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Fruit- and vegetable-derived polyphenols improve metabolic and renal outcomes in adults with metabolic syndrome and chronic kidney disease: a systematic review of randomized controlled trials

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ABSTRACT

Background: Metabolic syndrome (MetS) and chronic kidney disease (CKD) share features such as inflammation and oxidative stress. Fruit- and vegetable-derived polyphenols may modulate these mechanisms.

Objective: To evaluate effects of fruit- and vegetable-based polyphenol interventions on metabolic and renal outcomes in adults with MetS or CKD/ESRD.

Methods: We systematically reviewed randomized controlled trials (2000-2024) from PubMed/MEDLINE, Scopus, Cochrane Library, and Semantic Scholar, adhering to PRISMA guidelines. Adults (≥18 years) with clinically diagnosed MetS (WHO/NCEP-ATP III/IDF criteria) or CKD/ESRD were included. Data were grouped as: (1) Metabolic outcomes: lipids, blood pressure, glucose; (2) Renal outcomes: eGFR, albuminuria; (3) Cardiovascular events. Glycemic benefits were limited and inconsistent.

Results: Twenty-eight RCTs (n = 20–108) were included. In MetS, bergamot extract (six months) reduced LDL by 22 % and triglycerides by 23 % ($p < 0.01$). Grape powder (60 g/day for four weeks) lowered triglycerides and improved HDL function. Freeze-dried blueberry (45 g/day for six weeks) enhanced endothelial function ($p < 0.05$). Blood pressure reductions occurred with grape polyphenols; glycemic improvements were limited to polyphenol-rich diets and high-dose resveratrol. In CKD, fruit and vegetable diets (up to five years) slowed eGFR decline and increased plasma bicarbonate to levels comparable to sodium bicarbonate. Long-term interventions (five years) reported zero cardiovascular events versus six in controls ($p < 0.01$). Isolated supplements (*e.g.*, cranberry, resveratrol) showed minimal effects on renal function. No serious adverse events were reported.

Conclusions: Whole-food polyphenol interventions improve lipid profiles, endothelial function, and slow renal decline in MetS and CKD populations. Glycemic benefits are modest. Standardized, long-term RCTs are needed to refine dietary guidelines.

KEYWORDS

Chronic diseases, Nutritional strategies, Clinical outcomes, Clinical markers, Comprehensive health, Dietary intervention, Non-communicable diseases, Polyphenols, Metabolic syndrome, Chronic kidney disease.

INTRODUCTION

Metabolic syndrome (MetS) and end-stage renal disease (ESRD) represent interconnected global health epidemics, collectively affecting over a billion individuals worldwide[1,2]. These conditions share underlying pathophysiological mechanisms, including chronic inflammation, oxidative stress, and endothelial dysfunction, which drive progressive cardiorenal damage[3]. Despite pharmacological advancements, residual

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morbidity and mortality remain significant, highlighting the critical need for evidence-based nutritional interventions that target these shared pathways[4].

Dietary polyphenols derived from fruits and vegetables—notably flavonoids, anthocyanins, and phenolic acids—offer promising therapeutic potential due to their multifaceted biological activities. These compounds exhibit potent antioxidant, anti-inflammatory, and vasodilatory properties, modulating key pathways implicated in metabolic and renal pathology[5,6]. Preclinical studies demonstrate their ability to scavenge free radicals, inhibit pro-inflammatory cytokines, and enhance nitric oxide bioavailability[7–9], positioning them as viable candidates for mitigating multisystem damage in high-risk populations.

Emerging clinical evidence supports the efficacy of polyphenol interventions in improving cardiometabolic and renal health. In adults with metabolic syndrome, grape- and blueberry-based products have yielded modest but statistically significant improvements, including reductions in triglycerides (up to 43.45 mg/dL in men) and body mass index[10]. Improvements in endothelial function and blood pressure were consistently observed across trials, and one study using a polyphenol-rich diet reported enhanced insulin secretion alongside reduced glucose area under the curve[11]. Similarly, in chronic kidney disease (CKD) and ESRD populations, fruit/vegetable interventions slowed declines in estimated glomerular filtration rate (eGFR), increased plasma CO_2, and reduced systolic blood pressure[12,13]. Across studies, adverse effects were minimal and compliance was generally high.

Despite these encouraging findings, significant knowledge gaps persist. First, heterogeneity in intervention sources—ranging from isolated supplements (e.g., resveratrol capsules) to whole-food matrices (e.g., berry powders)—complicates comparisons of efficacy[14]. Second, renal outcome data remain sparse, particularly for ESRD cohorts, with most studies prioritizing surrogate biomarkers over hard clinical endpoints like cardiovascular events or dialysis progression[15]. Third, the differential effects of polyphenols on glucose metabolism require clarification, as improvements were inconsistent and often dependent on intervention type[16]. No systematic review has comprehensively evaluated polyphenol efficacy across both MetS and renal disease populations using standardized randomized controlled trial (RCT) criteria.

To address these gaps, this systematic review investigates the following question: In adults with metabolic syndrome and/or end-stage renal disease, how does dietary intake or supplementation of fruit- and vegetable-derived polyphenols, compared to a standard diet without extra polyphenols, affect metabolic parameters (lipids, glucose, blood pressure) and renal function outcomes (eGFR, albuminuria, cardiovascular events)? By synthesizing evidence from 28 RCTs, we aim to elucidate source-specific effects, identify high-impact clinical applications, and inform targeted dietary recommendations for these populations.

METHOD

Search Strategy and Initial Screening

Comprehensive searches (January 2000-April 2025) were conducted in PubMed/MEDLINE, Scopus, Cochrane Library, and Semantic Scholar without algorithmic limits. Manual bibliography cross-referencing ensured completeness. The final search date was April 30, 2025, encompassing over 126 million academic publications. The primary query – "In adults with metabolic syndrome and/or end-stage renal disease, how does dietary intake or supplementation of fruit- and vegetable-derived polyphenols, compared to a standard diet without extra polyphenols, affect metabolic parameters and renal function outcomes?". Search terms included controlled vocabulary and keywords related to polyphenols, metabolic syndrome (MetS), chronic kidney disease (CKD), end-stage renal disease (ESRD), and randomized controlled trials (RCTs), combined with Boolean operators to optimize sensitivity.

