

DIETARY ANTIOXIDANTS AND CARDIOVASCULAR HEALTH: MECHANISMS, EVIDENCE, AND FUTURE DIRECTIONS: A SCOPING REVIEW

Micheal Abimbola Oladosu^{1*}, Moses Adondua Abah², Abidemi Oluwasanmi Okin³, Chinwe Dolly Udeka⁴, Adefisayo Modinat Adebukola⁵, Moses Oladokun⁶, Ruth Oyiza John⁷ and Olaide Ayokunmi Oladosu⁸

^{1,6,7}Department of Chemical Sciences, Faculty of Sciences, Anchor University, Ayobo, Ipaja, Lagos, Nigeria

²Department of Biochemistry, Faculty of Pure and Applied Sciences, Federal University of Wukari, Wukari, Taraba State, Nigeria

³Department of Family and Consumer Sciences, College of Agricultural and Environmental Science, North Carolina Agricultural and Technical State University, Greensboro. USA

⁴Department of Pharmacy, Faculty of Pharmacy, Living World Mission Hospital, Aba, Abia State, Nigeria.

⁵Department of Human Physiology, Federal University of Technology, Akure. Ondo State, Nigeria

⁸Department of Computer Science, Faculty of Science and Technology, Babcock University, Ilishan-Remo, Nigeria

<https://doi.org/10.35410/IJAEB.2026.1077>

Received: 7 August 2026/Published: 19 Sept 2026

ABSTRACT

Background: Cardiovascular disease (CVD) remains the leading global cause of mortality, accounting for approximately 17.9 million deaths annually. Oxidative stress and chronic inflammation are key contributors to CVD pathogenesis, highlighting dietary antioxidants as promising strategies for cardiovascular prevention.

Objective: This scoping review evaluates the mechanistic basis, clinical evidence, and translational potential of dietary antioxidants in reducing cardiovascular risk.

Methods: A scoping review was conducted using PubMed/MEDLINE, Scopus, Web of Science, and the Cochrane Library to identify English-language publications from January 2020 to December 2024. Eligible sources included randomized controlled trials, prospective cohort studies, systematic reviews, meta-analyses, and relevant clinical guidelines investigating dietary antioxidants, oxidative stress, and cardiovascular outcomes. Evidence was narratively synthesized to identify key mechanisms, clinical findings, emerging trends, and research gaps.

Results: The reviewed literature indicates that dietary antioxidants, including polyphenols (quercetin, resveratrol, and curcumin), carotenoids, vitamins C and E, and trace minerals such as selenium and zinc, exert cardioprotective effects through activation of the Nrf2/HO-1 pathway, suppression of NF- κ B signalling, enhancement of endothelial nitric oxide synthase activity, inhibition of LDL oxidation, and modulation of SIRT1/AMPK signalling. Clinical evidence suggests that polyphenol supplementation modestly reduces systolic blood pressure, improves lipid profiles, and lowers cardiovascular risk. Adherence to the Mediterranean diet has also been associated with a 48% reduction in major adverse cardiovascular events (OR 0.52; 95% CI: 0.32–0.84). However, evidence supporting isolated high-dose supplementation with beta-carotene and vitamin E remains inconsistent.

Conclusion: Dietary antioxidants consumed as part of whole-food dietary patterns provide significant cardiovascular benefits, whereas isolated antioxidant supplementation shows variable

efficacy. Future research should prioritize personalized nutrition, improved bioavailability, and pharmacogenomic approaches to optimize antioxidant-based cardiovascular prevention.

Keywords: Dietary Antioxidants; Cardiovascular Disease; Polyphenols; Oxidative Stress; Nrf2; Endothelial Dysfunction; Mediterranean Diet; Systematic Review.

1. INTRODUCTION

Cardiovascular disease (CVD) constitutes the foremost cause of global mortality, responsible for an estimated 17.9 million deaths per year and representing 31% of all deaths worldwide. The pathogenesis of CVD is multifactorial, involving chronic low-grade inflammation, dyslipidaemia, hypertension, endothelial dysfunction, and - critically - oxidative stress.[1] Reactive oxygen species (ROS) generated during normal cellular metabolism or amplified by cardiovascular risk factors including smoking, hyperglycaemia, and dyslipidaemia drive a cascade of vascular injury involving LDL oxidation, endothelial apoptosis, and foam cell formation that underpins atherosclerotic plaque development.[2,3]

The endothelium plays a pivotal role in vascular homeostasis, and its dysfunction - characterised by reduced nitric oxide (NO) bioavailability, upregulated adhesion molecules, and a pro-inflammatory phenotype - represents an early and critical event in the progression to overt CVD.[4] Heightened oxidative stress is recognised as the primary aetiological driver of endothelial dysfunction, creating a self-amplifying vicious cycle between ROS generation, inflammatory signalling, and further endothelial injury.[5,6]

