexes with various (poly)phenols including chlorogenic acids, potentially reducing their bioavailability and subsequent endothelial benefits^{113,114}. Evidence suggests milk protein-(poly)phenol complexes may decrease antioxidant capacity, thus attenuating

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(poly)phenol-driven improvements in FMD^{115–117}. Moreover, the type of coffee was also found to influence FMD in a study investigating the consumption of boiled Greek coffee in comparison other types of coffee, noting a linear increase in FMD (4.33% to 6.47%, $p=0.032$) with increased coffee consumption but interestingly a higher FMD (5.26% vs 3.65%, $p=0.035$) was found with higher intake of boiled Greek coffee compared to other coffees respectively¹¹⁸. Therefore, both the choice of coffee type and consumption patterns regarding additives are crucial considerations when evaluating coffee's overall vascular impact.

Further research explored the time-dependent FMD response to high-(poly)phenol coffee (HPC) and low-(poly)phenol coffee (LPC) finding a significant biphasic FMD increase at 1 hour for both LPC (1.10%, $p<0.05$) and HPC (1.34%, $p<0.05$). At 5 hours, only HPC showed sustained improvement (1.52%, $p<0.0001$)¹¹⁹, highlighting the importance of (poly)phenol content in maintaining persistent vascular improvements. The researchers further explored the acute effects of varying doses of CGA metabolites, specifically 5-caffeoylquinic acid (5-CQA) on FMD, finding that a 450mg dose of 5-CQA increased FMD from 6.02% to 6.77% at 1-hour post-ingestion, nearing statistical significance ($p=0.06$)¹¹⁹. These results suggest that while caffeine may induce short-term reductions in FMD, the (poly)phenol content, particularly CGAs, can mitigate these effects and even improve endothelial function over time. This is supported by earlier research which demonstrated improvements in continuous FMD response following doses of 450mg (0.47%, $p=0.016$) and 900mg (0.65%, $p<0.001$) of 5-CQA, with the higher dose showing sustained benefits up to 4 hours post-ingestion¹²⁰. Furthermore, consumption of 600mg of CGAs before a high-calorie meal was found to mitigate the postprandial decline in FMD, preserving endothelial function at 6 hours (5.6% vs. 4.0%, $p<0.05$) compared to placebo¹²¹. However, not all studies align with these findings. In fact, caffeinated coffee (270mg caffeine, 95mg 5-CQA) was found to have significantly higher continuous FMD response (4.081%, $p<0.001$) compared to DC (132mg 5-CQA) and control¹¹¹, emphasizing the need to consider individual variation and other external factors that may affect FMD response to coffee consumption. Individual differences in response to coffee consumption, especially concerning caffeine, are influenced by genetic variability, notably polymorphisms in genes encoding cytochrome P450 enzymes such as CYP1A2^{122–125}. Individuals with fast caffeine metabolism (homozygous CYP1A21A alleles) generally experience fewer negative cardiovascular effects from caffeine¹²⁶, whereas those with slow metabolism (carrying the CYP1A21F allele) may show heightened sensitivity to caffeine-induced vasoconstriction and endothelial impairment^{126,127}. These genetic variations highlight the complexity of assessing coffee's cardiovascular effects across populations, underscoring the necessity of personalized nutritional recommendations. These findings underscore the potential of CGA extracts

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DOI: 10.1039/D3FO01106J



to improve endothelial function through their antioxidant and NO-mediated mechanisms, offering more predictable benefits than whole coffee.

2.6 Black and Green Tea

Tea is another commonly consumed beverage globally and represents approximately 35-40% of dietary (poly)phenol intake in certain populations, contributing significantly to the reduction of cardiovascular disease risk and improvements in vascular health through its bioactive compounds^{39,128,129}. For instance, daily consumption of black tea (450ml) significantly improved FMD in patients with CAD, increasing from 5.2% ± 0.7% to 9.4% ± 1.0% immediately after consumption (p<0.001), with further gains to 10.7% ± 1.2% after four weeks¹³⁰. These sustained benefits were attributed to enhanced NO bioavailability, mediated in part by the catechins in black tea, which upregulate antioxidative pathways, reducing reactive oxygen species (ROS) and protecting NO from degradation. In comparison, studies investigating green tea have shown more variable effects, ranging from significant improvements in FMD (2.3% ± 0.4%, p<0.01), concurrent with reductions in oxidative stress among hypertensive patients consuming five cups of green tea daily for eight weeks¹³¹, to no significant change in FMD following short-term green tea consumption in healthy participants¹³². Black tea and green tea differ substantially in their (poly)phenolic composition, notably regarding catechins. Green tea predominantly contains unoxidised catechins such as epigallocatechin gallate (EGCG), epicatechin gallate, epigallocatechin, and epicatechin^{133,134}. Conversely, black tea undergoes enzymatic oxidation, converting catechins into polymerized forms like theaflavins and thearubigins, significantly altering their bioavailability and their putative bioactivity^{135–138}. Interestingly, one study that demonstrated beneficial improvements in FMD (4% ± 1%, p<0.05) following consumption of black tea, also noted that the addition of milk nullified this benefit, likely due to milk proteins binding to tea catechins and reducing their bioavailability¹³⁹. This suggests that black tea, consumed without milk, may be more effective in promoting endothelial health. The importance of bioavailability was further highlighted in a study observing that higher plasma concentrations of catechins were associated with greater FMD improvements⁴². Participants consuming five cups of green tea daily for one week had plasma levels of 90nmol/L for epicatechin and 180nmol/L for catechin, correlating with an increase in FMD from 6.3% ± 0.7% to 7.9% ± 0.9% (p<0.05)⁴², underscoring the importance of catechin absorption and individual metabolic differences in determining vascular outcomes.

Studies comparing populations with compromised versus healthy endothelial function highlight notable differences in FMD responses to tea (poly)phenols.¹⁴⁰ showed that black tea consumption significantly increased FMD from 8.3% ± 1.5% to 14.0% ± 2.0% (p<0.05) in renal transplant recipients, a population with compromised endothelial function, suggesting that tea (poly)phenols may provide

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greater benefits to individuals with existing cardiovascular or endothelial impairments. Similarly, Grassi and colleagues found significant improvements in hypertensive patients¹³¹, while studies on healthy individuals^{132,139,141,142}, have often reported less pronounced or transient effects, and may arise due to a potential 'ceiling effect', limiting the magnitude of measurable FMD improvements following (poly)phenol consumption. This may indicate that (poly)phenols beneficial vascular effects are more pronounced in individuals with baseline endothelial impairment, however a recent meta-analysis comparing n=26 studies investigating flavan-3-ols found a linear increase in chronic Δ FMD % response with increasing baseline FMD, indicating that those with a lower baseline FMD may have a diminished effect, which may be resultant of a compromised endothelial cellular function¹⁴³.

In summary, both black and green tea have demonstrated their capacity to improve endothelial function^{129,144,145}. However, the bioavailability of catechins, influenced by factors such as milk addition and individual metabolic differences, plays a crucial role in determining the efficacy of tea (poly)phenols. Populations with compromised endothelial function appear to experience greater benefits from tea consumption, suggesting that regular intake may be effective in reducing cardiovascular risk among individuals with existing vascular impairments. However, the recent evidence from Lagou and colleagues suggests that it may be the opposite of this and warrants further investigation.

3. Relationship between circulating metabolites and FMD

(Poly)phenols exert their beneficial effects on cardiovascular health primarily through the action of their circulating metabolites, which modulate endothelial function and FMD^{146,147}. These metabolites, including phase II conjugates such as ferulic acid, vanillic acid, homovanillic acid, play a critical role by reducing oxidative stress, modulating inflammation, and enhancing NO bioavailability^{148–150}. One of the key mechanisms by which these metabolites function is through their modulation of redox-sensitive cell signalling pathways, particularly those regulating endothelial NO production^{12,15,151}. This action prevents the degradation of NO, ensuring its availability for cell signalling and vasodilation^{9,152,153}. Moreover, these metabolites have also been shown to upregulate eNOS through activation of the PI3K/Akt and AMPK/SIRT1 signalling pathways, which enhance eNOS phosphorylation, transcription, and enzymatic stability^{151,154,155}, further increasing NO bioavailability.

Cranberries, blueberries, and other berries are particularly rich in anthocyanins and ellagitannins. However, their cardiovascular benefits are primarily mediated through the action of their metabolites. Cranberry-derived metabolites, such as cinnamic acid-4'-glucuronide and 3'-hydroxycinnamic acid, have been identified as predictors of FMD improvements, suggesting that the vascular benefits of (poly)phenol-rich foods are closely tied to bioavailability and metabolite profiles. These metabolites





support NO bioavailability and reduce oxidative stress, contributing to improvements in FMD within the range of 1% to 3%. Similarly, after consuming blueberries, phenolic metabolites such as vanillic acid (30–40nmol/L) and homovanillic acid (40–50nmol/L) have been linked to FMD improvements ranging from 2% to 4%^{46,53,156}. Additionally, microbial-derived metabolites including urolithins, also play a significant role. Urolithins are produced from the breakdown of ellagitannins by the gut microbiota and have been shown to enhance FMD by regulating the Nrf2 pathway¹⁵⁷. This pathway activates antioxidant genes such as heme-oxygenase-1 (HO-1), which reduces endothelial oxidative stress. Although urolithins do not directly impact NO bioavailability, their strong antioxidant properties contribute to improvements in vascular function⁶⁵. The extent of these benefits can vary due to differences in gut microbiota composition among individuals, affecting the metabolism and circulation of (poly)phenol-derived metabolites^{147,157}. Together, the metabolites from berries and the microbial-derived urolithins highlight the complexity of (poly)phenol metabolism and its role in sustaining vascular health.

Cocoa and tea, rich in flavan-3-ols such as epicatechin and catechins, have also been shown to improve FMD through similar mechanisms^{158,159}. Cocoa-derived epicatechin, reaches concentrations of 600–800nmol/L approximately 1 - 2 hours post consumption, and is associated with FMD improvements in the range of 3% to 5%^{98,143,160}. Epicatechin and catechin metabolites enhance NO bioavailability by upregulating endothelial nitric oxide synthase (eNOS) and mitigating oxidative stress through the inhibition of nuclear factor kappa B (NF-κB), a key regulator of inflammation¹⁴⁴. These effects are sustained for several hours post-consumption, with cocoa metabolites remaining in the bloodstream reaching peak concentration between 4 – 6 hours and remaining in the circulation up to 48h hours post-consumption, contributing to prolonged vascular benefits^{161,162}. In tea, catechin metabolites present at 90–180nmol/L after consumption have been associated with FMD improvements of 1.5% to 4%, further supporting the hypothesis that (poly)phenol metabolites from both tea and cocoa enhance NO bioavailability and promote endothelial health.

Coffee, rich in chlorogenic acids, follows a similar pathway. Ferulic acid, a metabolite of chlorogenic acid, reaches concentrations of 0.1–0.15μmol/L after consuming chlorogenic acid-enriched coffee. This metabolite is linked to modest FMD improvements in the range of 1% to 3%, attributed to enhanced antioxidant enzyme activity, such as superoxide dismutase (SOD), which reduces oxidative stress and preserves NO bioavailability¹¹⁹. Similar to other (poly)phenol-rich foods, the impact of coffee on FMD is strongly linked to the bioavailability of its circulating metabolites and the duration of their presence in the bloodstream. The duration and extent of metabolite presence in the bloodstream are critical for optimizing vascular benefits, however, the bioavailability and metabolism of (poly)phenols vary between individuals due to differences in gut microbiota composition, genetic

factors, and health status, which can affect circulating levels of active metabolites and the extent of endothelial improvements^{162–165}.

4. Potential for dietary guidance

(Poly)phenol dietary recommendations for cardiovascular health have gained considerable attention due to their potential role in various metabolic pathways^{36,63,166,167}. However, translating these recommendations into practical dietary guidelines remains challenging due to the natural variability of (poly)phenol content in foods. Factors such as climate, soil conditions, and harvest timing can significantly affect (poly)phenol levels in the same food type^{60,168,169}. For instance, wild blueberries contain approximately 487mg anthocyanins per 100 g in contrast to highbush blueberries (~130 mg per 100 g). Consequently, consuming 80 g wild blueberries would meet an efficacious dose (~390 mg anthocyanins), while nearly 200 g of highbush blueberries would be required to achieve similar bioactivity (Rodriguez-Mateos et al., 2019). Similarly, cocoa (poly)phenol content varies markedly due to cultivation and processing methods, ranging from 50 to 150 mg flavan-3-ols per 100 g in commercial dark chocolate^{98,170}. This variability underscores the importance of standardized (poly)phenol measurements to inform accurate dietary guidance. This variability complicates efforts to establish reliable guidelines based on total (poly)phenol content (TPC). Typically, dietary recommendations focus on portion sizes rather than precise nutrient quantities, which complicates ensuring optimal intake for cardiometabolic health.

Interestingly, habitual background (poly)phenol intake may influence the magnitude of cardiovascular benefits observed with supplementation or dietary interventions. Data from the EPIC study¹⁷¹ indicate that individuals in lowest percentile of flavan-3-ol consumption (<100 – 150 mg/day), were at higher risk for high BP and CVD Risk. Complimenting this, evidence from the COSMOS study⁷, suggests that individuals with lower baseline flavanol intake or poorer-quality habitual diets may experience more pronounced improvements in cardiovascular outcomes and biomarkers such as FMD when supplemented with cocoa flavanols. In line with this evidence, the Academy of Nutrition and Dietetics recently recommended a daily flavan-3-ol intake of 400 – 600mg³⁶, which not only aligns with typical dietary flavan-3-ol intakes (200–500mg/day)^{3,45,172,173} but also with tested dosages of cocoa and tea which elicited responses in FMD studies (Table 1 & 2). This recommendation is sufficient to attain the associative benefits while remaining below the plateau range (500 – 100mg/day). However dietary guidance for cocoa in particular is complicated, as the typical interventions used in clinical studies such as the COSMOS trial have more highly concentrated (poly)phenol compositions than that of commercially available cocoa and dark chocolate⁷. In contrast, anthocyanins, and chlorogenic acids, found in foods like berries and coffee respectively, have daily consumption levels generally below the dosages used in clinical intervention studies. For instance, average daily intake of anthocyanins ranges



from 10mg to 50mg/day, which is considerably lower than the quantities used in FMD studies (20-400mg), equivalent 100g to 300g which also falls outside the general recommendations for a portion (60 - 80g) of berries. Similarly, daily intake levels of hydroxycinnamic acids (up to 231.8mg/day), including (poly)phenols such as chlorogenic acids are lower than the typically tested ranges (>300mg), this is further complicated with variations in coffee consumption patterns, types of coffee used and preparation methods^{3,45,172,173}.