Study Selection Process

Two-phase screening was implemented using predefined PICOS criteria. First, titles and abstracts were evaluated for:

- Adult participants (≥18 years) with clinically diagnosed MetS (WHO/NCEP-ATP III/IDF criteria) or ESRD (including hemodialysis);
- Interventions featuring fruit/vegetable-derived polyphenols (whole foods, extracts, or supplements) as the primary exposure;
- Comparison to standard diets or placebo controls without polyphenol fortification;
- Measurement of ≥1 metabolic parameter (blood glucose, lipids, blood pressure) or renal outcome (eGFR, creatinine, albuminuria);
- RCT design with minimum 2-week duration, isolation from confounders (e.g., no concurrent exercise programs), human subjects, and control groups; and
- Full-text review resolved uncertainties, with holistic judgment applied to borderline cases. Two independent reviewers (E.H., F.N.) conducted double screening using Covidence software. Borderline cases (n=5) were resolved through consensus discussion with a third reviewer (N.A.T.) based on PICOS adherence. Studies failing any criterion were excluded.

Data Extraction Protocol

A large language model (GPT-4 architecture) performed structured extraction (study design, outcomes) under researcher supervision using standardized instructions:

- Study design documented randomization methods, blinding procedures (single/double/open-label), control group

types, and trial structures (crossover/parallel), with unclear designs flagged.

- Participant characteristics captured sample size, age (mean ± SD or range), sex distribution, diagnostic criteria, and key inclusion/exclusion criteria, noting partial data where applicable.
- Polyphenol interventions recorded sources (e.g., freeze-dried grape powder), daily dosage (e.g., 45g/day), duration (e.g., 6 weeks), delivery methods (capsule/powder/whole food), and quantified polyphenol content when reported. Imprecise descriptions were transcribed verbatim.
- Control conditions classified comparators as placebo, standard diet, or waitlist, noting nutritional matching status.
- Outcomes prioritized metabolic (lipids, glucose, BP) and renal (eGFR, CVD events) endpoints with measurement methods, timepoints, units, and statistical significance.
- Study context included geographic location, setting (clinic/community), and population subgroups (e.g., African American adults). All extractions underwent dual manual verification (E.H., F.N.), with 4.2% discrepancy rate resolved by consensus. Poorly described interventions (n=3) were transcribed verbatim and flagged.

Quality Assessment and Synthesis

Risk of bias was assessed using Cochrane's RoB 2.0 tool, with results tabulated, focusing on random sequence generation, allocation concealment, blinding integrity, and control group comparability. Heterogeneity in polyphenol sources (e.g., whole foods vs. isolates), doses, and outcome metrics precluded meta-analysis; thus, results were synthesized narratively. Data were tabulated to compare effect sizes (mean differences, percentage changes) and clinical significance across interventions, with safety (adverse events) and compliance metrics analyzed descriptively. The PRISMA flowchart documented screening attrition.

RESULTS

Characteristics of Included Studies

The review incorporated a diverse collection of 28 interventional studies, offering a comprehensive evaluation of the effects of various fruit- and polyphenol-based interventions on populations at cardiometabolic risk. The vast majority of included studies were randomized controlled trials (RCTs). Among these, 19 were placebo-controlled, 16 employed double-blind designs, and 11 utilized a crossover format, enhancing the internal validity and reliability of outcomes reported. Only one study was a systematic review and meta-analysis of randomized controlled trials, providing aggregated data on resveratrol supplementation.

Population characteristics varied across studies but primarily focused on individuals with increased cardiometabolic risk. Seventeen studies specifically targeted adults with Metabolic Syndrome, making this the predominant population group. Four studies involved patients with chronic kidney disease (CKD) not requiring dialysis, while five studies were conducted in hemodialysis populations—highlighting a significant representation of renal-compromised cohorts. Additionally, four studies included overweight or obese individuals, while a smaller number focused on populations with diabetic nephropathy, macroalbuminuric CKD, stage 1 hypertension, or specific demographic groups such as African American adults with hypertension.

Interventions were largely polyphenol- or fruit-derived and spanned a range of delivery methods, including whole foods, extracts, juices, and powders. Grape-based products were the most frequently investigated intervention, appearing in eight studies. Resveratrol, a key polyphenolic compound often derived from grapes, was evaluated in five trials. Whole fruit and vegetable interventions were also common, assessed in four studies, often emphasizing their potential benefits for renal and cardiovascular health. Cranberry-based interventions were tested in three studies, while blueberry was examined in two. Other interventions included fruit/vegetable/berry juice powders, as well as singular studies on pomegranate, bergamot, tart cherry, cocoa flavanols, strawberry powder, mulberry extract, and combinations such as grape seed, green tea, and quercetin.

Primary outcomes varied but centered on cardiometabolic health indicators. Lipid profiles were the most commonly assessed endpoint, featured in 16 studies. Blood pressure followed closely, evaluated in 15 trials. Glucose levels, insulin concentrations or insulin sensitivity, endothelial function (often measured via flow-mediated dilation or reactive hyperemia index), and anthropometric measures such as body mass index and weight were also frequently examined, each assessed in 8 studies. Inflammatory markers, such as C-reactive protein and cytokines, were reported in 9 studies, while 10 studies analyzed oxidative stress parameters, including antioxidant enzyme activity and lipid peroxidation products.

Less frequently reported outcomes included measures of kidney function (e.g., estimated glomerular filtration rate and albumin:creatinine ratio), which were assessed in only four studies. Emerging areas such as metabolomics (3 studies), arterial stiffness (1 study), adhesion molecules like sICAM-1 and sVCAM-1 (2 studies), and uremic toxins (1 study) were less consistently evaluated. Other unique endpoints—each investigated in a single study—included angiotensin-converting enzyme (ACE) activity, incretin hormone responses, vitamin K1 status, cardiovascular events, and gut microbiota composition.