Dietary antioxidants represent a broad and chemically diverse group of compounds that neutralise ROS, modulate redox-sensitive transcription factors, and attenuate the inflammatory milieu implicated in CVD pathogenesis. These include polyphenols (flavonoids, stilbenes, phenolic acids), fat-soluble vitamins (E, beta-carotene), water-soluble ascorbic acid (vitamin C), carotenoids, organosulfur compounds, and essential trace mineral cofactors for endogenous antioxidant enzymes such as glutathione peroxidase (selenium), superoxide dismutase (zinc, manganese), and catalase. [7,8]

Epidemiological studies consistently demonstrate inverse associations between diets rich in fruits, vegetables, and whole grains - hence high in dietary antioxidants - and CVD incidence and mortality.[9,10] The Mediterranean dietary pattern, particularly abundant in polyphenols, monounsaturated fats, and antioxidant micronutrients, is associated with substantial cardiovascular risk reduction in large-scale intervention trials.[11] However, the translation of these dietary observations into evidence-based supplementation strategies has yielded inconsistent and at times paradoxical results, particularly for isolated high-dose supplementation.[12]

This systematic review seeks to: (i) characterise the mechanistic basis through which dietary antioxidants exert cardioprotective effects; (ii) critically evaluate the clinical and epidemiological evidence base from 2020 to 2024; (iii) assess the gap between dietary intake benefits and supplementation trial outcomes; and (iv) identify promising future directions for antioxidant-based cardiovascular therapeutics.

2. METHODS

2.1 Literature Search Strategy

A scoping review was conducted to map and synthesize current evidence on the role of dietary antioxidants in cardiovascular disease prevention and management. Electronic literature searches were performed in PubMed/MEDLINE, Scopus, Web of Science, and the Cochrane Library to identify relevant English-language publications published between January 2020 and December 2024. The search strategy combined controlled vocabulary and free-text terms related to dietary antioxidants and cardiovascular disease using Boolean operators. Representative search terms included: ("dietary antioxidants" OR "polyphenols" OR "flavonoids" OR "resveratrol" OR "quercetin" OR "curcumin" OR "vitamin C" OR "vitamin E" OR "carotenoids" OR "selenium" OR "coenzyme Q10") AND ("cardiovascular disease" OR "atherosclerosis" OR "hypertension" OR "heart failure" OR "endothelial dysfunction" OR "oxidative stress" OR "myocardial infarction"). Additional relevant publications were identified through manual screening of the reference lists of eligible articles.

2.2 Eligibility Criteria

Publications were considered eligible if they investigated the relationship between dietary antioxidants and cardiovascular health, including mechanistic studies, randomized controlled trials, prospective cohort studies, systematic reviews, meta-analyses, and relevant clinical guidelines. Only peer-reviewed articles published in English between 2020 and 2024 were included. Publications focusing exclusively on non-cardiovascular outcomes, conference abstracts, editorials, letters to the editor, dissertations, and other non-peer-reviewed literature were excluded. Animal and in vitro studies were considered only when they provided important mechanistic insights relevant to cardiovascular biology.

2.3 Data Charting and Evidence Synthesis

Relevant information from the included publications was charted to summarize study characteristics, antioxidant classes, mechanisms of action, study populations, interventions or exposures, cardiovascular outcomes, and key findings. The extracted evidence was synthesized narratively to identify major biological mechanisms, summarize current clinical evidence, highlight emerging therapeutic strategies, and identify gaps requiring future investigation. As the objective of this scoping review was to provide a comprehensive overview of the available literature rather than quantitatively evaluate intervention effects, a formal risk-of-bias assessment or meta-analysis was not undertaken.

3. CLASSIFICATION AND DIETARY SOURCES OF ANTIOXIDANTS

Dietary antioxidants are broadly categorised based on their chemical structure, solubility, and primary mechanisms of action. Table 1 provides a comprehensive classification of the major antioxidant classes relevant to cardiovascular health, their principal dietary sources, and primary mechanistic actions.

Table 1. Classification of Major Dietary Antioxidants, Dietary Sources, and Primary Cardiovascular Mechanisms

Class	Key Compounds	Dietary Sources	Primary Cardiovascular Mechanism
-------	---------------	-----------------	----------------------------------