Fortification or enrichment may provide a practical solution to the variability in (poly)phenol content across natural sources^{63,174}. Enriching foods with (poly)phenols can ensure more consistent intake by controlling TPC levels and more importantly specific bioactive phenolics, making it easier to meet the dosages shown to be effective in clinical research^{61,175}. Importantly, (poly)phenols have been shown to remain stable during food processing preserving their bioactive properties and health benefits. For example, cereal products enriched with cranberry (poly)phenols maintained their anthocyanin content even after high-temperature processing, ensuring the bioactive compounds remain intact post-manufacture¹⁷⁶. Albeit stability does not guarantee that (poly)phenols will maintain their bioavailability as the food matrix may be altered, introducing other food components which may inhibit absorption, such as sugar, fat and proteins thus mitigating any potential benefits. For instance, blueberry buns fortified with (poly)phenols did not impact TPC although did alter the polyphenol composition, decreasing anthocyanins by ~42% and increasing chlorogenic acid content. This compositional change also impacted the C_{max} and AUC of various metabolites. Nonetheless, significant improvements in endothelial function were observed in comparison to non-enriched bun and comparable to the blueberry drink positive control, demonstrating that bioactivity was preserved following processing⁵⁶. Other studies also confirm (poly)phenol stability during food processing, for instance orange juice enriched with hesperidin, provided greater improvements in endothelial function than regular juice, showing the potential of enrichment in widely consumed beverages⁸³. While coffee fortified with cocoa¹⁷⁷ and enriched with chlorogenic acid¹²⁰ were demonstrated to be stable, yielding favourable endothelial modulation. However, implementation of (poly)phenol fortification in public health contexts is constrained by both regulatory and practical considerations^{36,178,179}. Regulatory frameworks for functional foods and nutraceuticals vary internationally, often requiring extensive safety and efficacy evaluations before approval^{178,179}. Additionally, practical barriers such as the cost of high-purity extracts and consumer acceptability / tolerance of fortified products must be considered to ensure safe and effective applications¹⁷⁸⁻¹⁸¹. Addressing these challenges is critical if fortification strategies are to complement dietary diversification as a means of maximising the cardiometabolic benefits of (poly)phenols.



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In conclusion, dietary (poly)phenols and (poly)phenol-rich foods beneficially modulate endothelial function as measured by FMD. While the development of dietary recommendations for cardiometabolic health is essential, their implementation is hindered by the lack of confirmed (poly)phenol content of various foods and the intrinsic variability in (poly)phenol content across food sources, making it challenging to establish precise intake guidelines. Whilst the estimated daily intake of (poly)phenols in Western populations can reach approximately 1000-1200 mg/day^{45,172}, exceeding efficacious dosages used in many clinical trial, this intake is largely derived from a limited range of sources, primarily tea, coffee, and cocoa providing specific subclasses such as flavan-3-ols and chlorogenic acids which may also be impaired by other food matrix components such as sugar and milk. Albeit, these compounds have well-established health benefits, yet the lack of diversity restricts exposure to other beneficial compounds including anthocyanins, flavanones etc. which limits potential complementary and/or distinct bioactive effects. Furthermore, these intake estimations rely on dietary self-reporting, which is subject to inaccuracies, and do not account for inter-individual differences in metabolism, absorption, or the influence of other dietary components on (poly)phenol bioavailability or the resulting bioactivity. Critically, evidence consistently suggests that greater (poly)phenol consumption is associated with enhanced health benefits, indicating that current dietary patterns may still be suboptimal. Moreover, if typical dietary sources were sufficient to maximize (poly)phenol-mediated health effects, higher intakes would not correspond with additional benefits. Given this, strategies to enhance (poly)phenol intake through fortification and enrichment technologies warrant further exploration. These approaches may offer a means of increasing overall intake and ensure the consistent delivery of bioactive compounds, however compositional changes present a challenge as the associated bioactivity may be altered or diminished dependant on the degree of the compositional and/or food matrix change and may warrant revaluation if potential nutrition or health claims are to be utilised by industry.

Nonetheless, the establishment of dietary recommendations remains a critical area of research, as it will define effective daily intakes while accounting for the plateau effects observed in many clinical trials. Understanding the thresholds beyond which additional intake does not confer further benefits will aid in optimizing recommendations, ensuring that individuals achieve sufficient (poly)phenol exposure without unnecessary overconsumption. Future research should focus on refining both dietary guidelines and fortification strategies, assessing their long-term efficacy in improving cardiovascular health outcomes.

Authors contributions: B.Ó.M and C.I.R.G., were involved in review design. The manuscript was prepared by B.Ó.M., H.R.N., N.M., E.J.R., L.K.P., P.R., C.P., D.G., S.R., L.B., D.D.R., A.R.M., A.C. and C.I.R.G with contributions from all the authors.

Acknowledgements: C.I.R.G., B.Ó.M and A.R.M acknowledge the Nutrition Society and the Phytochemicals and Health Special Interest Group (SIG) for supporting research in this field. We also acknowledge colleagues and collaborators for their valuable insights.

Conflict of interests: The authors report no conflicts of interest



762 5. Summary Tables

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DOI: 10.1039/D5FO01106J**Table 1:** Summary of acute flow-mediated dilation (FMD) responses within different food groups.

Food group	Proportion of studies demonstrating a significant effect on FMD	(Poly)phenol dose range (mg)	Acute FMD changes (%)
Whole food			
Berry (n=8)	5/8	200 – 1910	0.9 - 2.6
Grape (n=4)	3/4	NR	0.3 - 8.6
Citrus fruits (n=3)	1/1	32 – 345	1.5 - 2.1
Cocoa (n=12)	7/12	185 – 3282	0.7 - 5.7
Coffee (n=8)	5/8	89 – 900	1.1 - 3.4
Tea (n=3)	3/5	398 – 733	1.4 - 4.8
Extract			
Berry (n=7)	3/4	116 – 1791	1.0 - 2.4
Grape (n=0)	NA	NA	NA
Citrus fruits (n=1)	0/0	272 – 600	1.5
Cocoa (n=1)	1/1	150 – 3282	0.7 - 5.9
Coffee (n=2)	1/2	355	0.3 - 2.3
Tea (n=3)	1/3	330 - 1817	0.2 - 3.9
Pure phenolic			
Epicatechin (n=2)	1/2	10 – 100	1.2 - 2.9
Resveratrol (n=2)	1/2	30 – 270	2.5 - 3.6
Quercetin (n=1)	0/1	160	NA
Hesperidin (n=1)	0/1	450	NA

Acute changes in flow-mediated dilation (FMD) within different food grouped by whole foods (including whole fruits or derived products such as juices, wines etc.) extracts (including freeze-dried food components administered as capsules, reconstituted in water, or used to enrich derived food or a meal) and pure phenolic compounds. FMD, flow-mediated dilation; n, number of studies; mg, milligram; NR, not reported; NA, not applicable.

Table 2: Summary of chronic flow-mediated dilation (FMD) responses within different food groups.

Food group	Proportion of studies demonstrating a significant effect on FMD	(Poly)phenol dose range (mg)	Chronic FMD changes (%)
Whole food			
Berry (n=3)	2/3	12 – 835	0.9 - 1.1
Grape (n=3)	2/3	965	0.8 - 8.7
Citrus fruits (n=4)	2/4	212 – 419	0.2 - 2.2
Cocoa (n=14)	7/14	185 – 1113	1.0 – 5.6
Coffee (n=2)	1/2	300 – 780	3.3
Tea (n=6)	5/6	100 – 1188	1.2 - 3.8
Extract			
Berry (n=4)	2/4	116 – 1910	1.1 - 1.45
Grape (n=12)	6/12	1.65 (NR)	0.3 - 5.5
Citrus fruits (n=4)	3/4	500 – 600	2.0 - 7.2
Cocoa (n=3)	2/3	523 – 690	1.2 - 1.8
Coffee (n=0)	NA	NA	NA
Tea (n=1)	1/1	1350	3.5
Pure phenolic			
Epicatechin (n=1)	1/1	10 – 100	1.1
Quercetin (n=1)	0/1	160	NA

Chronic changes in flow-mediated dilation (FMD) within different food grouped by whole foods (including whole fruits or derived products such as juices, wines etc.) extracts (including freeze-dried food components administered as capsules, reconstituted in water, or used to enrich derived food or a meal) and pure phenolic compounds. FMD, flow-mediated dilation; n, number of studies; mg, milligram; NR, not reported; NA, not applicable.



Table 3: Summary of Human Intervention Trials Assessing the Effects of (Poly)phenol-Rich Foods and Extracts on Flow-Mediated Dilatation (FMD)

Author (Year) Population	Type of Intervention	Study design	Population ¹	Duration	Age (y)	BMI (kg/m ²)	Intervention and (Poly)phenol Content (mg)	FMD Outcomes
Gustas et al. (2018) ⁶⁵ n=10, 100% M	Whole food	Crossover	Healthy	Acute (2 hr) Chronic (24 hr)	27 ± 3	23 ± 2	200g Raspberry drink (TPC 201mg, Anthocyanins 125mg, Flavonols 5.7mg, Flavan-3-ols 0.6mg, Epicatechin 0.6mg, Catechin 0.01mg)	Acute (2 hr) 200g - **↑1.6% from baseline FMD % 400g - *↑1.2% from baseline FMD % Control - 0.0% from baseline FMD %
							400g Raspberry drink (TPC 403mg, Anthocyanins 328mg, Flavonols 11mg, Flavan-3-ols 1.2mg, Epicatechin 1.2mg, Catechin 0.02mg) Control (macro/micronutrient matched drink, with raspberry flavours)	Chronic (24 hr) 200g - **↑0.9% from baseline FMD % 400g - *↑0.5% from baseline FMD % Control - 0.1% from baseline FMD %
Alqurashi et al. (2016) ¹⁸² n=23, 100% M	Whole food	Crossover	Healthy	Acute (2 hr)	46 ± 1.9	27.6 ± 0.4	Açai Smoothie (TPC 694mg, Anthocyanins 493mg) Control (macro/micronutrient - matched smoothie)	Açai smoothie - **↑1.4% ± 0.6% from baseline FMD % Control - ↑0.4% ± 0.6% from baseline FMD %
Rodriguez-Mateos et al. (2016) ⁵⁸ n=10, 100% M	Whole food	Crossover	Healthy	Acute (2 hr)	24 ± 2	24 ± 2	Cranberry juice at: 25.1% (TPC 409mg, Flavan-3-ols 2.5mg, Flavonols 14.5mg, Anthocyanins 6.8mg) 48.2% (TPC 787mg, Flavan-3-ols 5.0mg, Flavonols 31.3mg, Anthocyanins 16.2mg) 75.8% (TPC 1238mg, Flavan-3-ols 6.8mg, Flavonols 48.9mg, Anthocyanins 23.2mg) 94% (TPC 1534mg, Flavan-3-ols 10.1mg, Flavonols 62.8mg, Anthocyanins 26.3mg) 117% (TPC 1910mg, Flavan-3-ols 12.3mg, Flavonols 76.9mg Anthocyanins 32.3mg) Control (macro/micronutrient matched drink)	25.1% - *↑0.9% from baseline FMD % 48.2% - *↑1.55% from baseline FMD % 75.8% - *↑1.8% from baseline FMD % 94% - *↑1.55% from baseline FMD % 117% - *↑1.7% from baseline FMD % Control - ↑0.4% from baseline FMD %



Shan et al. (2014) ⁵¹ n=64, 67% M	Whole food	Parallel	Low F&V consumers	Chronic (6 wk)	Low blackcurrant juice: 55 ± 10 High blackcurrant juice: 51 ± 11 Placebo: 51 ± 8	Low blackcurrant juice: 28.4 ± 5.4 High blackcurrant juice: 29.2 ± 6.9 Placebo: 28.9 ± 6.5	Low blackcurrant juice (TPC 273mg, Anthocyanins 40mg) High blackcurrant juice (TPC 815mg, Anthocyanins 143mg) Control (Flavoured water)	Blackcurrant juice Low - ↑0.7% from baseline FMD % High - *↑1.1% from baseline FMD % Control 1 wk - ↓0.9% from baseline FMD %
Shahadwa et al. (2011) ⁵⁷ n=44, 68% M	Whole food	Crossover	CAD	Acute (2-4 hr) Chronic (4 wk)	Juice-first: 61 ± 11 Placebo-first: 63 ± 9	Juice-first: 30 ± 5 Placebo-first: 29 ± 4	Cranberry juice (TPC 835mg, Anthocyanins 94.47mg, cyn-gal 18.7mg, cyn-glu 1.58mg, cyn-ara 16.47mg, peo-gal 30.83mg, peo-glu 5.85mg, and peo-ara 21.03mg)	Acute (2 hr) - ↑0.4% from baseline FMD % Acute (4 hr) - *↑1.0% from baseline FMD % Chronic - ↑0.4% from control baseline FMD %
Stas et al. (2019) ⁴⁹ n=66, 100% M	Whole food / Extract	Parallel	Healthy	Acute (2 hr) Chronic (12 wk)	24 ± 5.3	23 ± 2.1	Aronia whole fruit - (TPC 12mg (Flavonols 2.6mg, Anthocyanins 3.6mg, Proanthocyanidins 3.3mg, Epicatechin 0µg, Protocatechuic acid 450µg) Aronia Extract - TPC 116mg (Flavonols 35mg, Anthocyanins 30mg, Proanthocyanidins 16mg, Epicatechin 101µg, Protocatechuic acid 2396µg) Control (maltodextrin)	Acute: Whole fruit - ↑0.5% from baseline FMD % Extract - ↑1.4% from baseline FMD % Control - ↑0.3% from baseline FMD % Chronic: Whole fruit - *0.9% from baseline FMD % Extract - *1.0% from baseline FMD % Control - ↓0.2% from baseline FMD %
Rodriguez-Mateos et al. (2014) ⁵⁶ n=10, 100% M	Whole food / Extract	Crossover	Healthy	Acute (24 hr)	27 ± 1	25 ± 0.8	Drink containing freeze-dried blueberry 34g (TPC 692mg, Total anthocyanins 339mg, Total procyanidins 111mg, Monomers 29mg, Dimers 26mg, Trimers 15mg, Tetramers 14mg, Pentamers 9mg, Hexamers 8mg, Heptamers 6.5mg, Octamers 5mg, Nonamers 4mg, Decamers 0mg, Total oligomers 89mg, Quercetin 24mg, Chlorogenic acid 179mg, Caffeic acid 16mg, Ferulic acid 22mg) Blueberry buns (x3) made with freeze-dried blueberry 34g: (TPC 637mg, Total anthocyanins 196mg*, Total procyanidins 140mg, Monomers 29mg, Dimers 42mg*, Trimers 23mg*, Tetramers 17mg, Pentamers 11mg, Hexamers 8mg, Heptamers 5mg, Octamers 4mg, Nonamers 0mg*, Decamers 0mg, Total oligomers 111mg, Quercetin 25mg*, Chlorogenic acid 221mg*, Caffeic acid 17mg, Ferulic acid 38mg*) Control (Macro / micronutrient matched buns x 3)	Blueberry drink: 1 hr: *↑2.4% from baseline FMD % 2 hrs: *↑1.55% from baseline FMD % 4 hrs: *↑0.15% from baseline FMD % 6 hrs: *↑1.3% from baseline FMD % Blueberry bun: 1 hr: *↑1.8% from baseline FMD % 2 hrs: *↑2.6% from baseline FMD % 4 hrs: *↑0.25% from baseline FMD % 6 hrs: *↑1.0% from baseline FMD % Control 1 hr: ↑0.15% from baseline FMD % 2 hrs: ↑0.35% from baseline FMD % 4 hrs: ↑0.55% from baseline FMD % 6 hrs: ↑0.65% from baseline FMD %