In summary, the included studies demonstrated heterogeneity in study design, populations, intervention types, and

Table 1. Characteristics of Included Studies

Study	Study Design	Population Characteristics	Intervention Type/Duration	Primary Outcomes Measured
17	Randomized, placebo-controlled, crossover trial	n=20; 12M/8F; adults with metabolic syndrome	Freeze-dried grape powder, 60g/day, 4 weeks (crossover)	Plasma lipids, glucose, ALT, BMI, weight, Triglycerides, pulse, Total Cholesterol, Non-HDL-C
18	Randomized, double-blind, placebo-controlled, parallel-arm trial	n=44; >20y; metabolic syndrome (WHO criteria)	Freeze-dried blueberry powder, 45g/day, 6 weeks	Blood Pressure, endothelial function (RHI), insulin sensitivity, body weight/composition
19	Randomized, double-blind, placebo-controlled RCT	n=44; adults with metabolic syndrome	Blueberry bioactives, 22.5g x2/day, 6 weeks	Endothelial function (RHI), Blood Pressure
20	Randomized, double-blind, placebo-controlled, crossover/parallel	n=57; End-Stage Renal Disease on hemodialysis	Cocoa flavanol beverage, 900mg/day, 30 days	Flow-Mediated Dilation, Blood Pressure, Heart Rate
21	Randomized, placebo-controlled RCT	n=33; hemodialysis patients	Pomegranate extract, 1000mg/day, 6 months	Blood Pressure, paraoxonase-1, inflammation, oxidative stress, physical function
22	Randomized, double-blind, placebo-controlled, crossover	n=20; 32-70y; BMI 25.3-45.4	Freeze-dried grape powder, 60g/day, 4 weeks	PON1 activity, HDL function, plasma lipids, metabolic markers
23	Randomized controlled trial	n=80; 45±5y; 54%F/46%M; Metabolic Syndrome (NCEP-ATP III)	Bergamot phytocomplex tablet, 1/day, 6 months	Weight, BMI, waist, lipids, glucose, CRP
24	Randomized, single-blind, placebo-controlled pilot	n=19; 20-60y; Metabolic Syndrome	Tart cherry juice, 480mL/day, 12 weeks	Blood Pressure, arterial stiffness, blood biomarkers
25	Randomized, double-blind, placebo-controlled, crossover	n=24; men, 30-70y; Metabolic Syndrome	Freeze-dried grape polyphenol powder, 30 days	Blood Pressure, Flow-Mediated Dilation, NOx, sICAM-1, sVCAM-1
26	Randomized, double-blind, placebo-controlled, crossover	n=64; mean 56.9y; 52%F; Metabolic Syndrome (IDF)	Fruit/veg/berry juice powder, 4.5g/day, 8 weeks	Endothelial function (FMD), glucose, insulin, lipids, weight
27	Randomized crossover trial	n=34; Metabolic Syndrome, on standard therapy	Longevinex (resveratrol), 3 months	Endothelial function (FMD), Blood Pressure, insulin resistance, lipids, inflammation
12	Randomized controlled trial	n=108; macroalbuminuric, nondiabetic CKD stage 3	Fruits/vegetables (whole foods), 5 years	Plasma CO2, LDL, HDL, eGFR, Systolic Blood Pressure, CVD events
28	Randomized controlled trial	n=91; mean 58.3y; 66%F; AA adults with CKD/Hypertension	Fruit/vegetable intervention, 6 weeks	Albumin:creatinine, BMI, cholesterol, Systolic Blood Pressure, metabolomics
29	Randomized controlled trial	n=32; hemodialysis patients	Red grape juice, 14 days	Cholesterol, apoB, HDL, oxLDL, NADPH oxidase
30	Randomized, double-blind, placebo-controlled	n=34; 53y; 9M/7F per group; non-diabetic Hemodialysis	Grape powder, 500mg polyphenols/day, 5 weeks	GSH-Px, CRP, potassium, Kt/V

Table 1 continuation. Characteristics of Included Studies

Study	Study Design	Population Characteristics	Intervention Type/Duration	Primary Outcomes Measured
31	Randomized controlled, 2x2 factorial, single-blind	n=86; 35–70y; overweight/obese, Metabolic Syndrome (NCEP/ATP III)	Polyphenol-rich diet, 8 weeks	Postprandial lipids, glucose, insulin, OGIS, GLP-1
32	Randomized controlled trial	n=108; macroalbuminuric, nondiabetic CKD, metabolic acidosis	Fruits/vegetables, 5 years	eGFR, plasma CO2, Systolic BP, LDL, Lp(a), vitamin K1
33	Systematic review/meta-analysis of RCTs	24 RCTs; Metabolic Syndrome and related disorders	Resveratrol supplementation, various	CRP, TNF-α, IL-6, SOD
34	Randomized, double-blind, placebo-controlled	n=25; non-dialysis Chronic Kidney Disease	Cranberry extract, 1000mg/day, 2 months	LPS, IS, p-CS, IAA
35	Randomized, double-blind, crossover, placebo-controlled	n=20; 62y; 45%M; non-dialyzed CKD	Resveratrol, 500mg/day, 4 weeks	Nrf2, NF-κB, cytokines, antioxidant enzymes
36	Randomized, placebo-controlled	n=28; obese men with Metabolic Syndrome	Resveratrol, 2g/day, 35 days	Insulin resistance, GTT, adipose metabolism, microbiota
37	Randomized, double-blind, controlled, crossover	n=33; mean 53y; 2M/31F; Metabolic Syndrome features	Strawberry powder, 13g or 32g/day, 4 weeks	BCAA, phosphate, benzoic acid, HOMA-IR
38	Randomized controlled trial	n=60; diabetic nephropathy	Mulberry extract, 300mg/day, 12 weeks	Lipids, hs-CRP, glutathione, MDA
39	Randomized, double-blind, placebo-controlled	n=48; overweight/obese women with Metabolic Syndrome	Cranberry supplement, 8 weeks	Glucose, lipoproteins, MDA, hs-CRP, IL-6, Blood Pressure
40	Randomized, double-blind, placebo-controlled, crossover	n=64; adults with Metabolic Syndrome	Fruit/veg juice powder, 8 weeks	Endothelial function, glucose, insulin, lipids, weight
41	Randomized, double-blind, placebo-controlled	n=60; Hemodialysis patients; 53y	Grape powder, 500mg polyphenols/day, 5 weeks	CRP, GSH-Px, lipid profile
42	Double-blind, placebo-controlled, crossover	n=20; Metabolic Syndrome, Stage 1 Hypertension	Grape seed/skin, green tea, resveratrol, quercetin, 4 weeks	Blood Pressure, ACE, nitrate/nitrite, isoprostanes

outcome measures. While the breadth of evidence supports the potential cardiometabolic benefits of polyphenol-rich and fruit-based interventions, variability in methodological rigor, population health status, and measured endpoints highlights the need for further targeted research to refine clinical recommendations.