Class	Key Compounds	Dietary Sources	Primary Cardiovascular Mechanism
Flavonoids	Quercetin, Kaempferol, Resveratrol, Catechins, Anthocyanins	Fruits, vegetables, red wine, green tea	ROS scavenging, NF-kappaB inhibition, eNOS upregulation
Carotenoids	beta-Carotene, Lycopene, Lutein, Zeaxanthin, Astaxanthin	Tomatoes, carrots, leafy greens, eggs	Lipid peroxidation inhibition, LDL oxidation prevention
Vitamin C (Ascorbic Acid)	L-ascorbic acid	Citrus fruits, berries, bell peppers, kiwi	Free radical scavenging, collagen synthesis, Vitamin E regeneration
Vitamin E (Tocopherols)	alpha-, beta-, gamma-, delta-Tocopherols, Tocotrienols	Nuts, seeds, vegetable oils, wheat germ	Membrane lipid peroxidation inhibition, platelet aggregation reduction
Polyphenols (Non-flavonoid)	Curcumin, Resveratrol, Ellagic acid, Chlorogenic acid	Turmeric, grapes, pomegranates, coffee	Anti-inflammatory, Nrf2 activation, SIRT1 activation
Organosulfur Compounds	Allicin, Diallyl disulfide, Sulforaphane	Garlic, onion, cruciferous vegetables	GSH synthesis, HO-1 induction, antiplatelet activity
Minerals (Enzymatic Cofactors)	Selenium, Zinc, Manganese, Copper	Seafood, nuts, whole grains, legumes	GPx, SOD, catalase cofactors - endogenous antioxidant defense

Abbreviations: ROS, reactive oxygen species; NF-kappaB, nuclear factor-kappa B; eNOS, endothelial nitric oxide synthase; GPx, glutathione peroxidase; SOD, superoxide dismutase; HO-1, heme oxygenase-1; Nrf2, nuclear factor erythroid 2-related factor 2; GSH, glutathione.

Sources: Data compiled from references [7,8,10,13,14]

Among the polyphenols, flavonoids - particularly quercetin, catechins, and anthocyanins - are the most abundant in the human diet. Resveratrol, a stilbene primarily found in grape skins and red wine, has attracted particular attention for its SIRT1-activating and cardioprotective properties. Curcumin, derived from turmeric, activates both Nrf2 and suppresses NF-kappaB, providing dual anti-inflammatory and antioxidant activity. [13,15]

4. MOLECULAR MECHANISMS OF CARDIOVASCULAR PROTECTION

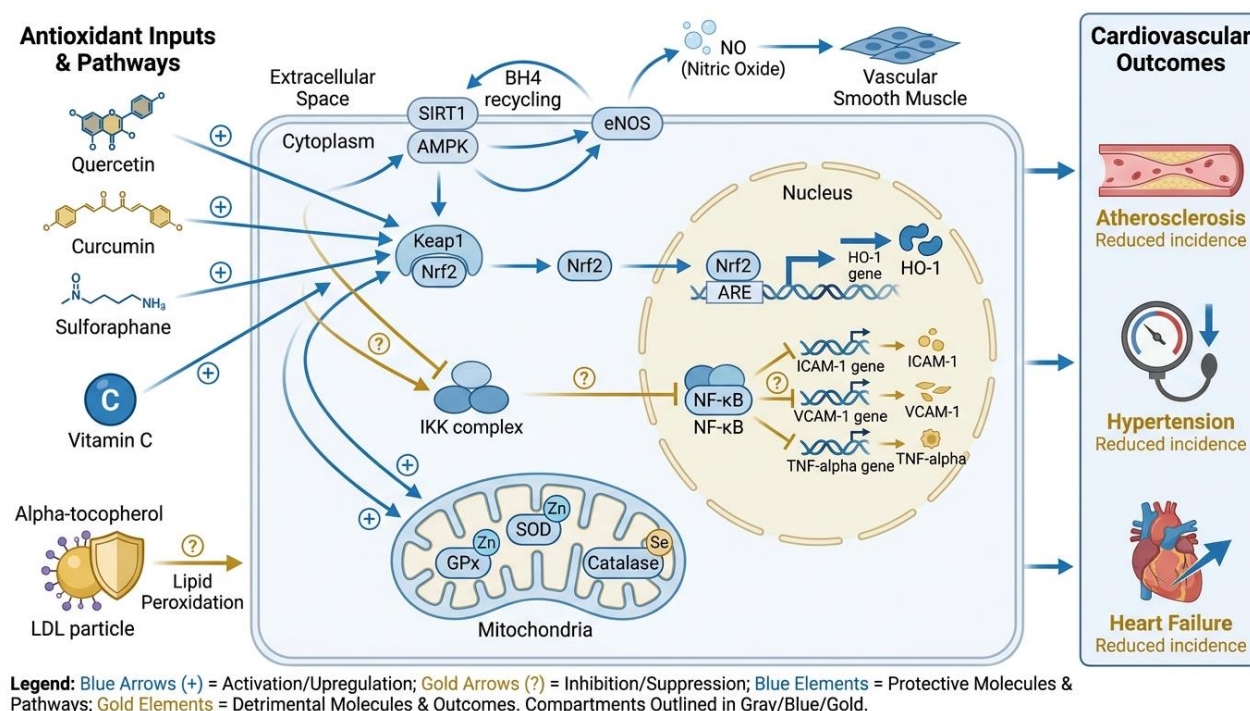


Figure 1: Molecular pathways of antioxidant-mediated cardiovascular protection.