Rodriguez-Mateos et al. (2013) ⁵³ =10, 100% M	Whole food / Extract	Crossover	Healthy	Acute (6 hr)	27 ± 1.3	25 ± 0.8	Drinks containing freeze-dried blueberry: 34 (TPC 766mg, Anthocyanins 310mg, Procyanidins 137mg, Flavan-3-ol monomers 24mg, Flavan-3-ol oligomers 112mg, Chlorogenic acid 273mg, Quercetin 26mg, Caffeic acid 17g, <i>p</i> -Coumaric acid 1.4mg, Ferulic acid 1.4mg) 57 (TPC 1278mg, Anthocyanins 517mg, Procyanidins 228mg, Flavan-3-ol monomers 40mg, Flavan-3-ol oligomers 188mg, Chlorogenic acid 455mg, Quercetin 43mg, Caffeic acid 30mg, <i>p</i> -Coumaric acid 2.4mg, Ferulic acid 2.4mg) 80 (TPC 1791mg, Anthocyanins 724mg, Procyanidins 320mg, Flavan-3-ol monomers 56mg, Flavan-3-ol oligomers 264mg, Chlorogenic acid 637mg, Quercetin 61mg, Caffeic acid 42g, <i>p</i> -Coumaric acid 3.4mg, Ferulic acid 3.4mg) Control (macro/micronutrient matched drink)	766mg TPC: 1 hr: ↑2.4% from baseline FMD % 2 hrs: ↑1.5% from baseline FMD % 4 hrs: ↑0.1% from baseline FMD % 6 hrs: ↑1.2% from baseline FMD % 1278mg TPC: 1 hr: ↑2.2% from baseline FMD % 2 hrs: ↑1.5% from baseline FMD % 4 hrs: ↑0.1% from baseline FMD % 6 hrs: ↑0.6% from baseline FMD % 1791mg TPC: 1 hr: ↑1.8% from baseline FMD % 2 hrs: ↑1.0% from baseline FMD % 4 hrs: ↑0.1% from baseline FMD % 6 hrs: ↑0.4% from baseline FMD % Control: 1 hr: ↓0.3% from baseline FMD % 2 hrs: ↓0.5% from baseline FMD % 4 hrs: ↓0.4% from baseline FMD % 6 hrs: ↓0.5% from baseline FMD %
Wolf et al. (2023) ⁵⁴ 43, 0% M	Extract	Parallel	Postmenopausal women with elevated BP	Chronic (12 wk)	Blueberry: 60 ± 1 Placebo: 61 ± 1	Blueberry: 27.6 ± 1 Placebo: 27.8 ± 1.1	Freeze-dried Blueberry Powder (TPC 726mg, Anthocyanins 224mg) Control (isocaloric and carbohydrate matched) *added to energy dense meal*	Freeze-dried Blueberry Powder 12 wk - ↑1.34% from baseline FMD % Control 12 wk - ↓0.4% from baseline FMD %



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Reiss et al. (2022) ⁵⁹ n=44, 100% M	Extract	Parallel	Healthy	Acute (2 hr) Chronic (1 mth)	Cranberry: 25 ± 3 Control: 25 ± 3	Cranberry: 23 ± 3 Control: 24 ± 3	Cranberry powder (TPC 525mg, Total proanthocyanidins (PACs) 374.2mg, Epicatechin 0.493mg, Catechin 0.019mg, Total flavonols 81mg, Quercetin-3-rhamnoside eq. 81mg, Quercetin 0.153mg, Kaempferol 0.001mg, Total anthocyanins 54mg, 3',4'-Dihydroxycinnamic acid equivalent (caffeic acid) 16mg, 5-O-Caffeoylquinic acid (chlorogenic acid) 0.720μg, 3,4-Dihydroxybenzoic acid (protocatechuic acid) 0.051μg, 4'-Hydroxycinnamic acid (p-coumaric acid) 0.034μg, 4'-Hydroxy-3',5'-dimethoxycinnamic acid (sinapic acid) 0.010μg, 4'-Hydroxy-3'-methoxycinnamic acid (ferulic acid) 0.007μg, 3-Hydroxybenzoic acid 0.006μg, 3,4-Dihydroxybenzaldehyde 0.004μg, 2,5-Dihydroxybenzoic acid 0.003μg, 2-Hydroxybenzoic acid 0.003μg, 4-Hydroxybenzoic acid 0.001μg, Dihydrocaffeic acid 0.001μg, 4-Hydroxy-3'-methoxycinnamic acid (isoferulic acid) 0.000μg, 4-Hydroxybenzaldehyde 0.000μg.) Control (Colour matched Maltodextrin) Freeze-dried Blueberry Powder (TPC 879mg, Anthocyanins 364mg) Control (isocaloric and carbohydrate matched) *added to energy dense meal*	Freeze-dried cranberry Powder: 2 hr: ***↑1.5% from baseline FMD % 1 mth: ***↑1.1% from baseline FMD % 1 mth, 2 hr: ***↑1.5% from baseline FMD % Control: 2 hr: ↓0.0% from baseline FMD % 1 mth: ↓0.0% from baseline FMD % 1 mth, 2 hr: ↓0.1% from baseline FMD %
Curtis et al. (2022) ⁵⁵ n=45, 64% M	Extract	Crossover	Metabolic syndrome	Acute (24 hr)	63.4 ± 7.4	31.4 ± 3.1	Freeze-dried Blueberry Powder: 3 hr: ↓0.6% from baseline FMD % 6 hr: ↓0.5% from baseline FMD % 24 hr: ↓0.2% from baseline FMD % Control: 3 hr: ↓1.1% from baseline FMD % 6 hr: ↓0.6% from baseline FMD % 24 hr: ↓0.2% from baseline FMD % Strawberry powder - *↑2.4% from baseline FMD % Control - ↑0.7% from baseline FMD %	
Huang et al. (2021) ⁶⁶ n=46, 46% M	Extract	Crossover	Hypercholesterolemia	Acute (1 hr)	53 ± 1	31 ± 1	Strawberry powder 50g - TPC 450.7mg (Flavan-3-ols 99mg, Flavonols 36.2mg, Anthocyanins 141.7mg, Ellagitannins 160.2mg, Phenolic acids 13.6mg) - (25g, =250g fresh fruit)	
Curtis et al. (2019) ⁴⁷ n=115, 68% M	Extract	Parallel	Metabolic syndrome	Chronic (6 mth)	62.8 ± 7.1	31.2 ± 3.0	Freeze-dried Blueberry Powder: 1 cup equivalent (TPC 879mg, Anthocyanins 364mg) 1/2 cup equivalent (TPC 439mg, Anthocyanins 182mg) Control (isocaloric and carbohydrate matched) *consumed within 8 standardized recipes*	Freeze-dried Blueberry Powder: 1 cup - *↑1.45% from baseline FMD % 1/2 cup - ↑0.00% from baseline FMD % Control - ↑0.45% from baseline FMD %

Philip et al. (2019) ¹⁸³ n=30, 47% M	Extract	Crossover	Healthy	Acute (2 hr)	18 - 25	21.3 ± 2.2	Memophenol (TPC 600mg, Flavonoids 260.4mg, Flavan-3-ols monomers 123.6mg, Anthocyanins 0.6mg, Phenolic acids 3mg, Oligomers 135mg, Stillbenes 0.6mg)	Memophenol - ***↓1.6% from baseline FMD % Control ***↓1.5% from baseline FMD %
Grape								
Lasos et al. (2014) ⁶⁷ n=26, 39% M	Whole food	Crossover	Healthy smokers	Chronic (2 wk)	26.34 ± 4.93	23.21 ± 4.10	Concord grape juice 490ml - (TPC 965mg, hydroxycinnamates 324 µmol/L, flavonols 152 µmol/L, flavan-3-ols 868 µmol/L, and anthocyanins 592 µmol/L) Control (Grapefruit juice)	Concord grape juice 7 days - *↑0.8% from baseline FMD % 14 days - *↑1.14% from baseline FMD % Control 7 days - ↓0.73% from baseline FMD % 14 days - ↓1.12% from baseline FMD %
Hashemi et al. (2011) ⁷¹ n=20, 54% M	Whole food	Parallel	Metabolic syndrome	Acute (4 hr) Chronic (2 wk)	13.4 ± 1.1	27.1 ± 1.1	Grape juice - 18ml/kg/day Pomegranate juice - 200ml/day	Grape juice 4 hrs - *↑8.55% from baseline FMD % 1 month - *↑8.66% from baseline FMD % Pomegranate juice 4 hrs - *↑4.50% from baseline FMD % 1 month - ↑4.28% from baseline FMD %
Hampton et al. (2010) ⁷⁴ n=10, 50% M	Whole food	Crossover	Healthy	Acute (30 - 60 min)	22.2 ± 3.8	23.7 ± 3.15	Meal + Red grape juice - 122.5ml + water - 52.5 mL Meal + Red grape juice - 122.5ml + 40% alcohol - 52.5 mL Meal + Control (water) - 175ml	Red grape juice 30 mins - ↑1.60% from baseline FMD % 60 mins - ↑0.35% from baseline FMD % Red grape juice + Alcohol 30 mins - ↑2.60% from baseline FMD % 60 mins - ↑0.10% from baseline FMD % Control 30 mins - ↓0.00% from baseline FMD % 60 mins - ↓1.05% from baseline FMD %
Coimbra et al. (2005) ¹⁸⁴ n=16, 50% M	Whole food	Crossover	Hypercholesterolemia	Chronic (2 wk)	51.6 ± 8.1	24.8 ± 1.5	Grape juice - 500ml/day Red wine - 250ml / day	Grape juice - *↑6.80% from baseline FMD % Red wine - ↑5.50% from baseline FMD %



apamichael et al. (2003) ⁷³ n=16, 50% M	Whole food	Crossover	Healthy smokers	Acute (90 min)	28.9 ± 6.5	23.4 ± 3.2	Smoking + Red wine (Dealcoholised) - 250ml (Caffeic acid 1.65mg) Smoking + Red wine (Alcoholised) - 250ml (Caffeic acid 1.63mg) Smoking (control)	Smoking + Red wine (Dealcoholised) 15 mins - ↓1.15% from baseline FMD % 30 mins - ↑0.28% from baseline FMD % 60 mins - ↓0.14% from baseline FMD % 90 mins - ↓0.69% from baseline FMD % Smoking + Red wine (Alcoholised) 15 mins - ↓1.67% from baseline FMD % 30 mins - ↓1.74% from baseline FMD % 60 mins - ↓0.92% from baseline FMD % 90 mins - ↓0.74% from baseline FMD % Smoking 15 mins - *↓4.61% from baseline FMD % 30 mins - *↓4.25% from baseline FMD % 60 mins - *↓2.42% from baseline FMD % 90 mins - ↓1.30% from baseline FMD %
hou et al. (2001) ⁷⁰ n=22, 82% M	Whole food	Parallel	CAD	Chronic (8 wk)	64 ± 10	NR	Purple grape juice (8ml/kg/day) - High dose Purple grape juice (4ml/kg/day) - Low dose	High dose - ↑2.0 ± 4.3% from baseline FMD % Low dose - ↑2.0 ± 3.6% from baseline FMD %
shimoto et al. (2001) ⁷² n=11, 100% M	Whole food	Crossover	Healthy	Acute (120 min)	34 ± 1	NR	Red wine (0.8g/kg ethanol) - 500ml Red wine (dealcoholised) - 500ml Japanese vodka (0.8g/kg ethanol) - 500ml Control (Water) - 500ml	Red wine (Dealcoholised) 30 mins - **↑4.8% from baseline FMD % 120 mins - **↑1.8% from baseline FMD % Red wine (Alcoholised) 30 mins - ↓0.1% from baseline FMD % 120 mins - **↑1.6 from baseline FMD % Japanese vodka 30 mins - *↓2.0 from baseline FMD % 120 mins - *↓2.4 from baseline FMD % Control 30 mins - ↑0.8% from baseline FMD % 120 mins - ↑0.7%from baseline FMD %
Martelli et al. (2021) ¹⁸⁵ n=30, 100% M	Extract	Parallel	Healthy	Chronic (12 wk)	24.46 ± 2.99	22.30 ± 4.87	Taurisolo 400mg x 2/d (TPC ND, Anthocyanins ND, Epicatechin 1.36mg, Catechin 1.99mg, Resveratrol 0.01mg) Control - Maltodextrin	Taurisolo - *↑5.00% from baseline FMD % Control - ↓0.07% from baseline FMD %
Odai et al. (2019) ¹⁸⁶ n=30, 100% M	Extract	Parallel	Prehypertension	Chronic (12 wk)	53.7 ± 7.7	23.4 ± 3.4	Low-dose (200mg/d) High-dose (400mg/d) Control ~85% proanthocyanidin and flavan-3-ol monomers	Low dose - ↓0.9% from baseline FMD % High dose - ↓1.2% from baseline FMD % Placebo - ↑0.1% from baseline FMD %

	Lee et al. (2019) ¹⁸⁷ n=11, 100% M	Extract	Crossover	Postmenopausal women	Chronic (4 wk)	53.6 ± 0.8	22.88	Grape seed extract (TPC 300mg) Control (NR)	Grape seed extract - ***↑5.5% from baseline FMD% Control - ↓4.6% from baseline FMD %
	Greyling et al. (2016) n=51, 100% M	Extract	Crossover	Hypertensive (on diuretic monotherapy)	Chronic (8 wk)	46.8 ± 9.0	26.1 ± 2.1	Grape/Wine extract (TPC 800mg (Anthocyanins 140.66mg, Phenolic acids 9.68mg, Flavan-3-ols 39.52mg, Epicatechin 10.64mg, Catechin 11.25mg, Flavonols 9.31mg, Stilbenes 0.92mg) Control (microcrystalline cellulose)	Grape/Wine extract - ↑0.2% from baseline FMD% Control - ↑0.4% from baseline FMD%
	Chaisman & Niv (2015) n=50, 100% M	Extract	Parallel	Pre & stage 1 hypertension	Chronic (12 wk)	57.5	27.46	RGC 200mg (TPC 11.2mg, Anthocyanins 1.34mg, Catechin 2.6mg, Resveratrol 3mg) RGC 400mg (TPC 22.4mg, Anthocyanins 2.68mg, Catechin 5.2mg, Resveratrol 6mg)	RGC 200mg - ↑1.13% from baseline FMD % RGC 400mg - **↑2.1% from baseline FMD % Control - ↑0.23% from baseline FMD %
	Clark et al. (2015) ⁶⁸ n=36, 42% M	Extract	Parallel	Prehypertension	Chronic (12 wk)	44 ± 10	32.5	Grape seed extract 150mg x 2/day (TPC 528.24mg, gallic acid 9.94mg, Epicatechin 12.78mg, Catechin 9.94mg) Control x2/day (TPC 236mg, gallic acid 0.5mg/l, Epicatechin ND, Catechin ND)	Grape seed extract - *↑0.3% from baseline FMD% Control - *↓1.7% from baseline FMD%
	Corona et al. (2012) ⁷⁶ n=35, 100% M	Extract	Crossover	Metabolic syndrome	Chronic (30 d)	30-70	NR	Freeze-dried grape powder 46g/d (TPC 266.8mg, Flavans 188.6mg, Anthocyanins 35.4mg, Flavonols 1.68mg, Quercetin 1.42mg, Myricetin 0.12mg, Kaempferol 0.14mg, Resveratrol 0.07mg) *reconstituted* Control (Macronutrient matched placebo)	Freeze-dried grape powder - *↑1.70% from control FMD% Control - 4.00% FMD
	Mellen et al. (2010) ⁷⁹ n=50, 100% M	Extract	Crossover	CVD risk	Chronic (6 wk)	55 ± 10	30 ± 4	Muscadine grape seed supplement (MGS) (TPC 83.98mg, Proanthocyanidins 92.12mg, Gallic Acid 1.99mg, Ellagic Acid 1.33mg, and Catechins 0.10mg (Catechin 0.10mg, Epicatechin 7.03mg, Catechin Gallate 0.03mg, Epicatechin Gallate 0.35mg, Epigallocatechin 0.002mg, Epigallocatechin Gallate 0.0006mg, and Resveratrol 0.0039mg) Control (methylcellulose USP powder)	MGS - ↓0.65% from baseline FMD % Control - ↓0.09% from baseline FMD %
	Weseler et al. (2010) ¹⁸⁸ n=28, 100% M	Extract	Parallel	Healthy	Chronic (6 wk)	MOF Supplement 46 (30-56) Control 48 (30-60)	MOF Supplement 24 ± 1 Control 25 ± 1	MOF Supplement 100mg x 2 (Total Catechins 51.2mg (including (+)-Catechin 21.8mg, (-)-Epicatechin 24.4mg, and (-)-Epicatechin-3-O-gallate 5.0mg). Total Dimers amount to 55.0mg, comprising Proanthocyanidin B1 15.4mg, Proanthocyanidin B2 16.6mg, Proanthocyanidin B3 5.6mg, Proanthocyanidin	MOF Supplement 4 wk - ↓0.5% from baseline FMD % 8 wk - 0% change from baseline FMD % Control 4 wk - ↓0.1% from baseline FMD % 8 wk - ↓1.1% from baseline FMD %