Effects on Metabolic Parameters

Lipid Profile Outcomes

The studies examining lipid-related and metabolic outcomes revealed a generally positive trend in response to polyphenol- and fruit-based interventions, though the magnitude and breadth of effects varied considerably across trials. Among the eight studies directly measuring lipid profile parameters—including triglycerides, total cholesterol, LDL, HDL, VLDL, and non-HDL cholesterol—three studies reported broad and clinically significant improvements across multiple lipid markers. For instance, [23] demonstrated robust lipid-lowering effects with bergamot supplementation, including a 22% reduction in LDL, a 23% reduction in triglycerides, and a 14% increase in HDL, alongside significant improvements in glucose and inflammation (CRP ↓ 40%). Similarly, [38] reported multiple favorable shifts with mulberry extract, including a 37.3 mg/dL reduction in triglycerides, a modest HDL increase, and notable antioxidant and anti-inflammatory effects (e.g., hs-CRP ↓ 2.3 mg/L, glutathione ↑ 87.8 units).

Table 2. Lipid Profile Outcomes

Study	Intervention Type	Parameters Measured	Effect Size	Clinical Significance
[17]	Grape powder	BMI, Triglycerides, Total Cholesterol, Non-HDL-C	BMI ↓ 0.22 kg/m² (p=0.048); Triglycerides ↓ 43.45 mg/dL (men, p=0.033); Total Chol ↑ 5.25 mg/dL (women, p=0.003); Non-HDL-C ↑ 7.5 mg/dL (women, p=0.010)	Modest, sex-specific effects
[18]	Blueberry powder	Endothelial function, Blood Pressure	RHI improved (p<0.05); Blood Pressure not significant	Improved endothelial function
[19]	Blueberry powder	Blood Pressure, RHI, insulin sensitivity	RHI improved (p=0.024); Blood Pressure, insulin sensitivity not significant	Endothelial function improved
[22]	Grape powder	PON1, HDL function, Triglycerides	Triglycerides ↓ (p=0.032); PON1, HDL function not significant	Triglyceride reduction only
[23]	Bergamot	Total Cholesterol, LDL, Triglycerides, HDL, glucose, CRP	Total Chol ↓ 15%, LDL ↓ 22%, Triglycerides ↓ 23%, HDL ↑ 14%, glucose ↓ 15%, CRP ↓ 40%	Broad, significant improvements
[25]	Grape powder	Blood Pressure, Flow-Mediated Dilation, sICAM-1	SBP ↓ (p=0.002), FMD ↑ (p=0.000), sICAM-1 ↓ (p=0.017)	Improved vascular function
[31]	Polyphenol-rich diet	Postprandial lipids, glucose	Glucose AUC ↓ (p=0.038), early insulin secretion ↑ (p=0.048), OGIS ↑ (p=0.05)	Improved glucose metabolism
[38]	Mulberry extract	Triglycerides, VLDL, HDL, hs-CRP, glutathione, MDA	Multiple: TG ↓ 37.3, VLDL ↓ 7.4, HDL ↑ 0.5, hs-CRP ↓ 2.3, GSH ↑ 87.8, MDA ↓ 0.03 (all significant)	Multiple favorable changes
[39]	Cranberry	HDL-c	HDL-c ↑ (p<0.05); other parameters not significant	HDL-c improved only
[37]	Strawberry powder	BCAA, HOMA-IR	Valine/leucine ↓ (high dose); HOMA-IR not significant	BCAA reduction
[41]	Grape powder	CRP, GSH-Px, lipids	GSH-Px ↑ ; CRP stable; lipids not significant	Antioxidant effect
[42]	Polyphenol mix	Blood Pressure	DBP ↓ 4.7 mmHg, MAP ↓ 4.8 mmHg (p<0.05)	Blood Pressure reduction

Four studies reported improvements in vascular function, either independently or alongside lipid outcomes. These include [18,19,25], and [42], which documented improvements in flow-mediated dilation (FMD), reactive hyperemia index (RHI), and blood pressure metrics. These findings suggest a consistent endothelial benefit of polyphenol interventions, even in cases where lipid outcomes were not significantly altered. Improvements in endothelial function (FMD/RHI) occurred in four studies [18,19,25] and [42], irrespective of lipid outcomes (Table 2).

In contrast, several studies yielded more modest or isolated benefits. For example, [22] found a significant reduction in triglycerides (p=0.032) with grape powder supplementation, but no change in HDL functionality or PON1 activity [39] and a study with missing authorship details both noted increases in HDL-c with cranberry supplementation, but other metabolic or inflammatory parameters remained unchanged. These findings suggest that while some interventions selectively enhance specific lipid fractions (e.g., HDL), their broader metabolic impact may be limited.

Interestingly, [17] presented sex-specific responses, with men experiencing a significant decrease in triglycerides and women showing paradoxical increases in total and non-HDL cholesterol. While statistically significant, the clinical implications of these small shifts remain uncertain, emphasizing the importance of examining subgroup responses in dietary intervention trials.

Beyond lipid outcomes, a subset of studies also addressed glucose metabolism, antioxidant status, and inflammation. For example, [31] reported improvements in glucose tolerance and

insulin sensitivity following a polyphenol-rich diet, while [41] and [38] observed antioxidant enhancements via increased GSH-Px and glutathione, respectively. However, only one study [31] clearly demonstrated clinically significant improvements in glucose metabolism, indicating this as a less consistently observed benefit across trials.

Collectively, while no study reported entirely null findings across all measured outcomes, the extent and specificity of benefits varied, ranging from broad metabolic improvements to narrowly focused effects on individual markers like triglycerides or HDL. These variations highlight both the potential utility and the complexity of interpreting polyphenol-based interventions, which may exert differential effects depending on compound type, population, sex, dosage, and baseline metabolic status.

Glucose Metabolism

The results from studies examining the effects of polyphenol-rich or fruit-based interventions on glucose metabolism reveal a mixed but generally limited pattern of effectiveness. Of the seven studies reviewed, five did not report significant improvements in glucose regulation or insulin sensitivity. These include interventions using blueberry powder [18], strawberry powder [37], fruit/vegetable/berry powder [26], and cranberry [39]. Despite assessing commonly used indicators such as fasting glucose, insulin, and HOMA-IR, these studies failed to produce clinically meaningful outcomes. This suggests that not all polyphenol-rich foods consistently impact glycemic control, particularly in the general populations and timeframes evaluated.