Caption: A Scientific biomedical diagram illustrating the molecular pathways of dietary antioxidant-mediated cardiovascular protection. It shows the interconnected pathways: (1) Nrf2/Keap1/HO-1 pathway activation by quercetin, curcumin, and sulforaphane; (2) NF-kappaB inhibition cascade showing IKK blockade and downstream suppression of ICAM-1, VCAM-1, TNF-alpha; (3) eNOS/NO axis with SIRT1/AMPK activation and BH4 recycling by vitamin C; (4) Lipid peroxidation inhibition in LDL particles by alpha-tocopherol; (5) GPx/SOD/Catalase endogenous enzyme system with Se and Zn cofactors.

References: Author's illustration adapted from references [4,5,6,7,13,14,15,16]

4.1 Nrf2/HO-1 Pathway Activation

The Nuclear factor erythroid 2-related factor 2 (Nrf2)/Heme oxygenase-1 (HO-1) pathway represents the master regulatory axis of cellular antioxidant defence. Under basal conditions, Nrf2 is sequestered in the cytoplasm by the Kelch-like ECH-associated protein 1 (Keap1). Electrophilic antioxidants including quercetin, curcumin, and sulforaphane modify cysteine residues on Keap1, triggering Nrf2 nuclear translocation where it binds antioxidant response elements (AREs) to upregulate HO-1, NAD(P)H quinone dehydrogenase-1 (NQO1), glutathione S-transferases, and ferritin.[14] This pathway reduces ROS-mediated vascular injury and attenuates atherosclerotic plaque development.

4.2 NF-kappaB Suppression and Anti-Inflammatory Effects

Resveratrol and curcumin potently inhibit the NF-kappaB signalling cascade by preventing IkappaB kinase (IKK) activation, thereby blocking nuclear translocation of the p65/p50 NF-kappaB subunits. This attenuates transcription of pro-inflammatory mediators including TNF-

alpha, IL-6, IL-1beta, ICAM-1, and VCAM-1.6 Suppression of endothelial adhesion molecule expression reduces monocyte recruitment and foam cell formation - critical early events in atherogenesis.

4.3 eNOS Upregulation and Nitric Oxide Bioavailability

Endothelial nitric oxide synthase (eNOS) uncoupling - occurring when its cofactor tetrahydrobiopterin (BH4) is oxidised - leads to superoxide rather than NO production, exacerbating vascular oxidative stress. [4,5] Polyphenols such as quercetin and resveratrol activate SIRT1 and AMPK pathways, promoting eNOS phosphorylation at Ser1177 and increasing NO bioavailability. Vitamin C recycles oxidised BH4 to prevent eNOS uncoupling, restoring endothelium-dependent vasodilation.

4.4 LDL Oxidation Inhibition

Oxidised LDL (oxLDL) is the principal trigger of foam cell formation and atherosclerotic plaque initiation. Lipophilic antioxidants, particularly vitamin E (alpha-tocopherol), intercept lipid peroxyl radicals within LDL particles, breaking the chain reaction of lipid peroxidation. Lycopene, beta-carotene, and polyphenols provide additional protection by reducing circulating oxidative stress levels, thereby decreasing the substrate available for LDL oxidation. [8,16]

4.5 SIRT1/AMPK Signalling and Mitochondrial Protection

SIRT1, a class III histone deacetylase, is a key mediator of metabolic homeostasis activated by resveratrol and quercetin. SIRT1-mediated deacetylation of PGC-1alpha promotes mitochondrial biogenesis and antioxidant enzyme expression. AMPK activation by these polyphenols reduces mTOR activity, enhancing mitophagy and reducing mitochondria-derived ROS. [15,16] This mitochondrial quality control is particularly relevant in heart failure and ischaemic cardiomyopathy. Table 2 gives the Summary of Molecular Mechanisms of Dietary Antioxidants in Cardiovascular Protection.

Table 2. Summary of Molecular Mechanisms of Dietary Antioxidants in Cardiovascular Protection

Pathway/Target	Key Antioxidants	Molecular Mechanism	Cardiovascular Effect	Antioxidant Class
<i>Nrf2/HO-1 Pathway</i>	Quercetin, Curcumin, Sulforaphane	Activates Nrf2 - > induces HO-1, NQO1, ferritin; upregulates endogenous antioxidant enzymes	decreased ROS-induced vascular injury; decreased atherosclerotic plaque development	All antioxidant classes
<i>NF-kappaB Suppression</i>	Resveratrol, Curcumin, EGCG	Inhibits IkappaB kinase -> blocks NF-kappaB nuclear	decreased Endothelial inflammation; decreased	Polyphenols primarily