Can Mierlo et al. (2010) ¹⁸⁹ n=35, 100% M	Extract	Crossover	Healthy males	Chronic (2 wk)	31.4 ± 9.0	23.2 ± 2.5	B4 3.2mg, and Proanthocyanidin B2-gallate 14.2mg) Control (microcrystalline cellulose) Grape seed solids - 6 x 500mg/d (TPC 800mg (Epicatechin 56mg, Catechin 64mg, Epicatechingallate 24mg) Wine/grape solids - 6 x 500mg/d (TPC 800mg (Anthocyanins 137.3mg, Phenolic acids 9.6mg, Catechin 4.2mg, Flavonols 0.9mg, Stilbenes 0.2mg) Control (microcrystalline cellulose)	GSE: After low-fat breakfast - ↑0.2 from Control FMD % After high-fat lunch - ↓0.2 from Control FMD % Wine/grape extract: After low-fat breakfast - ↓0.4 from Control FMD % After high-fat lunch - ↑0.7 from Control FMD % Control After low-fat breakfast - 3.9% FMD After high-fat lunch - 4.5% FMD
Ward et al. (2005) ¹⁹⁰ n=69, 70% M	Extract	Parallel	Treated hypertensive	Chronic (6 wk)	1) 59.5 ± 5.9 2) 61.3 ± 6.3 3) 62.3 ± 7.1 4) 63.6 ± 8.2	1) 28.7 ± 3.6 2) 27.7 ± 3.4 3) 28.6 ± 2.6 4) 29.3 ± 4.3	1) 500mg/day vitamin C and matched grape-seed (poly)phenol placebo 2) 1000mg/day grape-seed (poly)phenols and matched vitamin C placebo 3) 500mg/day vitamin C and 1000mg/day grape-seed (poly)phenols 4) Control (matched placebo tablets for both grape-seed (poly)phenols and vitamin C) Grape seed extract 2 x 1g (**TPC 592.5mg/g, gallic acid 49mg/g, catechin 41mg/g, epicatechin 66mg/g, proanthocyanidins 436.6mg CatechinEq/g**) Grape seed extract with Quercetin 2 x 1g+0.5g quercetin) Control (Yogurt (2 x 240g) <i>*Taken in Yogurt (2 x 240g)</i> <i>**https://www.sciencedirect.com/science/article/pii/S0027510708002571**</i>	1) ↑0.6 from baseline FMD % 2) ↑0.6 from baseline FMD % 3) ↓0.65 from baseline FMD %
Wifon et al. (2004) ⁷⁵ n=36, 67% M	Extract	Crossover	High-risk of CVD	Chronic (12 wk)	34-70	28.4	Grape seed extract 2 x 1g (**TPC 592.5mg/g, gallic acid 49mg/g, catechin 41mg/g, epicatechin 66mg/g, proanthocyanidins 436.6mg CatechinEq/g**) Grape seed extract with Quercetin 2 x 1g+0.5g quercetin) Control (Yogurt (2 x 240g) <i>*Taken in Yogurt (2 x 240g)</i> <i>**https://www.sciencedirect.com/science/article/pii/S0027510708002571**</i>	GSE - *↑1.1% from baseline FMD% GSE with Quercetin - ↓0.59 from baseline FMD % Control - ↓0.33 from baseline FMD %
Citrus fruit								
Li et al. (2020) ⁸¹ n=15, 33% M	Whole food	Crossover	Healthy	Acute (7 hr)	28.7 ± 6.5	29.8 ± 3.1	Blood orange juice 400ml/d; (Hesperidin 32.08mg, Narirutin 0.04mg) Control (Sugar-matched control drink)	Blood orange juice - **↑2.05% from baseline FMD % Control - ↓0.34% from baseline FMD %

Constans et al. (2015) n=25, 100% M	Whole food	Crossover	Mild hypercholesterol aemia	Chronic (4 wk)	53.8 ± 10	26 ± 5	Blood orange juice - 3 x 200ml/d (Hesperidin 266.25mg, Narirutin 37.43mg) Control (Matched placebo drink) - 3 x 200ml/day	Orange juice - **↑0.28% from baseline FMD % Control - ↓0.78% from baseline FMD %
Habauzit et al. (2015) n=52, 0% M	Whole food	Crossover	Healthy postmenopausal women	Chronic (6 Mth)	57.8 ± 3.7	25.7 ± 2.3	Grapefruit juice 340 mL/d (Naringenin glycosides 212.9mg) Control (Drink without flavonoids)	Grapefruit juice - ↓0.24% from baseline FMD % Control - ↑0.11% from baseline FMD %
Ascemi et al. (2012) n=33, 48% M	Whole food	Crossover	CVD risk	Chronic (1 wk)	CVR group - 48 ± 13 Control group - 35 ± 8	CVR group - 31.4 ± 2.9 Control group - 31.4 ± 3.5	Red orange juice 500 mL/d (TPC 419mg/l, Anthocyanins 71.3mg/L, Narirutin 43mg/L, Hesperidin 319mg/L) Control (Blend of water, sugars, and orange & colorants)	CVR Group: Red orange juice - **↑2.2% from baseline FMD % Control - ↓0.70% from baseline FMD % Healthy: Red orange juice - ↑0.1% from baseline FMD %
Valls et al. (2021) ⁸³ n=159, 67% M	Whole food / Extract	Parallel	Pre or stage 1 hypertension	Acute (2 – 6 hr) Chronic (12 wk)	Orange juice - 43.3 ± 12.0 Enriched OJ - 43.6 ± 11.8 Control - 45.4 ± 13.0	Orange juice - 26.4 ± 3.6 Enriched OJ - 26.1 ± 3.4 Control - 26.1 ± 3.8	Orange juice 500ml - (Hesperidin 345mg, Narirutin 64mg) Hesperidin-enriched orange juice 500ml - (Hesperidin 600mg, Narirutin 77.5mg) Control (Matched placebo drink) - 500ml	Orange juice 2 hrs - ↑0.45 AU from baseline IRH 4 hrs - ↑0.50 AU from baseline IRH 6 hrs - ↑0.70 AU from baseline IRH Enriched OJ 2 hrs - ↑1.00 AU from baseline IRH 4 hrs - ↑1.10 AU from baseline IRH 6 hrs - *↑1.45 AU from baseline IRH Control 2 hrs - ↑0.50 AU from baseline IRH 4 hrs - ↑0.70 AU from baseline IRH 6 hrs - ↑0.65 AU from baseline IRH OJ - *↓0.29% from baseline FMD % FOJ - **↓0.06% from baseline FMD % HWO - **↓0.05% from baseline FMD % Control - ↓3.70% from baseline FMD %
Rendeiro et al. (2016) ⁸⁶ n=28, 100% M	Whole food / Extract	Crossover	Healthy	Acute (7 hr)	48 ± 1	28.4 ± 0.4	Orange juice: 128.9mg/d; (Total flavonoids 128.88mg, Hesperidin 107.30mg, Narirutin 15.41mg, Others 6.17mg) Flavanone-rich orange juice: 272.1mg/d; (Total flavonoids 272.14mg, Hesperidin 220.46mg, Narirutin 34.54mg, Others 17.14mg)	Orange juice - *↓0.29% from baseline FMD % FOJ - **↓0.06% from baseline FMD % HWO - **↓0.05% from baseline FMD % Control - ↓3.70% from baseline FMD %



Macarro et al. (2020)	Extract	Parallel	Metabolic syndrome	Chronic (8 wk)	NR	NR	Homogenized whole orange: 452.8mg/d; (Total flavonoids 452.71, Hesperidin 352.80mg, Narirutin 76.58mg, Others 23.33mg) Control - Isocaloric drink; (Total flavonoids 0.10mg, Narirutin 0.08mg, Others 0.02mg) Citoven 500mg twice daily	Citoven - ***↑3.04 from baseline FMD % Control - ↑0.54% from baseline
Hashemi et al. (2015)	Extract	Parallel	Overweight / Obese	Chronic (1mth)	13.7 ± 7.0	23.38 ± 3.82	Lemon peel - 1000mg/d Sour orange peel - 1000mg/d Control (Cornstarch powder) - 1000mg/d	Lemon peel - ***↑6.49% from baseline FMD % Sour orange peel - ***↑7.24% from baseline FMD % Control - ↓0.05% from baseline FMD %
Alizadeh et al. (2011) ⁸⁵	Extract	Crossover	Metabolic syndrome	Chronic (4 wk)	52 ± 2	34.7 ± 1.5	Hesperidin extract - 500mg/d Control (Cellulose)	Hesperidin - *↑2.02% from baseline FMD % Control - ↓0.46% from baseline FMD %
Cocoa / Chocolate								
Payne et al. (2021)	Whole food		Healthy	Acute (2 hr)	23 ± 4.30	23.66 ± 3.19	hFCD (TPC 1052.5mg, Flavan-3-ols 681mg, Procyanidins 495.9mg, Epicatechin 150mg, Catechin 35.5mg), Theobromine 179.8mg, Caffeine 19.3mg IFCD (TPC 143mg, Flavan-3-ols 4.1mg, Procyanidins ND, Epicatechin <4mg, Catechin <4mg), Theobromine 179.8mg, Caffeine 19.3mg	hFCD - ***↑0.7% from baseline FMD % IFCD - ***↓1.0% from baseline FMD %
Marsh et al. (2017) ¹⁹¹	Whole food	Crossover	Postmenopausal women	Acute (80 min)	57.6 ± 4.8	24.3 ± 4.1	DC (TPC 394.8mg, Flavonoids 3600mg/kg, Epicatechin 587.1ug/g, Catechin 1394.2ug/g) MC (TPC 200.1mg, Flavonoids 980mg/kg, Epicatechin 288.4ug/g, Catechin 770.1ug/g) WC (TPC 34.9mg, Flavonoids 370mg/kg, Epicatechin ND, Catechin 38.4ug/g)	DC - ↑↑2.4% from baseline FMD % MC - ↓0.95% from baseline FMD % WC - ↑0.25% from baseline FMD %
Dower et al. (2016) ¹⁹²	Whole food	Crossover	Healthy	Acute (2 hr)	61.8 ± 9.3	25.1 ± 2.1	Dark chocolate - 70g and 2 x placebo capsules (Flavan-3-ols (DP1-10) 770mg, Flavan-3-ols (DP2-10) 578mg, Epicatechin 150mg, Catechin 42mg) White chocolate- 75g and 2 x epicatechin capsules (Epicatechin 150mg) White chocolate - 75g and 2 x placebo capsules (microcrystalline cellulose)	Dark chocolate - **↑0.96% from baseline FMD % Epicatechin - ↑0.75% from baseline FMD %
Pereira et al. (2014) ¹⁹³	Whole Food	Parallel	Healthy	Chronic (4 weeks)	20.23 ± 2.22	22.92 ± 3.66	10g dark chocolate (75% cocoa) Control - No intervention	Dark Chocolate - ***↑9.31% from baseline FMD % Control - ↑0.38% from baseline FMD %
Loffredo et al. (2014) ⁹¹	Whole Food	Crossover	PAD	Chronic (2 weeks)	69.9 ± 9	27 ± 3	Dark chocolate (TPC 799mg, Epicatechin 0.59 mg, Catechin 0.32 mg, Epigallocatechin gallate 1.8 mg) Control - Milk chocolate (TPC 296mg,	Dark Chocolate - **↑4.0% from baseline FMD % Control - ↑1.3% from baseline FMD %

Escher et al. (2013) ¹⁹⁴ n=41 100% M	Whole Food	Crossover	Overweight	Acute (2 hr) Chronic (4 weeks)	Acute - 64 ± 4 Chronic - 63 ± 5	Acute - 27.8 ± 2.6 Chronic - 27.6 ± 2.3	Epicatechin 0.16 mg, Catechin 0.13 mg, Epigallocatechin gallate 0.28 mg) High flavan-3-ol dark chocolate (1078 mg flavan-3-ols, 349 mg epicatechin) Normal flavan-3-ol dark chocolate (259 mg flavan-3-ols, 97 mg epicatechin)	Acute (2 hour) HFDC - ↓0.4% from baseline FMD % NFDC - ↑0.9% from baseline FMD % Chronic (4 weeks) HFDC - ↑1.2% from baseline FMD % NFDC - ↑0.9% from baseline FMD % Sugar-free cocoa - **↑2.4% from baseline FMD % Sugared-sweetened cocoa - **↑1.5% from baseline FMD % Control - ↓0.8% from baseline FMD %
van der Griend et al. (2011) ⁹⁵ n=44 85% M	Whole Food	Crossover	Overweight	Chronic (6 weeks)	52.2 ± 11	30.5 ± 3.4	Sugar-free cocoa (Total procyanidins 805mg, catechin 21mg, epicatechin 48mg, procyanidin dimer 92mg, procyanidin trimer 98mg, procyanidin tetramer 31mg, procyanidin pentamer and hexamer 55mg) – theobromine 436mg, caffeine 28mg Sugar-sweetened cocoa (Total procyanidins 805mg, catechin 21mg, epicatechin 48mg, procyanidin dimer 92mg, procyanidin trimer 98mg, procyanidin tetramer 31mg, procyanidin pentamer and hexamer 55mg) – theobromine 436mg, caffeine 28mg Control - Placebo drink (no cocoa) High-Flavan-3-ol Cocoa (Total flavan-3-ols 918.00 mg, monomers 145.96 mg, epicatechin 120.25 mg, catechin 29.37 mg, dimers 113.83 mg, trimers-decamer 383.72 mg) - theobromine 210 mg, caffeine 40 mg Control - Low-Flavan-3-ol Cocoa (Total flavan-3-ols 14.68 mg, monomers 2.93 mg, epicatechin 0.73 mg, catechin 1.38 mg, dimers 4.77 mg, trimers-decamer 6.97 mg) - theobromine 220 mg, caffeine 40 mg. <i>*Postprandial - Fatty Meal</i> Treatment 1 - Placebo drink (Total flavan-3- ols 0 mg, epicatechin 0 mg) – theobromine 329 mg, caffeine 25 mg. Treatment 2 - Low-flavan-3-ol cocoa (Total flavan-3-ols 80 mg, epicatechin 17 mg) – theobromine 329 mg, caffeine 25 mg. Treatment 3 - Moderate-flavan-3-ol cocoa (Total flavan-3-ols 200 mg, epicatechin 42 mg) – theobromine 329 mg, caffeine 25 mg. Treatment 4 - High-flavan-3-ol cocoa (Total flavan-3-ols 500 mg, epicatechin 105 mg) – theobromine 329 mg, caffeine 25 mg. Treatment 5 - Very high-flavan-3-ol cocoa (Total flavan-3-ols 800 mg, epicatechin 168 mg) – theobromine 329 mg, caffeine 25 mg.	
Westphal & Luley (2010) ¹⁹⁵ n=18 11% M	Whole Food	Crossover	Healthy	Acute (6 hr)	25.2 ± 2.5	22.8 ± 2.0		High-Flavan-3-ol Cocoa 2 hours - ***↓1.1% from baseline FMD % 4 hours - *↓0.5% from baseline FMD % 6 hours - ↓0.3% from baseline FMD % Control 2 hours - ↓2.0% from baseline FMD % 4 hours - ↓0.9% from baseline FMD % 6 hours - ↓0.3% from baseline FMD %
Grassi et al. (2015) ¹⁹⁶ n=20 85% M	Whole Food	Crossover	Healthy	Chronic (1 weeks)	53.8 ± 8.9	25.4 ± 2.4		Treatment 2 - *↑1.07% from control FMD % Treatment 3 - *↑1.44% from control FMD % Treatment 4 - *↑1.97% from control FMD % Treatment 5 - *↑2.02% from control FMD %