Only two studies showed positive effects on glucose metabolism. [31] used a polyphenol-rich diet and reported significant improvements across multiple parameters, including a decrease in glucose AUC, an increase in early insulin secretion, and enhanced insulin sensitivity (measured via OGIS). These findings indicate a broad and clinically relevant benefit in managing glucose metabolism. Meanwhile, [36] studied resveratrol and found improvements specifically in Caucasian participants, including reduced glucose AUC and better insulin resistance. These subgroup-specific outcomes highlight that genetic, ethnic, or metabolic differences may influence the efficacy of such interventions.

In terms of the parameters assessed, glucose and insulin were the most commonly measured variables, each appearing in three studies. However, more sensitive or dynamic measures—such as OGIS, HOMA-IR, glucose tolerance tests (GTT), and markers of insulin resistance—were underutilized, each appearing in only one study. This limited application of more robust metabolic markers may have hindered the detection of subtler effects of the interventions.

In summary, the evidence supporting polyphenol-based interventions for improving glucose metabolism is limited and inconsistent. While a polyphenol-rich diet showed promising general effects and resveratrol offered benefits in a specific subgroup, most other interventions did not yield significant results. These findings suggest that the effectiveness of polyphenols on glycemic control is likely dependent on the specific type of intervention, the characteristics of the study population, and the sensitivity of the metabolic markers used. As such, these interventions should not be universally expected to enhance glucose metabolism without considering individual variability and dietary context.

Table 3. Glucose Metabolism Outcomes

Study	Intervention Type	Parameter Measured	Effect Size	Clinical Significance
[18]	Blueberry powder	Insulin sensitivity	Not Significant	No effect
[31]	Polyphenol-rich diet	Glucose AUC, insulin secretion, OGIS	Glucose AUC ↓ (p=0.038), insulin secretion ↑ (p=0.048), OGIS ↑ (p=0.05)	Improved glucose metabolism
[36]	Resveratrol	GTT, insulin resistance	Glucose AUC ↓ , IR improved (Caucasians)	Subgroup-specific benefit
[37]	Strawberry powder	HOMA-IR	Not Significant	No effect
[26]	Fruit/veg/berry powder	Glucose, insulin	Not Significant	No effect
[39]	Cranberry	Glucose, insulin	Not Significant	No effect

Effects on Renal Function

Markers of Renal Function

Table 4. Markers of Renal Function

Study	Intervention Type	Renal Parameter	Effect Size	Clinical Significance
[12]	Fruits/vegetables	eGFR, plasma CO_2	eGFR decline less in F+V vs. UC; plasma CO_2 ↑	Comparable to $NaHCO_3$, fewer CVD events
[32]	Fruits/vegetables	eGFR, plasma CO_2, Systolic BP	eGFR decline less in F+V vs. UC; Systolic BP ↓	F+V superior to $NaHCO_3$ for CVD risk
[28]	Fruit/veg intervention	Albumin:creatinine	Small, not significant reduction	Metabolomic markers improved
[34]	Cranberry	LPS, IS, p-CS, IAA	Not Significant	No effect
[35]	Resveratrol	Nrf2, NF-κB	Not Significant	No effect
[30]	Grape powder	GSH-Px, CRP	GSH-Px ↑, CRP stable	Antioxidant effect
[41]	Grape powder	CRP, GSH-Px	GSH-Px ↑, CRP stable	Antioxidant effect

Clinical Outcomes

Table 5. Clinical Outcomes

Study	Intervention Type	Renal Parameter	Effect Size	Clinical Significance
[12]	Fruits/vegetables	CVD events	0 in F+V, 6 in UC, 2 in NaHCO3	Fewer events in F+V
[32]	Fruits/vegetables	CVD risk indicators	LDL, Lp(a) ↓, vitamin K1 ↑	Improved CVD risk

The clinical outcomes related to polyphenol-rich dietary interventions were primarily examined in two studies, both of which focused on the impact of fruits and vegetables on cardiovascular disease (CVD) outcomes in individuals with renal concerns. These studies suggest that dietary interventions emphasizing fruits and vegetables may confer cardiovascular benefits beyond their effects on kidney function.

In the study by [12], the incidence of cardiovascular events was used as a clinical endpoint. The results were notable: there were no cardiovascular events in the fruits and vegetables group, compared to six events in the usual care (UC) group and two events in the sodium bicarbonate ($NaHCO_3$) group. This finding indicates a potential protective effect of the fruits and vegetables intervention against cardiovascular events in patients with chronic kidney disease.

In a complementary study by [32], the focus was on cardiovascular risk indicators rather than clinical events. This study reported reductions in low-density lipoprotein cholesterol (LDL) and lipoprotein(a) [Lp(a)], both of which are known contributors to cardiovascular risk. Additionally, there was an increase in vitamin K1 levels, a nutrient associated with vascular health. These changes collectively reflect an improvement in cardiovascular risk profile among participants receiving the fruits and vegetables intervention.

Overall, these findings provide supportive evidence that fruits and vegetables can play a significant role in reducing cardiovascular risk and events in populations at risk due to renal impairment. This adds to the broader body of research suggesting that dietary strategies rich in plant-based, polyphenol-containing foods may have clinically meaningful effects beyond traditional biochemical markers.

Safety and Tolerability

Reported Adverse Effects

The overall safety and tolerability of polyphenol-rich interventions appeared favorable across the studies reviewed. Most studies did not report significant adverse effects, suggesting that these dietary strategies are generally safe for consumption. Specifically, [20] found cocoa flavanol ingestion to be well tolerated, and [36] similarly reported good tolerability for resveratrol. Importantly, there were no serious adverse events mentioned in the majority of studies. However, it is worth noting that systematic reporting of adverse effects was often lacking, limiting the ability to fully assess the safety profile across interventions.

Compliance and Adherence

Compliance and adherence to interventions varied and were not consistently reported. In shorter-term, crossover studies, adherence was generally high, likely due to the limited duration and frequent monitoring, which support participant engagement. In contrast, longer-term studies such as those b y[12,32] did not provide detailed information on adherence. This lack of data on long-term compliance may impact the interpretation of results, particularly when assessing the sustainability and real-world applicability of these dietary interventions. Overall, while the interventions appear safe and well tolerated, better and more consistent reporting on adverse events and adherence is needed to strengthen conclusions about their practical use.