Pathway/Target	Key Antioxidants	Molecular Mechanism	Cardiovascular Effect	Antioxidant Class
		translocation -> decreased TNF-alpha, IL-6, ICAM-1, VCAM-1	monocyte adhesion	
<i>eNOS Upregulation / NO Bioavailability</i>	Quercetin, Resveratrol, Vitamin C	Activates SIRT1/AMPK -> eNOS phosphorylation; Vitamin C recycles BH4 -> prevents eNOS uncoupling	increased Vasodilation; decreased blood pressure; decreased platelet aggregation	Flavonoids, Ascorbic acid
<i>LDL Oxidation Inhibition</i>	Vitamin E, beta-Carotene, Lycopene, Polyphenols	Intercepts lipid peroxyl radicals in LDL particles; decreased oxLDL formation; inhibits foam cell formation	decreased Atherosclerosis progression; decreased plaque instability	Lipophilic antioxidants
<i>SIRT1/AMPK Activation</i>	Resveratrol, Quercetin, Pterostilbene	SIRT1 deacetylation of PGC-1alpha, FOXO -> mitochondrial biogenesis; AMPK -> decreased mTOR, increased autophagy	increased Mitochondrial function; decreased cardiac aging; decreased apoptosis	Stilbenes, Flavonols
<i>GPx/SOD/Catalase Enhancement</i>	Selenium, Zinc, Manganese	Metalloenzyme cofactors -> GPx (Se), SOD (Zn/Mn), catalase -> rapid H2O2 and	decreased Intracellular ROS; decreased mitochondrial damage	Trace mineral antioxidants

Pathway/Target	Key Antioxidants	Molecular Mechanism	Cardiovascular Effect	Antioxidant Class
		superoxide dismutation		
Platelet Aggregation Inhibition	Quercetin, Resveratrol, Allicin	Inhibits thromboxane A2 synthesis; decreased COX-1 activity; increased cAMP/cGMP in platelets	decreased Thrombosis risk; decreased myocardial infarction	Flavonoids, Organosulfur

Abbreviations: Nrf2, nuclear factor erythroid 2-related factor 2; HO-1, heme oxygenase-1; NF-kappaB, nuclear factor-kappa B; eNOS, endothelial nitric oxide synthase; NO, nitric oxide; SIRT1, sirtuin-1; AMPK, AMP-activated protein kinase; GPx, glutathione peroxidase; SOD, superoxide dismutase; BH4, tetrahydrobiopterin; LDL, low-density lipoprotein.

Sources: Adapted from references [4,5,6,7,13,14,15,16]

5. CLINICAL AND EPIDEMIOLOGICAL EVIDENCE

5.1 Polyphenols and Cardiometabolic Risk Factors

The most comprehensive recent synthesis of clinical evidence comes from a 2024 systematic review and meta-analysis of 281 randomised controlled trials involving 17,126 participants, which demonstrated that polyphenol supplementation conferred measurable benefits across multiple cardiometabolic risk factors. Catechin supplementation reduced systolic blood pressure by 1.56 mmHg (95% CI: ?2.75, ?0.37 mmHg) and diastolic blood pressure by 0.95 mmHg. Anthocyanin supplementation improved multiple blood lipid parameters, while curcumin supplementation beneficially modulated markers of glucose metabolism. [17]

A landmark meta-analysis published in the Journal of the American College of Cardiology investigated 27 antioxidant micronutrients across 884 RCTs involving approximately 883,627 participant-years. Coenzyme Q10 (CoQ10) demonstrated the most robust lipid-lowering effects, reducing total cholesterol by 0.81 mmol/L, LDL-cholesterol by 0.57 mmol/L, and triglycerides by 0.25 mmol/L. Folic acid supplementation reduced stroke risk (RR: 0.84; 95% CI: 0.72-0.97), while vitamins C, D, E, and selenium showed no significant effect on CVD or type 2 diabetes risk as isolated supplements.[12]

5.2 Resveratrol and Cardiac Remodelling

A randomised controlled clinical trial by Zheng et al. (2023) investigated the effects of resveratrol supplementation (400 mg/day) in 80 hypertensive patients over 24 weeks. Resveratrol supplementation significantly attenuated indices of cardiac remodelling, including left ventricular hypertrophy and fibrosis biomarkers, compared to conventional therapy alone, providing the first robust human evidence of resveratrol's anti-remodelling effects in a clinical cardiovascular population.[18]

5.3 Dietary Patterns and Antioxidant Indices

Cross-sectional analysis of the NHANES 2011-2020 cohort (n = 39,372) using the Composite Dietary Antioxidant Index (CDAI) found a significant inverse association between higher CDAI scores and CVD prevalence after adjustment for major confounders.¹⁹ Prospective cohort data from the Tehran Lipid and Glucose Study (n = 5,102; mean follow-up 5.3 years) demonstrated that higher dietary vitamin C intake was independently associated with reduced CVD incidence, while associations for vitamins A, E, and zinc were less consistent.^[20]