Hammer et al. (2015) n=21 71% M	Whole Food	Crossover	PAD	Acute (2 hour)	66.9	NR	Dark chocolate (TPC 780mg, Epicatechin 45 mg, Catechin 13.5 mg) Control - Milk chocolate	Dark Chocolate - ↑0.4% from baseline FMD % Control - ↓2.0% from baseline FMD %
Leiss et al. (2010) ¹⁹⁸ n=16 100% M	Whole Food	Crossover	CAD	Chronic (4 week)	64 ± 3	27.8 ± 1.8	HiFi (Total Flavan-3-ol 375mg, Monomers 65mg, Epicatechin 59mg, Catechin 6mg, Dimers 53mg, Trimers-decamers 258mg) - theobromine 93mg, caffeine 11mg. Control - LoFi (Total Flavan-3-ol 9mg, Monomers 3mg, Epicatechin 1mg, catechin 2mg, Dimers 2mg, Trimers-decamers 3mg) - theobromine 96mg, caffeine 9mg.	HiFi - ***↑3.8% from baseline FMD % Control - ↑1.3% from baseline FMD %
Faridi et al. (2008) ⁹⁵ n=45, 22% M	Whole food	Parallel	Overweight	Acute (2 hr)	52.8 ± 11.	30.1 ± 3.3	Placebo chocolate (TPC ND, Flavan-3-ol ND, Epicatechin ND, Catechin ND, Procyanidin dimer ND, Procyanidin trimer ND, Procyanidin tetramer ND, Procyanidin penta/hexamer ND) Solid dark chocolate (TPC 3282mg, Flavan-3-ol 821mg, Epicatechin 21.5mg, Catechin 10.4mg, Procyanidin dimer 81.4mg, Procyanidin trimer 67.3mg, Procyanidin tetramer 37mg, Procyanidin penta/hexamer 67mg) Sugar-free cocoa (TPC 3282mg, Flavan-3-ol 805.2mg, Epicatechin 48.4mg, Catechin 20.9mg, Procyanidin dimer 92mg, Procyanidin trimer 98.1mg, Procyanidin tetramer 30.6mg, Procyanidin penta/hexamer 54.8mg) Sugared cocoa (TPC 3282mg, Flavan-3-ol 805.2mg, Epicatechin 48.4mg, Catechin 20.9mg, Procyanidin dimer 92mg, Procyanidin trimer 98.1mg, Procyanidin tetramer 30.6mg, Procyanidin penta/hexamer 54.8mg) Placebo cocoa (TPC 17.6mg, Flavan-3-ol 8.8mg, Epicatechin ND, Catechin ND, Procyanidin dimer ND, Procyanidin trimer 3.3mg, Procyanidin tetramer ND, Procyanidin penta/hexamer 5.5mg)	Placebo chocolate - ↓1.8% from baseline FMD % Solid dark chocolate - ***↑4.3% from baseline FMD % Sugar-free cocoa - ***↑5.7% from baseline FMD % Sugared cocoa - ***↑2.0% from baseline FMD % Placebo cocoa - ↓1.5% from baseline FMD %
Davison et al. (2008) ¹⁹⁹ n=49 37% M	Whole Food	Parallel	Healthy	Chronic (12 weeks)	HF+Ex - 45.2 ± 4.0 HF+Ex - 45.5 ± 4.0 LF+Ex - 44.4 ± 4.4 LF+Ex - 45.3 ± 4.4	HF+Ex - 33.5 ± 1.1 HF+Ex - 33.2 ± 1.6 LF+Ex - 34.5 ± 1.8 LF+Ex - 32.8 ± 1.1	High-Flavan-3-ol Cocoa Drink (Flavan-3-ols 451mg) - theobromine 337 mg, caffeine 18 mg. Control Cocoa Drink (Flavan-3-ols 18mg) - theobromine 327 mg, caffeine 21 mg.	No exercise HF+Ex - *↑1.8% from baseline FMD % LF+Ex - ↓0.3% from baseline FMD % Exercise HF+Ex - *↑1.5% from baseline FMD % LF+Ex - ↓0.4% from baseline FMD %

Hammer et al. (2008) ⁹³ n=49 37% M	Whole Food	Parallel	CHF	Acute (2 hr) Chronic (4 weeks)	FRC - 60.3 ± 10.1 CC - 58.1 ± 11.9	FRC - 25.9 ± 5.1 CC - 25.6 ± 3.5	Flavanoid-rich chocolate (TPC 624mg, Epicatechin 36mg, Catechin 10.8mg) Control chocolate	Acute (2 hour) FRC - *↑1.0% from baseline FMD % Control - ↓0.59% from baseline FMD % Chronic (4 weeks) FRC - **↑1.88% from baseline FMD % Control - ↓1.02% from baseline FMD %
Grassi et al. (2008) ²⁰¹ n=19 58% M	Whole Food	Parallel	Hypertensive	Chronic (2 weeks)	44.8 ± 8.0	26.5±1.9	Dark Chocolate (TPC 1008mg, Epicatechin 110.9mg, Catechin 36.12mg, quercetin 2.5mg, kaempferol 0.03mg, isohamnetin 0.2mg) - theobromine 1.7mg, caffeine 136mg. Control - White Chocolate (Epicatechin 0.13mg, Catechin 0.04mg)	Dark Chocolate - ***↑1.4% from baseline FMD % Control - ↑0.2% from baseline FMD %
Walzer et al. (2008) ⁹⁴ n=41 29% M	Whole Food	Crossover (feasability) Parallel (efficay)	T2DM	Acute (6 hr) Chronic (4 weeks)	Feasibility - 64.7 ± 9.9 Treatment - 63.1 ± 8.3 Control - 64.4 ± 8.6	Feasibility - 27.8 ± 3.6 Treatment - 32.1 ± 5.1 Control - 31.1 ± 5.1	High-Flavan-3-ol Cocoa Drink (Flavan-3-ols 963mg, Monomers 253.8 mg, epicatechin 203.0 mg, catechin 50.8 mg, dimers 180.9 mg, trimers-decamer 528.3 mg) - theobromine 586.2 mg, caffeine 31.8 mg. Medium-Flavan-3-ol Cocoa Drink (Flavan-3-ols 371mg, Monomers 98.6 mg, epicatechin 78.9 mg, catechin 19.7 mg, dimers 74.3 mg, trimers-decamer 198.1 mg) - theobromine 575.6 mg, caffeine 35.2 mg. Control Cocoa Drink (Flavan-3-ols 371mg, Monomers 21.0 mg, epicatechin 16.8 mg, catechin 4.2 mg, dimers 21.0 mg, trimers-decamer 30.3 mg) - theobromine 570.3 mg, caffeine 36.9 mg. hFCD - 100ml (Total Flavan-3-ol 185mg, Monomers 74mg, Epicatechin 22mg, Procyanidins 111mg) Control - IFCD (Total Flavan-3-ol <11mg, Monomers <1mg, Epicatechin <1mg, Procyanidins <11.4mg)	Acute (2 hour) High-Flavan-3-ol - *↑1.8% from baseline FMD % Medium-Flavan-3-ol - ↑0.9% from baseline FMD % Control - ↑0.2% from baseline FMD % Chronic (8 Days) Medium-Flavan-3-ol x3/day - ***↑0.8% from baseline FMD % Control - ↓0.4% from baseline FMD % Chronic (4 weeks) Medium-Flavan-3-ol x3/day - *↑1.0% from baseline FMD % Control - ↑0.1% from baseline FMD %
Heiss et al. (2007) ⁹⁰ n=11, 100% M	Whole food	Crossover	Healthy smokers	Acute (2 hr) Chronic (1 wk)	27 ± 1	22 ± 1		Acute: (100 ml) Day 1 - ↑12.4% from baseline FMD % Chronic (300ml) Day 3 - ↑12.4% from baseline FMD % Day 5 - ↑12.7% from baseline FMD % Day 8 - ↑12.4% from baseline FMD %



Vang-Polagruto et al. (2006) ²⁰² n=32, 0% M	Whole Food	Parallel	Postmenopausal women	Chronic (6 weeks)	HCF- 57.7 ± 2.2 LCF - 55.4 ± 1.7	HCF - 24.9 ± 1.0 LCF - 25.3 ± 0.8	High Cocoa Flavan-3-ol (Total Flavan-3-ols 446mg) Control - Low Cocoa Flavan-3-ol (Total Flavan-3-ols 43mg)	HFC - **↑2.0% from baseline FMD % Control - ↓1.5% from baseline FMD %
Chroetaler et al. (2006) ²⁰³ n=10, 100% M	Whole food	Crossover	Healthy	Acute (2 hr)	25–32	19-23	hFCD (Flavan-3-ols 917mg) IFCD (Flavan-3-ols 37mg)	hFCD - *↑~5.65% from baseline FMD % IFCD - ↓0.05% from baseline FMD %
Fisher & Hollenberg (2006) ²⁰⁴ n=34, 38% M	Whole food	Crossover	15 young adults 19 older adults	Chronic (4 wk)	47.9 ± 3.0	Young - 28.4 ± 1.3 Older - 28.0 ± 1.9	hFCD (TPC 910.2mg, Flavan-3-ol 821mg, Epicatechin 9.2mg, Catechin 10.7mg, and Flavan-3-ol oligomers 69.3mg) IFCD (TPC ND, Flavan-3-ol ND, Epicatechin ND, Catechin ND, and Flavan-3-ol oligomers ND)	Younger - **↑3.5% from baseline FMD % Older - **↑4.5% from baseline FMD %
Reiss et al. (2005) ⁸⁹ n=11, 55% M	Whole food	Crossover	Healthy smokers	Acute (2 hr)	30 ± 1	21.8 ± 0.7	hFCD (Total Flavan-3-ol 306mg, Monomers 74mg, Epicatechin 59mg, Catechin 15mg, Dimers 57mg. Trimer-decamers 175mg) Control - IFCD (Total Flavan-3-ol 312mg, Monomers 3mg, Epicatechin 2mg, Catechin 1mg, Dimers 2mg. Trimer-decamers 7mg)	Acute hFCD- *↑2.7% from baseline FMD % IFCD - ↓0.9% from baseline FMD %
Engler et al. (2004) ⁹³ n=22, 50% M	Whole food	Parallel	Healthy	Chronic (2 wk)	Low-flavanoid - 32.5 ± 2.9 High-flavanoid - 31.8 ± 3.2	Low-flavanoid - 21.9 ± 0.5 High-flavanoid - 23.2 ± 0.5	HFC (TPC 259mg, Procyanidins 213mg, Epicatechin 46mg) LFC (TPC 0mg, Procyanidins 0mg, Epicatechin 0mg)	HFC - **↑1.3% from baseline FMD % LFC - ↓0.96% from baseline FMD %
Rodriguez-Mateos et al. (2018) ⁹⁶ n=45, 100% M	Extract	Parallel	Healthy	Acute (2 hr) Chronic (4 wk)	DP1-10 - 23 ± 2 DP2-10 - 25 ± 2 Control - 23 ± 2	DP1-10 - 23.6 ± 0.5 DP2-10 - 24.1 ± 2.2 Control - 23.1 ± 2.4	DP1-10 Cocoa flavan-3-ols extract (Total Flavan-3-ol 690mg, Epicatechin 130mg, Dimers-decamers 560mg) DP2-10 Cocoa flavan-3-ols extract (Total Flavan-3-ol 560mg, Epicatechin 20mg, Dimers-decamers 540mg) Control (Matched placebo)	Acute Chronic DP1-10 - *↑1.8% from baseline FMD % DP2-10 - ↓0.1% from baseline FMD % Control - ↑0.4% from baseline FMD %
Sansone et al. (2015) ⁹² n=100, 52% M	Extract	Crossover	Healthy	Chronic (4 wk)	Flavan-3-ol - 45 ± 8 Control - 44 ± 9	Flavan-3-ol - 25 ± 3 Control - 26 ± 3	Intervention (TPC 523mg, Flavan-3-ol 450mg, Epicatechin 64mg, Catechin 9mg) Control (TPC ND, Flavan-3-ol ND, Epicatechin ND, Catechin ND)	Chronic - ↑1.2% from baseline FMD % Acute - ↑0.7% from baseline FMD % Acute - ↑0.1% from baseline FMD %

Coffee								
Yajikawa et al. (2019) ¹⁰⁵ n=37, 70% M	Whole Food	Crossover	Pre - or stage 1 hypertension	Acute (2hr)	Study 1 (S1): 53 ± 19 Study 2 (S2): 56 ± 15	Study 1 (S1): 24.5 ± 4.1 Study 2 (S2): 23.2 ± 3.2	Beverage A (Chlorogenic acids 412 mg, Hydroxyhydroquinone: 0.11 mg) Beverage B (Chlorogenic acids 373 mg, Hydroxyhydroquinone 0.76 mg) Beverage C (Chlorogenic acids: 0 mg, Hydroxyhydroquinone: 0.1 mg) LPC (Chlorogenic acids 89mg, 3-Caffeoylquinic acid 20mg, 4-Caffeoylquinic acid 22mg, 3-Feruloylquinic acid 4mg, 5-Caffeoylquinic acid 29mg, 4-Feruloylquinic acid 4mg, 5-Feruloylquinic acid 5mg, 3, 4-Dicaffeoylquinic acid 2mg, 3, 5-Dicaffeoylquinic acid 1mg, 4, 5-Dicaffeoylquinic acid 2mg) HPC (Chlorogenic acids 310mg, 3-Caffeoylquinic acid 43mg, 4-Caffeoylquinic acid 45mg, 3-Feruloylquinic acid 10mg, 5-Caffeoylquinic acid 124mg, 4-Feruloylquinic acid 6mg, 5-Feruloylquinic acid 24mg, 3, 4-Dicaffeoylquinic acid 23mg, 3, 5-Dicaffeoylquinic acid 17mg, 4, 5-Dicaffeoylquinic acid 2mg) Caffeinated (CC) ground coffee - 200ml x 2 (270 mg caffeine) CC (TPC 300mg, 5-chlorogenic acid 95mg) Decaffeinated (DC) ground coffee - 200ml x 2 (ND caffeine) DC (TPC 287mg, 5-chlorogenic acid 132mg) Hot water (Control) - 200ml Treatment 1 (5-chlorogenic acid 450mg) Treatment 2 (5-chlorogenic acid 900mg) Treatment 3 (Epicatechin 200mg) Control (Maltodextrin) Coffee bean (poly)phenols (TPC/CGA 600 mg; Caffeoylquinic Acids 349.8 mg (3-CQA, 4-CQA, 5-CQA), Feruloylquinic Acids 119.4 mg (3-FQA, 4-FQA, 5-FQA), Dicaffeoylquinic Acids 130.8 mg (3,4-diCQA, 3,5-diCQA, 4,5-diCQA)) Placebo - no coffee bean (poly)phenols beverage	Study 1: Beverage A - ↑1.5% from baseline FMD % Beverage B - ↑1.0% from baseline FMD % Study 2: Beverage A - ↑1.5% from baseline FMD % Beverage C - ↓0.4% from baseline FMD % 1 hour LPC - *↑1.10% from baseline FMD % HPC - **↑1.34% from baseline FMD % Control - ↑0.07% from baseline FMD % 3 hours LPC - ↑0.25% from baseline FMD % HPC - ↓0.1% from baseline FMD % Control - ↓0.45% from baseline FMD % 5 hours LPC - *↑0.79% from baseline FMD % HPC - ***↑1.52% from baseline FMD % Control - ↓0.46% from baseline FMD %
Leon et al. (2017) ¹¹¹ n=12, 58.3% M	Whole Food	Crossover	Healthy	Acute (2hr)	59.4 ± 6.4	24.7 ± 3.3		CC - ↑6.1% from 0% continuous FMD % DC - ↑6.0% from 0% continuous FMD % Control - ↑4.9% from 0% continuous FMD %
Ward et al. (2016) ¹²⁰ n=16, 37.5% M	Whole Food	Crossover	Healthy	Acute (1hr)	59.9 ± 8.2	24.7 ± 3.3		Treatment 1 - *↑0.6% from baseline FMD % Treatment 2 - *↑1.1% from baseline FMD % Treatment 3 - ↑0.9% from baseline FMD % Control - ↑0.4% from baseline FMD %
Ochiai et al. (2015) ¹²¹ n=13, 100% M	Whole Food	Crossover	Healthy	Acute (2hr)	44.9 ± 1.3	21.9 ± 0.5		Coffee bean (poly)phenols 1 hour - ↓0.50% from baseline FMD % 2 hours - ↑0.70% from baseline FMD % 4 hours - ↓0.00% from baseline FMD % 6 hours - *↓0.20% from baseline FMD % Control Beverage 1 hour - ↑0.40% from baseline FMD % 2 hours - ↓0.10% from baseline FMD % 4 hours - ↓0.90% from baseline FMD % 6 hours - ↑↓1.90% from baseline FMD % CC - *↑1.7% from baseline FMD % DC - ↑1.6% from baseline FMD %
Buscemi et al. (2010) ¹⁰¹ n=20, 50% M	Whole Food	Crossover	Healthy	Acute (1hr)	31 ± 2	23.9 ± 0.7	Caffeinated (CC) Italian espresso coffee - 25ml (caffeine:130 mg) Decaffeinated (DC) Italian espresso coffee - 25ml (caffeine: 5 mg)	