DISCUSSION

This review highlights the diverse effects of polyphenol-rich interventions across multiple health domains, particularly in lipid metabolism, glucose regulation, renal function, and cardiovascular risk. Among lipid profile outcomes, several interventions demonstrated modest but clinically relevant effects. Grape and blueberry powders, as well as bergamot, consistently yielded improvements in triglycerides, HDL levels, or endothelial function[43,44]. Notably, the effects of grape powder appeared to be sex-specific in some cases, suggesting that biological factors such as hormonal status may influence responsiveness. Bergamot stood out for its broad lipid-lowering and anti-inflammatory effects, indicating its potential as a comprehensive cardiometabolic aid.

In contrast, glucose metabolism outcomes were more variable. While the majority of studies examining blueberry, cranberry, strawberry, and mixed berry powders did not demonstrate significant effects, interventions such as a polyphenol-rich diet [31] and resveratrol [36] showed promise, the latter mainly in a specific subgroup (Caucasians). These findings may reflect the complexity of glucose homeostasis and the necessity for targeted approaches. Furthermore, discrepancies in study design, population characteristics, and the bioavailability of polyphenols could contribute to the inconsistency of glucose-related outcomes.

Renal function markers were favorably influenced by fruits and vegetables interventions in studies by [12,32], which reported slower eGFR decline, increased plasma CO_2, and reduced systolic blood pressure. These interventions were also associated with reduced cardiovascular risk and fewer adverse clinical events, making them the most robust in terms of renal and cardiovascular benefits. In contrast, studies using cranberry, resveratrol, and grape powder did not show meaningful changes in primary renal parameters. However, grape powder demonstrated increased GSH-Px activity, indicating antioxidant support that could contribute indirectly to renal protection [30].

Several methodological limitations warrant acknowledgment. Semantic Scholar's initial exclusivity and algorithmic result cap (n=500) were mitigated by complementary searches in PubMed/MEDLINE, Scopus, and Cochrane Library. The 2-week minimum intervention duration may inadequately capture renal outcomes; however, sensitivity analysis restricted to trials ≥12 weeks (n=9) corroborated primary trends. While dual-independent screening and PROSPERO registration enhanced rigor, clinical heterogeneity in polyphenol sources and dosing precludes broad generalizations.

Clinical outcomes, though limited in number, reinforced the potential benefit of fruits and vegetables in reducing cardiovascular events and risk markers. In the study, such interventions were associated with favorable changes in LDL, lipoprotein(a), and vitamin K1 levels, alongside a complete absence of cardiovascular events in one study arm [32]. These findings underscore the value of whole food interventions that provide a spectrum of bioactive compounds, possibly acting synergistically to promote vascular and renal health.

Safety and tolerability of polyphenol-rich interventions were generally favorable, with few adverse effects reported. Most interventions, including cocoa flavanols and resveratrol, were well tolerated. However, the limited and inconsistent reporting of safety data across studies limits definitive conclusions. Adherence varied by study duration and design, with crossover trials showing higher compliance than longer interventions, where reporting was often lacking. This variability could influence both the efficacy and generalizability of findings.

Overall, the evidence supports the use of specific polyphenol-rich foods—particularly fruits and vegetables, grape powder, and bergamot—in promoting lipid control, renal preservation, and cardiovascular risk reduction. However, inconsistencies in glucose metabolism outcomes highlight the need for more targeted or individualized approaches. Methodological limitations such as small sample sizes, short durations, and heterogeneous interventions further complicate the interpretation of results.

One plausible explanation for the varied findings is the differing polyphenol profiles and bioavailability of each intervention. Whole foods may provide a complex matrix of nutrients that interact synergistically, while isolated extracts might lack this effect. Individual metabolic differences, baseline health status, and gut microbiota composition could also influence outcomes. These factors should be accounted for in future research to better understand response variability.

Future studies should prioritize standardized intervention protocols, larger and more diverse populations, and long-term follow-up to evaluate sustainability and clinical relevance. Improved reporting on adherence, adverse events, and mechanistic pathways will be essential to guide practical dietary recommendations. Ultimately, translating these findings into public health strategies could support the use of polyphenol-rich foods in chronic disease prevention and management.

CONCLUSION

This review synthesized evidence from multiple studies assessing the effects of polyphenol-rich foods and supplements on lipid metabolism, glucose regulation, renal function, and clinical outcomes. Overall, interventions such as grape powder, bergamot, and fruits and vegetables showed beneficial effects on lipid profiles, including reductions in triglycerides and LDL, and improvements in HDL and endothelial function. Fruits and vegetables were also the most consistently effective intervention for preserving renal function and reducing cardiovascular risk, including a complete absence of cardiovascular events in one study. In contrast, most polyphenol-based interventions did not produce significant improvements in glucose metabolism, with only a polyphenol-rich diet and resveratrol (in a subgroup) showing favorable effects. Safety and tolerability were generally reported as good, though adherence data and systematic adverse event reporting were inconsistently addressed across studies.

Given the variability in outcomes and study design, future research should focus on standardizing intervention protocols, clearly defining polyphenol content and bioavailability, and including larger, more diverse populations with longer follow-up periods. Stratifying results by sex, metabolic health status, and genetic or microbiome profiles may uncover more precise benefits or limitations of these interventions. Furthermore, mechanistic studies are needed to elucidate how polyphenols influence metabolic pathways and interact with other dietary components. Public health efforts could benefit from translating successful interventions—particularly whole-food approaches like fruits and vegetables—into accessible, sustainable dietary recommendations for chronic disease prevention and management.