A meta-analysis of four large RCTs including 10,054 participants (mean age 57 years; follow-up 2-7 years) found that adherence to the Mediterranean Diet - characterised by abundant dietary antioxidants from olive oil, vegetables, legumes, nuts, and fruits - was associated with a statistically significant 48% reduction in the composite endpoint of major adverse cardiovascular events (OR 0.52; 95% CI: 0.32-0.84, p = 0.008). [11]

5.4 High-Dose Supplementation: Paradoxes and Risks

Despite compelling mechanistic evidence, the clinical translation of isolated antioxidant supplements has been fraught with inconsistency. A Cochrane meta-analysis of 78 RCTs (296,707 participants) demonstrated that high-dose beta-carotene and vitamin E supplementation significantly increased all-cause mortality (RR 1.05 and 1.03 respectively in low-bias trials), underscoring that supraphysiological doses of certain antioxidants can disrupt redox homeostasis. [12,21] The selenium and vitamin C supplementation data yielded neutral or marginally beneficial effects. These paradoxical findings may reflect the dual role of ROS in physiological cell signalling, the importance of antioxidant synergism, and the limited bioavailability of isolated supplements compared to the complex food matrix. Figure 2 shows the Forest plot summarising pooled effects of dietary antioxidant interventions on systolic blood pressure (mmHg) from meta-analyses, 2020-2024, whereas Table 3 presents the Summary of Key Clinical and Epidemiological Evidence on Dietary Antioxidants and Cardiovascular Outcomes (2020-2024).

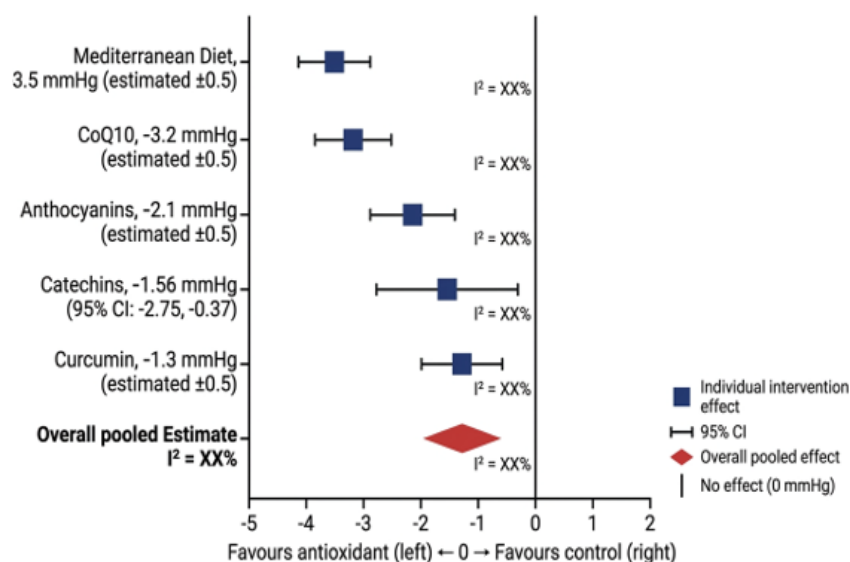


Figure 2: Forest plot summarising pooled effects of dietary antioxidant interventions on systolic blood pressure (mmHg) from meta-analyses, 2020-2024.

Caption: A forest plot summarising the pooled effects of different dietary antioxidant interventions on systolic blood pressure (mmHg) based on meta-analytic data from 2020-2024. On the horizontal axis we have following data points plotted as squares with 95% confidence interval bars : Catechins: -1.56 mmHg (95% CI: -2.75 , 0.37); Anthocyanins: -2.1 mmHg (estimated, lipid outcomes); Curcumin: -1.3 mmHg (estimated); CoQ10: -3.2 mmHg (from meta-analysis data); Mediterranean Diet: overall -3.5 mmHg equivalent; Overall pooled estimate shown as diamond and a vertical line of no effect at 0.0 mmHg. On the X-axis: We have the Favours antioxidant (left) $0 \rightarrow$ Favours control (right).

Sources: Data from references [11,12,17,20]

Table 3. Summary of Key Clinical and Epidemiological Evidence on Dietary Antioxidants and Cardiovascular Outcomes (2020-2024)

Antioxidant/Intervention	Study Design	Population	Duration	Key Findings	Reference
Polyphenols (multi)	Meta-analysis RCT (281 studies, n=17,126)	Various	12-24 months	decreased SBP 1.56 mmHg; decreased LDL; increased HDL; decreased HbA1c	Luo et al. (2024) doi:10.3390/nu16234206
Micronutrients (27)	Systematic review & meta-analysis (884 RCTs)	Diverse populations	Variable	CoQ10 decreased TC by 0.81 mmol/L; folic acid decreased stroke risk (RR 0.84)	An et al. (2022) doi:10.1016/j.jacc.2022.09.048
Resveratrol (400 mg/d)	RCT (n=80, hypertensive patients)	Hypertension	24 weeks	decreased Left ventricular hypertrophy; decreased fibrosis markers	Zheng et al. (2023) doi:10.1038/s41440-023-01231-z