Buscemi et al. (2009) ¹⁰⁰ n=15, 53% M	Whole Food	Crossover	Healthy	Acute (1hr)	29 ± 3	24.3 ± 0.9	Decaffeinated espresso coffee - 25 ml x 2 (10 mg caffeine) Decaffeinated espresso coffee - 25 ml (5 mg caffeine).	x1 cups - ↑1.6% from baseline FMD % x2 cups - ***↑3.4% from baseline FMD %
Apamichael et al. (2005) ¹⁰⁰ n=17, 53% M	Whole Food	Crossover	Healthy	Acute (0.5 -2hr)	28.9 ± 3.0	NR	Caffeinated (CC) instant coffee - 200ml (80 mg caffeine) Decaffeinated (DC) instant coffee - 200ml (<2 mg caffeine)	CC (30 min) - **↓4.92 from baseline FMD % CC (1hr)- ***↓5.66 from baseline FMD % DC (30 min) - ↓0.83 from baseline FMD % DC (1hr) - ↓1.86 from baseline FMD %
Agudelo-Ochoa et al. (2016) ²⁰⁶ n=75, 51% M#	Whole Food	Parallel	Healthy	Chronic (8 weeks)	38.5 ± 9	24.1 ± 2.6	High CGA coffee (Chlorogenic acid 780 mg, Cafesol 0.75mg, Kahweol 0.92mg) Medium CGA coffee (Chlorogenic acid 420 mg, Cafesol 0.75mg, Kahweol 0.89mg) Control - No coffee consumption	HCCGA - ↓0.2% from baseline FMD % MCCGA - ↑5.9% from baseline FMD % Control - ↑5.2% from baseline FMD %
Schiai et al. (2009) ²⁰⁷ n=21 -% M	Whole Food	Parallel	Healthy	Chronic (8 weeks)	30 - 64 years	Active: 24.2 ± 0.9 Placebo: 24.2 ± 1.1	Hydroxyhydroquinone (HHQ)-reduced coffee (Chlorogenic acid 300mg, Hydroxyhydroquinone 0.03mg) HHQ/CGA-reduced coffee (Chlorogenic acid 0mg, Hydroxyhydroquinone 0.03mg) Control - Canned coffee (Chlorogenic acid 134mg, Hydroxyhydroquinone 0.12mg)	Active (2 weeks) - ↑↑3.3% from baseline FMD % Placebo (2 weeks) - ↓0.6% from baseline FMD %
Taylor et al. (2021) n=18, 83% M	Extract	Crossover	Healthy	Acute (1 - 24hr)	56.2 ± 5.2	27.5 ± 3.7	Decaffeinated green coffee extract (DGCE) Dose 1 (TPC/CGA 156.4 mg; 156.4 mg; 3-O-Caffeoylquinic Acid 30.0 mg, 4-O-Caffeoylquinic Acid and 3-O-Feruloylquinic Acid 39.0 mg, 5-O-Caffeoylquinic Acid 38.1 mg, 3,4-O-Dicaffeoylquinic Acid 12.5 mg, 3,5-O-Dicaffeoylquinic Acid 4.6 mg, 4,5-O-Dicaffeoylquinic Acid 9.8 mg, 4-O-Feruloylquinic Acid 9.3 mg, 5-O-Feruloylquinic Acid 12.1 mg, Caffeic Acid 0.6 mg, Ferulic Acid 0.3 mg) Dose 2 (TPC/CGA 312.8 mg; 3-O-Caffeoylquinic Acid 60.0 mg, 4-O-Caffeoylquinic Acid and 3-O-Feruloylquinic Acid 78.1 mg, 5-O-Caffeoylquinic Acid 76.2 mg, 3,4-O-Dicaffeoylquinic Acid 25.0 mg, 3,5-O-Dicaffeoylquinic Acid 9.2 mg, 4,5-O-Dicaffeoylquinic Acid 19.6 mg, 4-O-Feruloylquinic Acid 18.7 mg, 5-O-Feruloylquinic Acid 24.2 mg, Caffeic Acid 1.3 mg, Ferulic Acid 0.7 mg) Dose 3 (TPC/CGA 439.9 mg; 3-O-Caffeoylquinic Acid 84.3 mg, 4-O-Caffeoylquinic Acid and 3-O-Feruloylquinic Acid 109.8 mg, 5-O-Caffeoylquinic Acid 107.1 mg, 3,4-O-Dicaffeoylquinic Acid 35.2 mg, 3,5-O-Dicaffeoylquinic Acid 13.0 mg, 4,5-O-Dicaffeoylquinic Acid 27.5 mg, 4-O-Feruloylquinic Acid 26.3 mg, 5-O-	1 Hour Dose 1 (302 mg) - ↓0.01% from baseline FMD % Dose 2 (604 mg) - ↑0.69% from baseline FMD % Dose 3 (906 mg) - ↑0.46% from baseline FMD % Control (Placebo) - ↑0.35% from baseline FMD % 3 Hours Dose 1 (302 mg) - ↑0.45% from baseline FMD % Dose 2 (604 mg) - ↑0.47% from baseline FMD % Dose 3 (906 mg) - ↑0.69% from baseline FMD % Control (Placebo) - ↑0.85% from baseline FMD % 5 Hours Dose 1 (302 mg) - ↑0.75% from baseline FMD % Dose 2 (604 mg) - ↑1.09% from baseline FMD % Dose 3 (906 mg) - ↑0.99% from baseline FMD % Control (Placebo) - ↑0.17% from baseline FMD % 7 Hours Dose 1 (302 mg) - ↑0.90% from baseline FMD % Dose 2 (604 mg) - ↑1.17% from baseline FMD % Dose 3 (906 mg) - ↑0.75% from baseline FMD % Control (Placebo) - ↑1.11% from baseline FMD % 8.5 Hours Dose 1 (302 mg) - *↑1.93% from baseline FMD % Dose 2 (604 mg) - ↑1.10% from baseline FMD % Dose 3 (906 mg) - ↑1.36% from baseline FMD % Control (Placebo) - ↑0.86% from baseline FMD % 10 Hours Dose 1 (302 mg) - ↑1.24% from baseline FMD % Dose 2 (604 mg) - ↑1.36% from baseline FMD % Dose 3 (906 mg) - ↑1.32% from baseline FMD %



Mubarak et al. (2012)²¹¹
n=23, 17% M

Tea

Sanguigni et al. (2017)²¹²
n=14 50% M

Lorenz et al. (2017)⁴²
n=50 100% M

Uzaki et al. (2019) ²¹⁰ n=34, 100% M	Extract	Parallel	Healthy	<i>Chronic (2 weeks)</i>	44.6 ± 5.3	21.9 ± 1.7
Okura et al. (2015) ²¹⁰ n=19, 100% M	Extract	Crossover	Healthy	<i>Acute (4hr)</i>	21.8 ± 2.3	38.1 ± 8.4
Mubarak et al. (2012) ²¹¹ n=23, 17% M	Extract	Crossover	Healthy	<i>Acute (2hr)</i>	52.3 ± 10.6	25.6 ± 4.7
Sanguigni et al. (2017) ²¹² n=14 50% M	Whole Food / Extract	Crossover	Healthy	Acute (2 hr)	38 ± 3	NR
Lorenz et al. (2017) ⁴² n=50 100% M	Whole Food / Extract	Crossover	Healthy	Acute (2 hr)	33.9 ± 7.6	23.7 ± 2.5

Feruloylquinic Acid 34.0 mg, Caffeic Acid 1.8 mg, Ferulic Acid 0.9 mg)
Control - Maltodextrin

CGAs-enriched coffee bean extract (cGCE)
(Chlorogenic acid 300mg)
Water (Control) - 100ml
Coffee (poly)phenol extract containing beverage (TPC 355 mg; Chlorogenic Acids 256.02 mg (3-CQA, 4-CQA, 5-CQA), Feruloylquinic Acids 68.52 mg (3-FQA, 4-FQA, 5-FQA), Dicafeoylquinic Acids 29.47 mg (3,4-diCQA, 3,5-diCQA, 4,5-diCQA) and caffeine 54.9 mg)
Control (coffee-flavored , Free CGAs and 54.9 mg of caffeine)

CGA dissolved in water (3-O-cafeoylquinic acid 400mg)
Control (water) - 200ml

Ice cream + GTE (TPC 1817mg/ L GAE, catechin 1050mg, epicatechin 910mg)
Control - Milk chocolate ice cream (TPC 96mg/L GAE, catechin 6mg, epicatechin 3mg)

Brewed green tea (Gallic acid 15.65 mg, Gallocatechin 49.95 mg, Catechin 4.77 mg, Gallocatechin gallate 3.45 mg, Epicatechin 22.81 mg, Epicatechin gallate 39.38 mg, Epigallocatechin 62.32 mg, Epigallocatechin gallate 200.00 mg) - Theobromine 6.63 mg, Caffeine 117.13 mg.
Green tea extract (Gallic acid 5.36 mg, Gallocatechin 0.00 mg, Catechin 2.64 mg, Gallocatechin gallate 6.70 mg, Epicatechin 28.24 mg, Epicatechin gallate 28.64 mg, Epigallocatechin 58.91 mg, Epigallocatechin gallate 200.02 mg) - Theobromine 0.00 mg,

Control (Placebo) - ↑1.43% from baseline FMD %
12 Hours
Dose 1 (302 mg) - *↑1.37% from baseline FMD %
Dose 2 (604 mg) - ↑1.18% from baseline FMD %
Dose 3 (906 mg) - ↑1.19% from baseline FMD %
Control (Placebo) - ↑0.43% from baseline FMD %
24 Hours
Dose 1 (302 mg) - *↑0.75% from baseline FMD %
Dose 2 (604 mg) - ↑0.22% from baseline FMD %
Dose 3 (906 mg) - ↑0.70% from baseline FMD %
Control (Placebo) - ↓0.03% from baseline FMD %
cGCE - *↑0.6% from baseline FMD %
Control - ↓1.2% from baseline FMD %

60 mins
Coffee extract - ↓1.85% from baseline FMD %
Control - ↓3.15% from baseline FMD %
120 mins
Coffee extract - *↑0.08% from baseline FMD %
Control - ↓2.35% from baseline FMD %
180 mins
Coffee extract - *↑0.07% from baseline FMD %
Control - ↓0.95% from baseline FMD %
240 mins
Coffee extract - *↑0.1% from baseline FMD %
Control - ↓0.15% from baseline FMD %
CGA - ↑0.41% from control FMD %
Control - 9.60% FMD

Ice cream + GTE - ***↑3.9% from baseline FMD %
Control - ↓0.25% from baseline FMD %

Green Tea - **↑1.36% from baseline FMD %
Green Tea Extract - ↑0.18% from baseline FMD %
EGCG Supplement - ↓0.23% from baseline FMD %
Control - ↓0.84% from baseline FMD %



Buffy et al. (2001) ¹³⁰ n=50, 79% M	Whole food / Extract	Crossover	CAD	Acute (2 hr) Chronic (4 wk)	Water-first: 56 ± 8 Tea-first: 54 ± 8 Caffeine: 56 ± 8	Water-first: 30.9 ± 0.9 Tea-first: 28.4 ± 4.3 Caffeine: 31.5 ± 7.6	Caffeine 2.88 mg. EGCG supplement (Gallic acid 0.11 mg, Gallocatechin 0.00 mg, Catechin 0.15 mg, Gallocatechin gallate 0.00 mg, Epicatechin 1.07 mg, Epicatechin gallate 8.69 mg, Epigallocatechin 0.00 mg, Epigallocatechin gallate 200.30 mg) - Theobromine 0.00 mg, Caffeine 0.01 mg. Control - Hot water Brewed (TPC 733.5mg, Flavanoids 477mg, Epicatechin 6.3mg, Catechin 59.85mg, Epigallocatechin 9mg, Epicatechin gallate 27mg, Epigallocatechin gallate 17.55mg, Theoflavins 27mg) Freeze-dried (TPC 1350mg, Flavanoids 873mg, Epicatechin 19.8mg, Catechin 116.1mg, Epigallocatechin 207mg, Epicatechin gallate 32.4mg, Epigallocatechin gallate 27mg, Theoflavins 22.5mg) Water - 450ml (Acute) & 900ml (Chronic) Caffeine (200mg) Black tea (TPC 300mg, Catechins 24.2mg, Theaflavins 10mg, Gallic acid 9mg)	Acute Brewed- ***↑3.4% from baseline FMD % Water - ↓0.3% from baseline FMD % Chronic Freeze-dried black tea - ***↑3.5% from baseline FMD % Water - ↑0.1% from baseline FMD %
Grassi et al. (2016) ¹³¹ n=19, 26% M	Whole food	Crossover	Hypertensive	Chronic (1 wk)	51.3 ± 8.2	27.1 ± 1.2	Black tea (TPC 1188.24mg, Gallic acid 197.34 mg, Gallocatechin 186.72 mg, Epigallocatechin 164.16 mg, Catechin 105.42 mg, Epigallocatechin gallate 486.42 mg, Epicatechin 9.06 mg, Gallocatechin gallate 1.50 mg, Epicatechin gallate 37.62 mg) - caffeine 103.92 mg. Black tea + milk (TPC 1188.24mg, Gallic acid 197.34 mg, Gallocatechin 186.72 mg, Epigallocatechin 164.16 mg, Catechin 105.42 mg, Epigallocatechin gallate 486.42 mg, Epicatechin 9.06 mg, Gallocatechin gallate 1.50 mg, Epicatechin gallate 37.62 mg, Theobromine 40 mg, Theogallin 136 mg) - caffeine 103.92 mg. Control - Hot water Black tea (TPC 300mg, Catechins 24.2mg, Theaflavins 10mg, Gallic acid 9mg) Control (Matched placebo) - 100 - 200 ml x 2/d Black tea -150ml x 3 & 300ml (TPC 600mg, Flavanoids 500mg)	Chronic - ***↑3.8% from control baseline FMD % Acute on Chronic - ***↑1% from baseline FMD % Black tea - ***↑1.0% from control continuous FMD % Black tea + milk - ***↓0.64% control continuous FMD %
Grassi et al. (2016) ¹³¹ n=19, 26.3% M	Whole Food	Crossover	Hypertensive	Chronic (1 week)	51.3 ± 8.2	27.1 ± 1.2	Black tea (TPC 1188.24mg, Gallic acid 197.34 mg, Gallocatechin 186.72 mg, Epigallocatechin 164.16 mg, Catechin 105.42 mg, Epigallocatechin gallate 486.42 mg, Epicatechin 9.06 mg, Gallocatechin gallate 1.50 mg, Epicatechin gallate 37.62 mg, Theobromine 40 mg, Theogallin 136 mg) - caffeine 103.92 mg. Control - Hot water Black tea (TPC 300mg, Catechins 24.2mg, Theaflavins 10mg, Gallic acid 9mg) Control (Matched placebo) - 100 - 200 ml x 2/d Black tea -150ml x 3 & 300ml (TPC 600mg, Flavanoids 500mg)	Chronic - ***↑3.8% from control baseline FMD % Acute on Chronic - ***↑1% from baseline FMD %
Schreuder et al. (2014) ¹⁴² n=20, 40% M	Whole food	Crossover	Healthy	Acute (1.5 hr) Chronic (1 wk)	54 ± 8	25.1 ± 2.8	Black tea -150ml x 3 & 300ml (TPC 600mg, Flavanoids 500mg)	Black Tea - *↑1.4% from baseline FMD % Hot water - ↑0.1% from baseline FMD %