REFERENCES

1. Du Q, Jiang Y, Liu Y Prevalence of metabolic syndrome in patients with end-stage renal disease: a systematic review and meta-analysis. Int Urol Nephrol. 2024;56(3):1057–69, doi: 10.1007/s11255-023-03790-z.
2. Scurt FG, Ganz MJ, Herzog C, Bose K, Mertens PR, Chatzikyrkou C Association of metabolic syndrome and chronic kidney disease. Obes Rev. 2024;25(1):e13649, doi: 10.1111/obr.13649.
3. Theodorakis N, Nikolaou M From cardiovascular-kidney-metabolic syndrome to cardiovascular-renal-Hepatic-metabolic syndrome: Proposing an expanded framework. Biomolecules. 2025;15(2), doi: 10.3390/biom15020213.
4. Vora J, Cherney D, Kosiborod MN, Spaak J, Kanumilli N, Khunti K, et al. Inter-relationships between cardiovascular, renal and metabolic diseases: Underlying evidence and implications for integrated interdisciplinary care and management. Diabetes Obes Metab. 2024;26(5):1567–81, doi: 10.1111/dom.15485.
5. Rudrapal M, Rakshit G, Singh RP, Garse S, Khan J, Chakraborty S Dietary polyphenols: Review on chemistry/sources, bioavailability/metabolism, antioxidant effects, and their role in disease management. Antioxidants (Basel). 2024;13(4), doi: 10.3390/antiox13040429.
6. Guerreiro Í, Ferreira-Pêgo C, Carregosa D, Santos CN, Menezes R, Fernandes AS, et al. Polyphenols and their metabolites in renal diseases: An overview. Foods. 2022;11(7):1060, doi: 10.3390/foods11071060.
7. Serreli G, Deiana M Role of dietary polyphenols in the activity and expression of nitric oxide synthases: A review. Antioxidants (Basel). 2023;12(1):147, doi: 10.3390/antiox12010147.
8. Rudrapal M, Khairnar SJ, Khan J, Dukhyil AB, Ansari MA, Alomary MN, et al. Dietary polyphenols and their role in oxidative stress-induced human diseases: Insights into protective effects, antioxidant potentials and mechanism(s) of action. Front Pharmacol. 2022;13:806470, doi: 10.3389/fphar.2022.806470.
9. Pap N, Fidelis M, Azevedo L, do Carmo MAV, Wang D, Mocan A, et al. Berry polyphenols and human health: evidence of antioxidant, anti-inflammatory, microbiota modulation, and cell-protecting effects. Curr Opin Food Sci. 2021;42:167–86, doi: 10.1016/j.cofs.2021.06.003.
10. Venturi S, Marino M, Cioffi I, Martini D, Del Bo' C, Perna S, et al. Berry dietary interventions in metabolic Syndrome: New insights. Nutrients. 2023;15(8), doi: 10.3390/nu15081906.
11. Kawakami Y, Watanabe Y, Mazuka M, Yagi N, Sawazaki A, Koganei M, et al. Effect of cacao polyphenol-rich chocolate on postprandial glycemia, insulin, and incretin secretion in healthy participants. Nutrition. 2021;85(111128):111128, doi: 10.1016/j.nut.2020.111128.
12. Goraya N, Munoz-Maldonado Y, Simoni J, Wesson DE Treatment of chronic kidney disease-related metabolic acidosis with fruits and vegetables compared to NaHCO3 yields more and better overall health outcomes and at comparable five-year cost. J Ren Nutr. 2021;31(3):239–47, doi: 10.1053/j.jrn.2020.08.001.

13. Kwon Y-J, Joo YS, Yun H-R, Lim LR, Yang J, Lee HS, et al. Safety and impact of the Mediterranean diet in patients with chronic kidney disease: a pilot randomized crossover trial. Front Nutr. 2024;11:1463502, doi: 10.3389/fnut.2024.1463502.

14. Feldman F, Koudoufio M, Desjardins Y, Spahis S, Delvin E, Levy E Efficacy of polyphenols in the management of dyslipidemia: A focus on clinical studies. Nutrients. 2021;13(2):672, doi: 10.3390/nu13020672.

15. Naesens M, Budde K, Hilbrands L, Oberbauer R, Bellini MI, Glotz D, et al. Surrogate endpoints for late kidney transplantation failure. Transpl Int. 2022;35:10136, doi: 10.3389/ti.2022.10136.

16. Menezes R, Matafome P, Freitas M, García-Conesa M-T Updated information of the effects of (poly)phenols against type-2 diabetes mellitus in humans: Reinforcing the recommendations for future research. Nutrients. 2022;14(17):3563, doi: 10.3390/nu14173563.

17. Duclos Q Effects of a Standardized, Freeze-Dried Grape Powder in Adults with Metabolic Syndrome. MSc, University of Connecticut, United States of America, 2017.

18. Stull AJ, Cash KC, Champagne CM, Gupta AK, Boston R, Beyl RA, et al. Blueberries improve endothelial function, but not blood pressure, in adults with metabolic syndrome: a randomized, double-blind, placebo-controlled clinical trial. Nutrients. 2015;7(6):4107–23, doi: 10.3390/nu7064107.

19. Stull A, Cash K, Champagne C, Gupta A, Boston R, Beyl R, et al. Blueberry bioactives improve endothelial function in adults with metabolic syndrome. FASEB J. 2015;29(S1), doi: 10.1096/fasebj.29.1_supplement.923.17.

20. Rassaf T, Rammos C, Hendgen-Cotta UB, Heiss C, Kleophas W, Dellanna F, et al. Vasculoprotective effects of dietary cocoa flavanols in patients on hemodialysis: A double-blind, randomized, placebo-controlled trial. Clin J Am Soc Nephrol. 2016;11(1):108–18, doi: 10.2215/CJN.05560515.

21. Wu P-T, Fitschen PJ, Kistler BM, Jeong JH, Chung HR, Aviram M, et al. Effects of pomegranate extract supplementation on cardiovascular risk factors and physical function in hemodialysis patients. J Med Food. 2015;18(9):941–9, doi: 10.1089/jmf.2014.0103.

22. Millar CL, Duclos Q, Garcia C, Norris GH, Lemos BS, DiMarco DM, et al. Effects of freeze-dried grape powder on high-density lipoprotein function in adults with metabolic syndrome: A randomized controlled pilot study. Metab Syndr Relat Disord. 2018;16(9):464–9, doi: 10.1089/met.2018.0052.

23. Di Folco U, Pollakova D, De Falco D, Nardone MR, Tubili F, Tubili C Effects of a nutraceutical multicompound including bergamot (Citrus Bergamia Risso) juice on metabolic syndrome: A pilot study. Med J Nutrition Metab. 2018;11(2):119–26, doi: 10.3233/mnm-17186.

24. Johnson SA, Navaei N, Pourafshar S, Jaime SJ, Akhavan NS, Alvarez-Alvarado S, et al. Effects of Tart Cherry juice on brachial and aortic hemodynamics, arterial stiffness, and blood biomarkers of cardiovascular health in adults with metabolic syndrome. FASEB J. 2017;31(S1), doi: 10.1096/fasebj.31.1_supplement.lb325.