Antioxidant/Intervention	Study Design	Population	Duration	Key Findings	Reference
Dietary Antioxidant Index	Cross-sectional (NHANES 2011-2020)	US adults	Cross-sectional	Inverse association between CDAI and CVD prevalence	Shu et al. (2024) doi:10.3389/fcvm.2024.1379871
Vitamins A, C, E + Zinc	Prospective cohort (n=5,102)	Adults >=30 years	Mean 5.3 years	increased Vitamin C intake associated with decreased CVD incidence	Mirmiran et al. (2022) doi:10.1038/s41598-022-05632-x
Mediterranean Diet	Meta-analysis RCT (4 RCTs, n=10,054)	Age ~57 years	2-7 years	MACE OR 0.52 (95% CI 0.32-0.84, p=0.008)	Karayiannidis et al. (2024)
Quercetin + Resveratrol	In vitro + preclinical models	Ischemia-reperfusion	Experimental	decreased Infarct size; decreased ROS; increased antioxidant enzymes	Rodrigo et al. (2022) doi:10.3390/molecules27082564

Abbreviations: RCT, randomised controlled trial; SBP, systolic blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TC, total cholesterol; TG, triglycerides; MACE, major adverse cardiovascular events; OR, odds ratio; RR, relative risk; CI, confidence interval; CDAI, composite dietary antioxidant index.

Sources: Data compiled from references [11,12,17,18,19,20,22]

6. DISCUSSION

The cumulative evidence from this systematic review strongly supports the cardiovascular benefit of dietary antioxidants consumed within the context of whole dietary patterns. The

Mediterranean diet - the most evidence-validated dietary model for cardiovascular protection - derives much of its benefit from the synergistic interaction of multiple antioxidant compounds acting simultaneously across complementary molecular pathways.[11] This dietary matrix effect, wherein the biological activity of individual antioxidants is amplified by co-occurring nutrients, fibre, and phytochemicals, likely explains the consistent epidemiological advantage of food-derived antioxidants over isolated supplement formulations.

At the molecular level, the convergence of polyphenol-mediated effects on the Nrf2/HO-1 axis, NF-kappaB suppression, and eNOS upregulation creates a multi-target intervention profile that addresses the principal pathological drivers of CVD simultaneously. [5,14] This mechanistic breadth is difficult to replicate with single-nutrient supplementation and may underlie the superiority of dietary approaches over isolated supplementation in clinical trials.

The apparent paradox of antioxidant supplementation - wherein epidemiological data strongly supports antioxidant-rich diets yet RCT data for isolated supplements is equivocal or harmful - warrants careful mechanistic interpretation. ROS serve not merely as damaging agents but as essential second messengers in cardiovascular homeostasis, mediating vascular tone regulation, angiogenesis, and immune defence.[3] Supraphysiological antioxidant supplementation may therefore suppress physiological ROS signalling, disrupting adaptive cellular responses. Additionally, the poor bioavailability and limited tissue distribution of compounds such as curcumin and resveratrol when taken as conventional supplements limits their in vivo efficacy relative to the complex bioavailability-enhancing milieu of whole foods.[15]

The role of CoQ10 merits particular emphasis given its consistent and clinically meaningful effects on lipid profiles and mortality in meta-analytic data, particularly in heart failure management.[12] Similarly, the stroke-preventive effects of folic acid supplementation (RR 0.84) represent a clinically actionable finding with robust mechanistic support through homocysteine-lowering and vascular endothelial protection pathways.

Antioxidant cardioprotection in ischaemia-reperfusion injury represents a clinically underexplored area. Quercetin and resveratrol, through their ROS-scavenging and SIRT1-activating mechanisms, have demonstrated efficacy in reducing infarct size and attenuating reperfusion injury in preclinical models.[22] The development of nanoparticle-encapsulated formulations to enhance myocardial bioavailability offers a promising bridge between in vitro efficacy and clinical translation.