John et al. (2014) ¹⁴¹ n=77 35% M	Whole Food	Parallel	Healthy	Chronic (3-6 months)			Black tea (TPC 429 mg) Control	Chronic (3 months) Tea - ↓0.27% from baseline FMD % Control - ↑0.32% from baseline FMD % Chronic (6 months) Tea - ↓0.13% from baseline FMD % Control - ↑0.41% from baseline FMD % 100mg - **↑1.2% from control FMD % 200mg - **↑1.3% from control FMD % 400mg - ***↑1.8% from control FMD % 800mg - ***↑2.5% from control FMD % Black tea - ***↑4.1% from baseline FMD % Green tea - ***↑4.8% from baseline FMD % Hot water - ↑0.9% from baseline FMD %
Grassi et al. (2009) ²¹³ n=19, 100% M	Whole food	Crossover	Healthy	Chronic (1 wk)	32.9 ± 10.2	23.9 ± 2.5	Black tea - 150ml x 2 (100, 200, 400, 800mg flavonoids)	
Schumann et al. (2008) ¹⁴² n=24, 0% M	Whole food	Crossover	Postmenopausal women	Acute (2 hr)	58.7 ± 4.5	23.1 ± 1.7	Black tea (Total catechins 560uM, Epigallocatechin-3-gallate 324uM, Epicatechin gallate 116uM, Epigallocatechin 70uM, Epicatechin 50uM, Gallocatechin 0uM, Catechin 0uM, Gallic acid 91uM) Green tea (Total catechins 1012uM, Epigallocatechin-3-gallate 464uM, Epicatechin gallate 130uM, Epigallocatechin 257uM, Epicatechin 79uM, Gallocatechin 52uM, Catechin 30uM, Gallic acid 30uM)	
Frenz et al. (2007) ²¹⁴ n=16 0% M	Whole Food	Crossover	Postmenopausal	Acute (2 hr)	59.5 ± 5	23 ± 2	Black tea (TPC 505.52 mg, Gallic acid 30.96 mg, Epigallocatechin 42.88 mg, Epigallocatechin gallate 279.02 mg, Epicatechin 29.03 mg, Epicatechin gallate 102.63 mg) Black tea + milk (TPC 1188.24mg, Gallic acid 197.34 mg, Gallocatechin 186.72 mg, Epigallocatechin 164.16 mg, Catechin 105.42 mg, Epigallocatechin gallate 486.42 mg, Epicatechin 9.06 mg, Gallocatechin gallate 1.50 mg, Epicatechin gallate 37.62 mg) Control - Hot water	Black tea - **↑4.3% from control continuous FMD % Black tea + milk - ↑0.8% control continuous FMD % Control - ↑1.00% control continuous FMD %
Sapper et al. (2016) ²¹⁵ n=15 100% M	Extract	Crossover	Normoglycemic	Acute (2 hr)	25.3 ± 1.0	22.4 ± 1.8	Starch confection + GTE (Epigallocatechin gallate 489.1 mg, Epigallocatechin 144.5 mg, Epicatechin gallate 65.7 mg, Epicatechin 75.5 mg) - caffeine 7.4 mg. Control - Starch confection	Starch confection + GTE - ↑↓0.5% from baseline FMD % Control - ↑↓0.48% from baseline FMD %
Pure phenolic								
Alañón et al. (2020) ²¹⁶ n=20, 100% M	Extract	Crossover	Healthy	Acute (2hr)	23.4 ± 1.30	23.2 ± 1.51	Water-based test drink containing 0.1, 0.5 and 1.0 mg/kg BW of epicatechin Control (water)	Low dose - ↑0.5% from baseline FMD % Medium dose - **↑1.2 ± 0.3% from baseline FMD % High dose - ***↑2.9 ± 0.3% from baseline FMD % Control - ↓0.05% from baseline FMD %
van der Made (2017) ²¹⁷ n=45, 55% M	Extract	Parallel	Overweight/obese	Chronic (4 wk)	61 ± 7	28.4 ± 3.1	Trans-resveratrol (trans-resveratrol 150mg) Control (2 × 58 mg/day cellulose)	Trans-resveratrol ↓0.7% from baseline FMD % Control ↑0.2% from baseline FMD %



alden et al. (2016) ²¹⁸ =68, 68% M	Extract	Parallel	Healthy	Acute (2hr) Chronic (6 wk)	53 ± 14	29.0 ± 2.6	Hesperidin 2S (450 mg supplied as 500 mg Cordiart) Control (Cellulose (500 mg microcrystalline cellulose))	Acute Hesperidin 2S - ↓0.27% from baseline FMD % Control - ↓0.49% from baseline FMD % Chronic Hesperidin 2S - ↓0.21% from baseline FMD % Control - ↓0.14% from baseline FMD %
Wong et al. (2013) ²¹⁷ =28, 43% M	Extract	Crossover	Overweight/obese	Chronic (6 wk)	61 ± 1.3	33.3 ± 0.6	Resveratrol (75 mg) Control (Calcium Hydrogen Phosphate, microcrystalline cellulose)	30mg Resveratrol - *↑0.57% from baseline FMD% Control - ↓0.81% from baseline FMD%
Wong et al. (2011) ⁶⁹ =19, 74% M	Extract	Crossover	Overweight/obese	Acute (1 hr)	56 ± 2	28.7 ± 0.6	Resveratrol (30, 90, 270 mg) Control (Calcium Hydrogen Phosphate, microcrystalline cellulose)	30mg Resveratrol - *↑2.50% from Control FMD% 90mg Resveratrol - *↑2.40% from Control FMD% 270mg Resveratrol - *↑3.60% from Control FMD% Control - 4.10% FMD

Age and BMI values are presented as mean ± standard deviation (where not available, the range is provided). Significance compared to control denoted using; *, p<0.05;**p<0.01;***p<0.001. Significance compared to baseline denoted using; †, p<0.05; ††, p<0.01; †††, p<0.001. **BMI**, body mass index; **CC**, caffeinated coffee; **CAD**, coronary artery disease; **CVD**, cardiovascular disease; **CVR**, cardiovascular risk; **DC**, dark chocolate or decaffeinated coffee (context-dependent); **DP1-10**, degree of polymerization 1-10; **DP2-10**, degree of polymerization 2-10; **d**, day(s); **F&V**, fruit and vegetables; **FMD**, flow-mediated dilation; **g**, grams; **GSE**, grape seed extract; **HCCGA**, high CGA coffee; **hFCD**, high flavan-3-ol cocoa drink; **hr**, hour(s); **IFCD**, low flavan-3-ol cocoa drink; **kg**, kilograms; **IFCD**, low flavan-3-ol cocoa drink; **M**, males; **MC**, milk chocolate; **MCCGA**, medium CGA coffee; **mg**, milligrams; **MGS**, muscadine grape seed; **MOF**, monomeric and oligomeric flavan-3-ols; **mth**, month(s); **n**, number of participants; **ND**, not disclosed; **NR**, not reported; **RGC**, red grape concentrate; **TPC**, total (poly)phenol content; **uM**, micromolar; **WC**, white chocolate; **wk**, week(s); **y**, years.

7. References

View Article Online
DOI: 10.1039/D5FO01106J

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8. Figures:

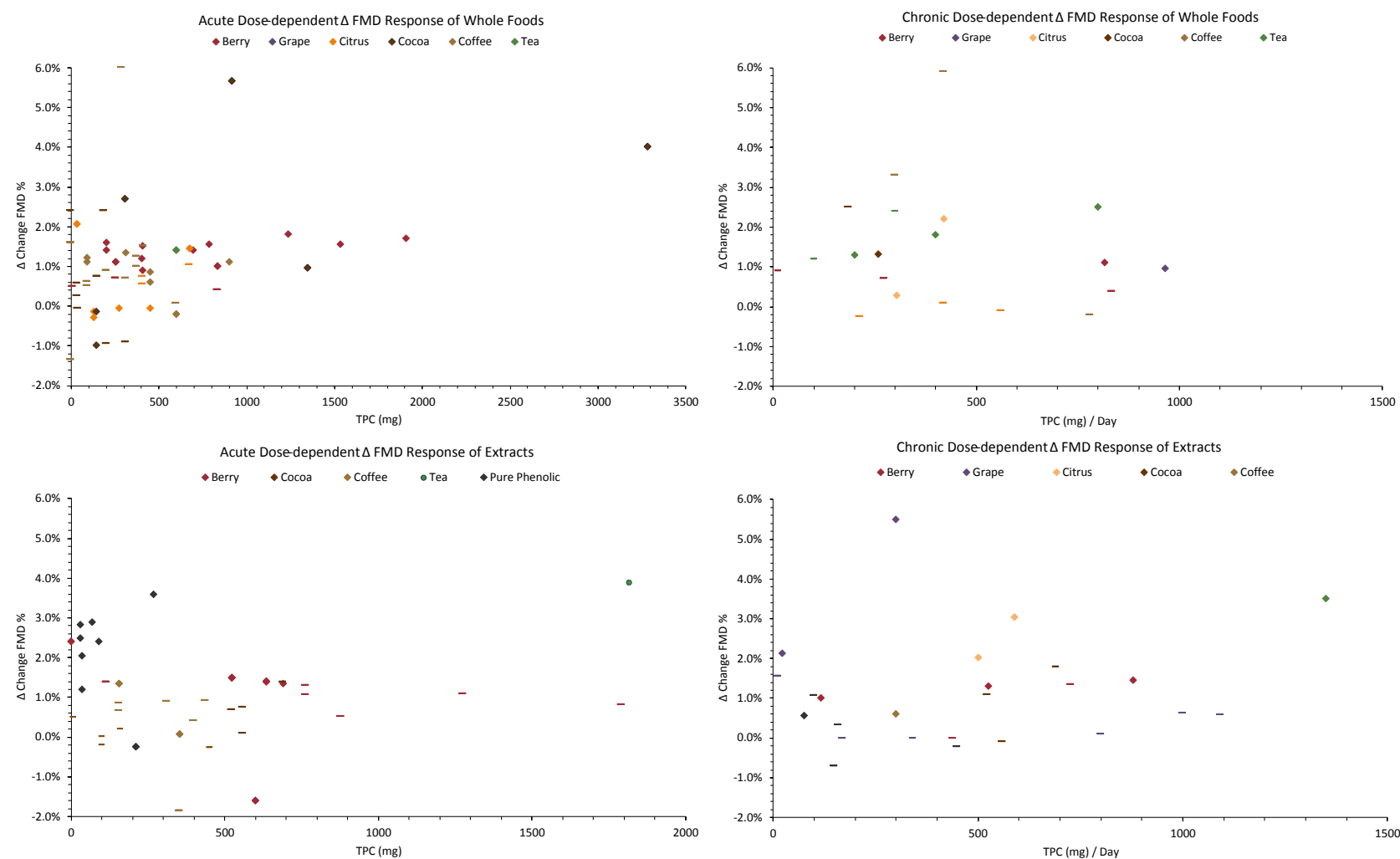


Figure 1: Comparison of dose-dependent acute and chronic FMD responses for Whole Foods and Extracts, within each food category. Diamonds represent significant values ($p < 0.05$) and Straight lines represent non-significant values ($p > 0.05$). FMD, flow-mediated dilation; TPC, total (poly)phenol content; mg, milligrams.