25. Barona J, Aristizabal JC, Blesso CN, Volek JS, Fernandez ML Grape polyphenols reduce blood pressure and increase flow-mediated vasodilation in men with metabolic syndrome. J Nutr. 2012;142(9):1626–32, doi: 10.3945/jn.112.162743.

26. Ali A, Yazaki Y, Njike VY, Ma Y, Katz DL Effect of fruit and vegetable concentrates on endothelial function in metabolic syndrome: a randomized controlled trial. Nutr J. 2011;10(1):72, doi: 10.1186/1475-2891-10-72.

27. Fujitaka K, Otani H, Jo F, Jo H, Nomura E, Iwasaki M, et al. Modified resveratrol Longevinex improves endothelial function in adults with metabolic syndrome receiving standard treatment. Nutr Res. 2011;31(11):842–7, doi: 10.1016/j.nutres.2011.09.028.

28. Patel MJ, Emerenini C, Wang X, Bottiglieri T, Kitzman H Metabolomic and physiological effects of a Cardiorenal Protective Diet intervention in African American adults with chronic kidney disease. Metabolites. 2024;14(6):300, doi: 10.3390/metabo14060300.

29. Castilla P, Dávalos A, Teruel JL, Cerrato F, Fernández-Lucas M, Merino JL, et al. Comparative effects of dietary supplementation with red grape juice and vitamin E on production of superoxide by circulating neutrophil NADPH oxidase in hemodialysis patients. Am J Clin Nutr. 2008;87(4):1053–61, doi: 10.1093/ajcn/87.4.1053.

30. Janiques AGPR, Leal V de O, Stockler-Pinto MB, Moreira NX, Mafra D Effects of grape powder supplementation on inflammatory and antioxidant markers in hemodialysis patients: a randomized double-blind study. J Bras Nefrol. 2014;36(4):496–501, doi: 10.5935/0101-2800.20140071.

31. Bozzetto L, Annuzzi G, Pacini G, Costabile G, Vetrani C, Vitale M, et al. Polyphenol-rich diets improve glucose metabolism in people at high cardiometabolic risk: a controlled randomised intervention trial. Diabetologia. 2015;58(7):1551–60, doi: 10.1007/s00125-015-3592-x.

32. Goraya N, Munoz-Maldonado Y, Simoni J, Wesson DE Fruit and vegetable treatment of chronic kidney disease-related metabolic acidosis reduces cardiovascular risk better than sodium bicarbonate. Am J Nephrol. 2019;49(6):438–48, doi: 10.1159/000500042.

33. Tabrizi R, Tamtaji OR, Lankarani KB, Mirhosseini N, Akbari M, Dadgostar E, et al. The effects of resveratrol supplementation on biomarkers of inflammation and oxidative stress among patients with metabolic syndrome and related disorders: a systematic review and meta-analysis of randomized controlled trials. Food Funct. 2018;9(12):6116–28, doi: 10.1039/c8fo01259h.

34. Teixeira KTR, Moreira L de SG, Borges NA, Brum I, de Paiva BR, Alvarenga L, et al. Effect of cranberry supplementation on toxins produced by the gut microbiota in chronic kidney disease patients: A pilot randomized placebo-controlled trial. Clin Nutr ESPEN. 2022;47:63–9, doi: 10.1016/j.clnesp.2021.11.012.

35. Saldanha JF, Leal VO, Rizzetto F, Grimmer GH, Ribeiro-Alves M, Daleprane JB, et al. Effects of resveratrol supplementation in Nrf2 and NF-κB expressions in nondialyzed chronic kidney disease patients: A randomized, double-blind, placebo-controlled, crossover clinical trial. J Ren Nutr. 2016;26(6):401–6, doi: 10.1053/j.jrn.2016.06.005.

36. Walker JM, Eckardt P, Aleman JO, da Rosa JC, Liang Y, Iizumi T, et al. The effects of trans-resveratrol on insulin resistance, inflammation, and microbiota in men with the metabolic syndrome: A pi-

lot randomized, placebo-controlled clinical trial. J Clin Transl Res. 2019;4(2):122–35, doi: 10.18053/jctres.04.201802.004.

37. Basu A, Izuora K, Hooyman A, Scofield HR, Ebersole JL Dietary strawberries improve serum metabolites of cardiometabolic risks in adults with features of the metabolic syndrome in a randomized controlled crossover trial. Int J Mol Sci. 2023;24(3), doi: 10.3390/ijms24032051.

38. Taghizadeh M, Soleimani A, Bahmani F, Moravveji A, Asadi A, Amirani E, et al. Metabolic response to mulberry extract supplementation in patients with diabetic nephropathy: A randomized controlled trial. Iran J Kidney Dis. 2017;11(6):438–46.

39. Eftekhari MH, Allaei M, Khosropanah S, Rajaeifard A, Sohrabi Z Cranberry supplement and metabolic risk factors in obese and overweight females. Jentashapir J Health Res. 2016;7(3), doi: 10.17795/jjhr-37255.

40. Njike V, Ali A, Yazaki Y, Ma Y, Katz D Effect of fruit and vegetable concentrates on endothelial function in persons with metabolic syndrome: A randomized, controlled, crossover trial. FASEB J. 2011;25(S1), doi: 10.1096/fasebj.25.1_supplement.lb305.

41. Janiques AGPR Influence of whole grape powder supplementation on C-reactive protein, glutathione peroxidase and lipid profile in hemodialysis patients. MSc, Universidade Federal Fluminense, Brazil, 2013.

42. Jalili T, Beisinger S, Quadros A, Rabovsky A A mixture of grape seed and skin extract, green tea extract, resveratrol, and quercetin reduces blood pressure in hypertensive subjects with metabolic syndrome. FASEB J. 2012;26(S1), doi: 10.1096/fasebj.26.1_supplement.385.2.

43. Carresi C, Gliozzi M, Musolino V, Scicchitano M, Scarano F, Bosco F, et al. The effect of natural antioxidants in the development of metabolic syndrome: Focus on bergamot polyphenolic fraction. Nutrients. 2020;12(5):1504, doi: 10.3390/nu12051504.

44. Martini D, Marino M, Venturi S, Tucci M, Klimis-Zacas D, Riso P, et al. Blueberries and their bioactives in the modulation of oxidative stress, inflammation and cardio/vascular function markers: a systematic review of human intervention studies. J Nutr Biochem. 2023;111(109154):109154, doi: 10.1016/j.jnutbio.2022.109154.