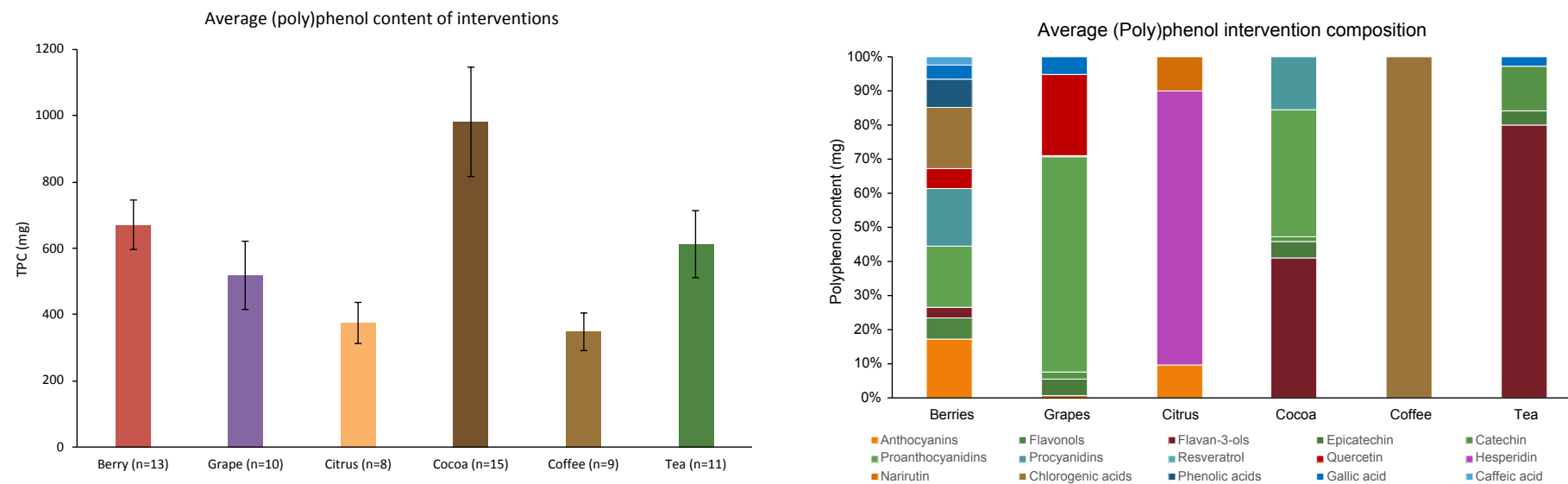


Figure 2: Total polyphenol content and composition of dietary polyphenol interventions associated with significant effects. (Left) Mean $\pm$ SEM total polyphenol content (TPC) of interventions, expressed in milligrams (mg). (Right) Relative composition of polyphenol subclasses within interventions, displayed as a percentage (%) of total polyphenol content

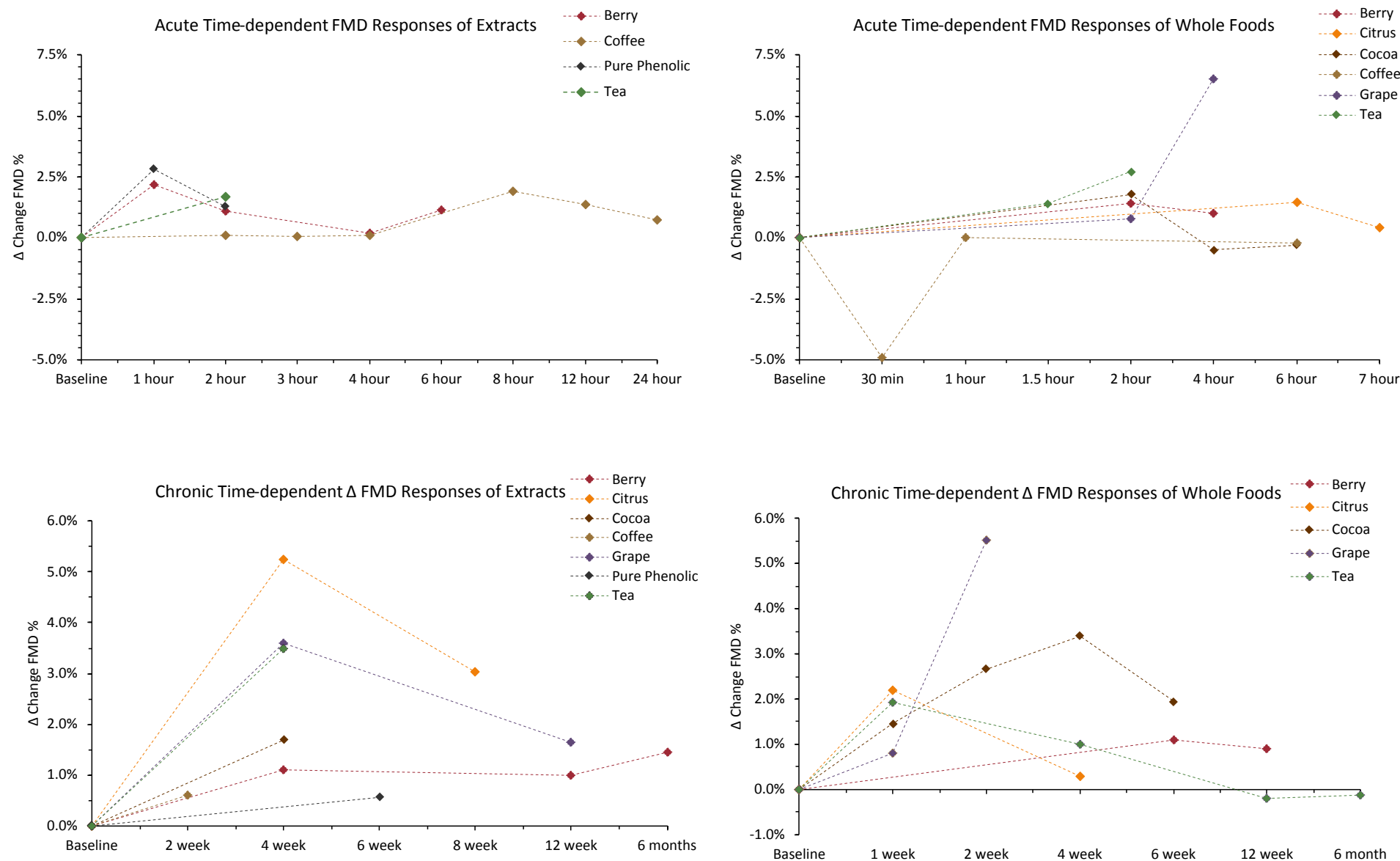


Figure 3: Acute and chronic time-dependent changes in flow-mediated dilation (Δ FMD %) in response to extracts (left panels) and whole foods (right panels)

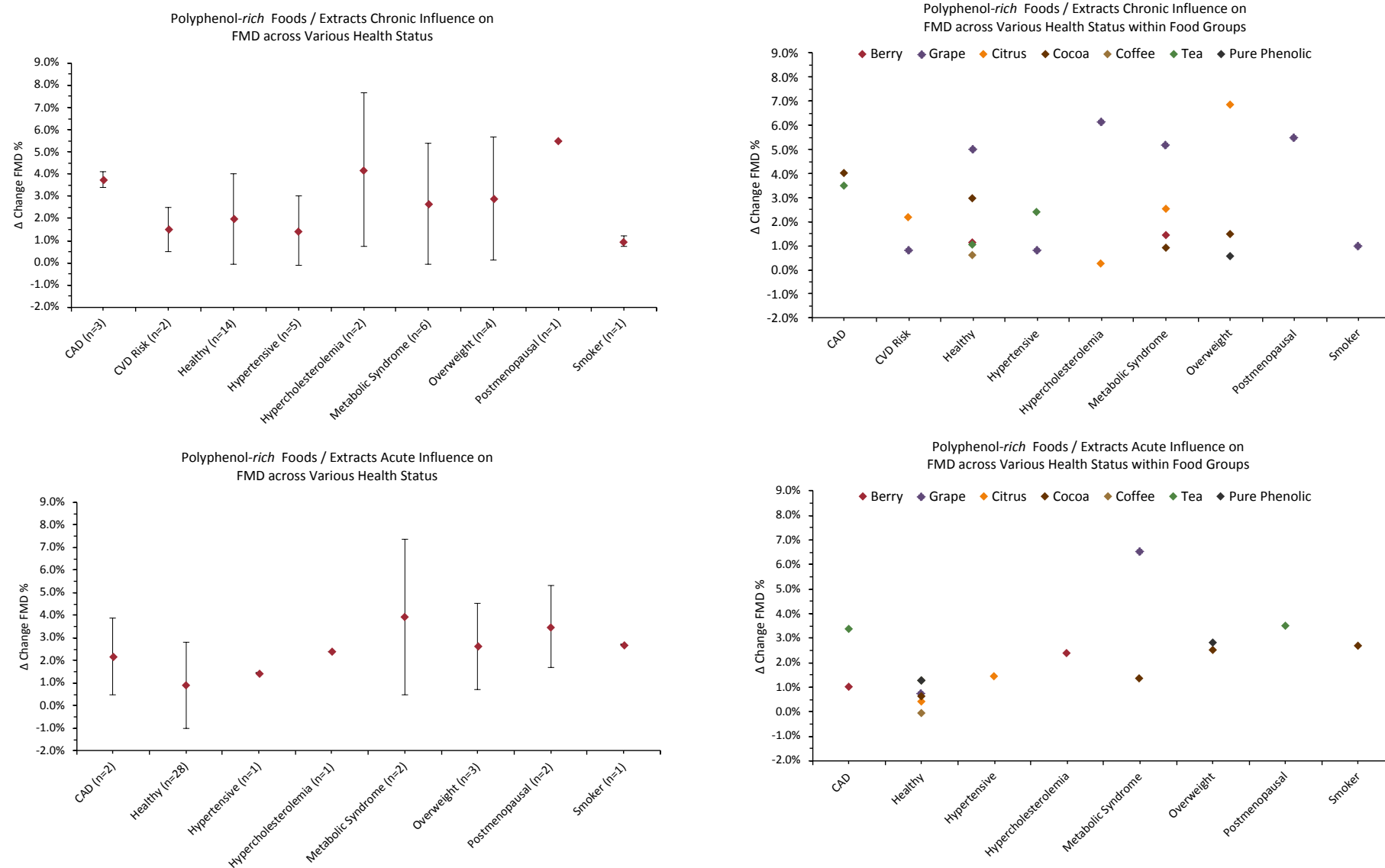


Figure 4: Effect of polyphenol-rich foods and extracts on flow-mediated dilation (Δ FMD%) following chronic and acute interventions across different health statuses and polyphenol-rich food groups. (Left panels) Mean $\pm$ SEM change in FMD (%) following acute and chronic polyphenol intervention across different health statuses. (Right panels) Mean Δ FMD% for each polyphenol-rich food group, calculated from relevant studies within each category for acute and chronic interventions.

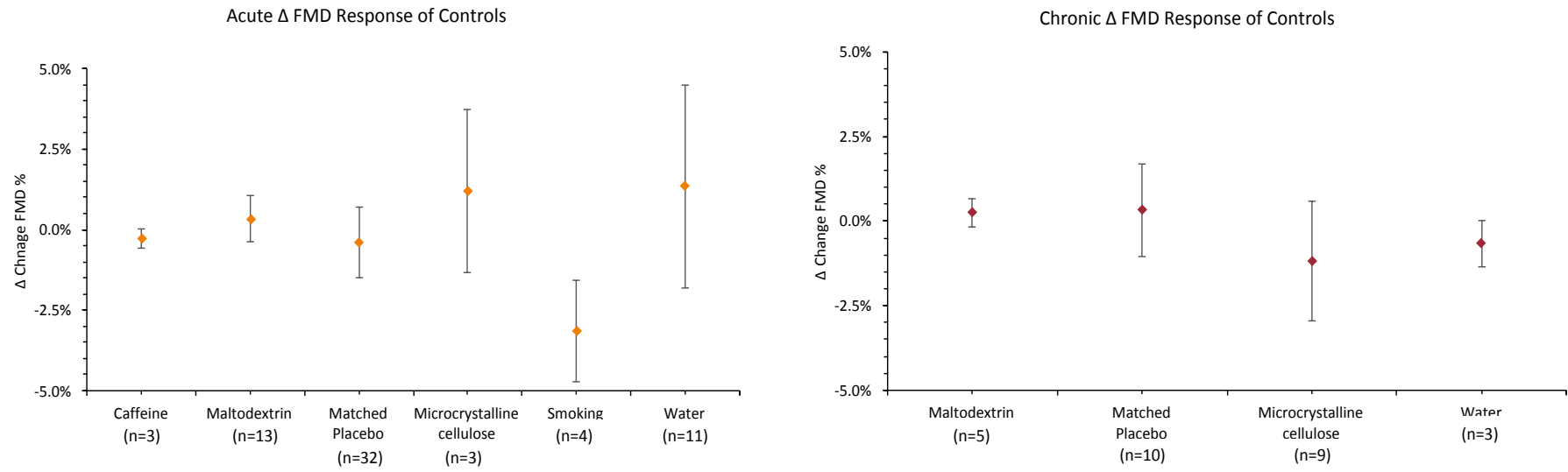


Figure 5: Acute and chronic changes in flow-mediated dilation (Δ FMD %) among in response to various controls. Data presented as Mean $\pm$ SD

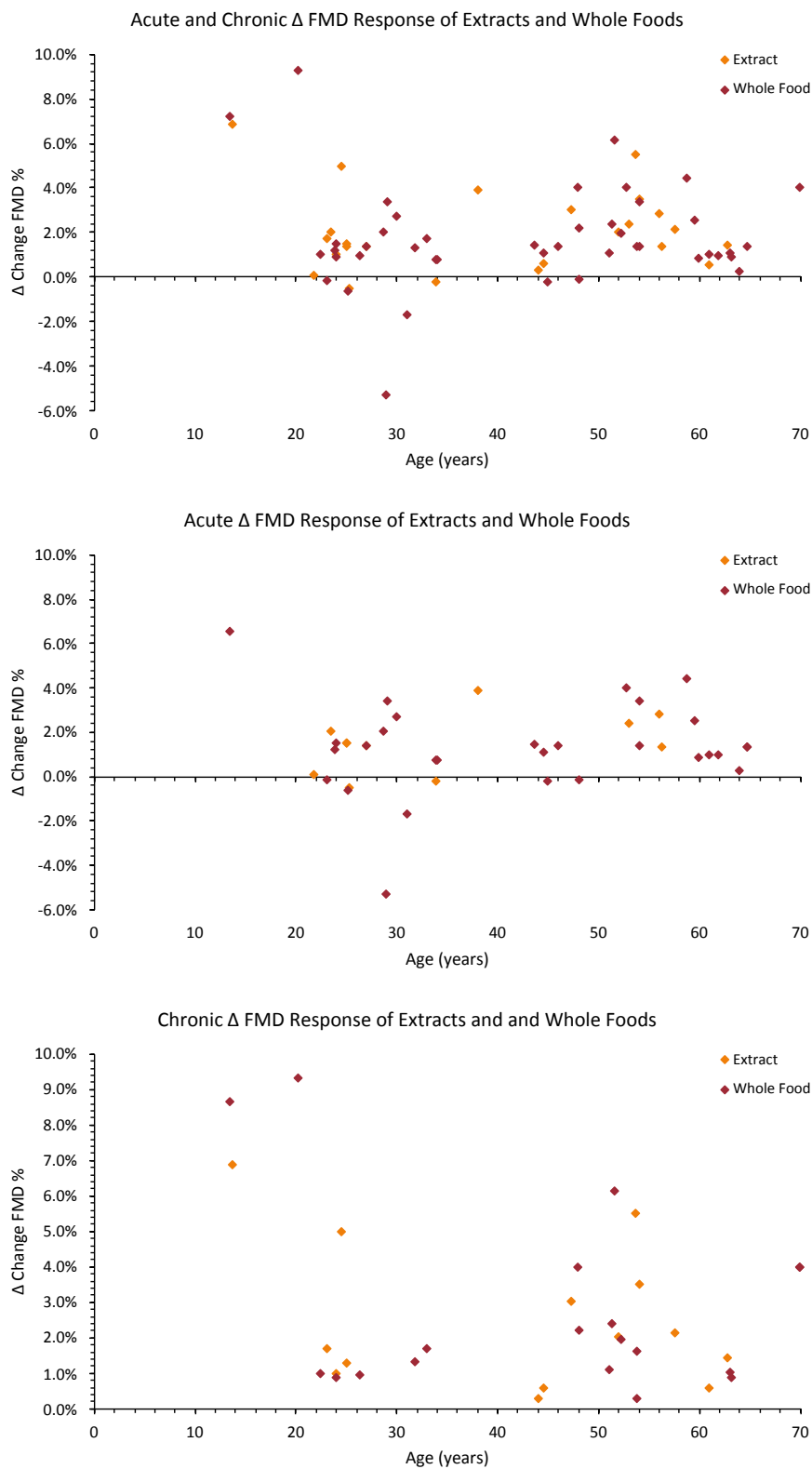


Figure 6: Relationship between Age and polyphenol-rich foods and extracts on flow-mediated dilation (ΔFMD%) following chronic and acute interventions. Data presented as the delta change in FMD (%), calculated from relevant studies within each category for acute and chronic interventions.

The Impact of (Poly)phenol-Rich Foods and Extracts on Flow-Mediated Dilation (FMD): A

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DOI: 10.1039/D5FO01106J

Narrative Review

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Data Availability

No new data were generated or analysed in this narrative review. All data discussed in this article are derived from previously published studies, which are appropriately cited in the manuscript. As this is a secondary analysis of existing literature, no primary research results, datasets, software, or code have been included.