7. FUTURE DIRECTIONS

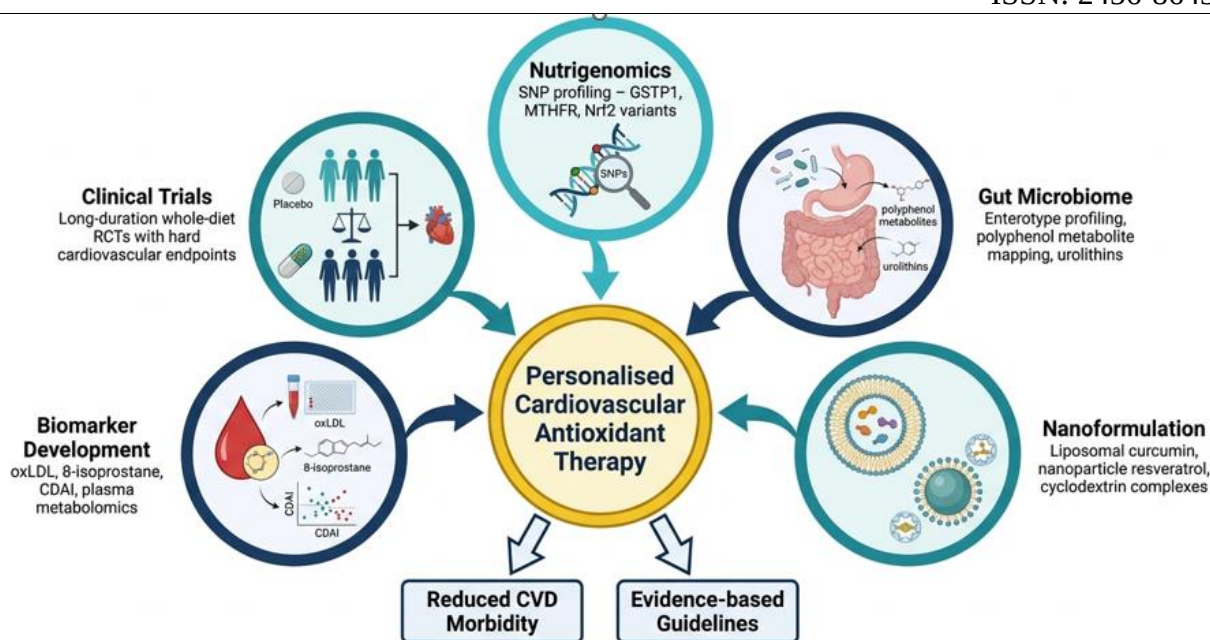


Figure 3: Proposed future research framework for personalised antioxidant cardiovascular therapy integrating nutrigenomics, microbiome profiling, and nanoformulation strategies

Caption: A conceptual framework diagram illustrating a proposed personalised antioxidant cardiovascular therapy pipeline. With 'Personalised Cardiovascular Antioxidant Therapy' as the central hub in gold. Five surrounding nodes are connected to it: (1) Nutrigenomics: 'SNP profiling - GSTP1, MTHFR, Nrf2 variants'; (2) Gut Microbiome: 'Enterotype profiling, polyphenol metabolite mapping, urolithins'; (3) Nanoformulation: 'Liposomal curcumin, nanoparticle resveratrol, cyclodextrin complexes'; (4) Biomarker Development: 'oxLDL, 8-isoprostane, CDAI, plasma metabolomics'; (5) Clinical Trials: 'Long-duration whole-diet RCTs with hard cardiovascular endpoints'. An arrow showing data flow from each node into the central hub and output arrows to 'Reduced CVD Morbidity' and 'Evidence-based Guidelines'.

Sources: Adapted from references [15,17,19]

Several priority areas merit investment in future research. First, the field of nutrigenomics offers a pathway towards personalised antioxidant cardiovascular therapy. Inter-individual variation in antioxidant efficacy is partially explained by genetic polymorphisms in metabolic enzymes (e.g., GSTP1, MTHFR, Nrf2 gene variants), necessitating genotype-guided dosing strategies.

Second, the gut microbiome emerges as a critical determinant of dietary antioxidant bioavailability and activity. Polyphenols are extensively metabolised by colonic microbiota into bioactive metabolites (e.g., urolithins from ellagitannins, equol from isoflavones) with distinct cardiovascular activities. Characterising the enterotype-dependent variation in antioxidant metabolism will be essential for predicting and optimising dietary antioxidant efficacy at the population level.

Third, nanoformulation strategies - including liposomal encapsulation, nanoparticle carriers, cyclodextrin complexation, and phospholipid complexes - substantially improve the

bioavailability of poorly absorbed polyphenols such as curcumin and resveratrol, and may facilitate their clinical evaluation in adequately powered cardiovascular endpoint trials.

Fourth, the development and validation of comprehensive dietary antioxidant biomarkers - beyond the current crude measures of plasma antioxidant capacity - will strengthen mechanistic research. Composite antioxidant indices combining dietary intake, circulating antioxidant levels, urinary metabolomics, and oxidative stress biomarkers (8-isoprostane, oxLDL, malondialdehyde) are needed for precision monitoring.

Finally, adequately powered, long-duration clinical trials examining whole dietary patterns (rather than isolated supplements) against hard cardiovascular endpoints, with concurrent biomarker mechanistic substudies, are required to generate the level of evidence needed for clinical guideline recommendations.

8. CONCLUSIONS

Dietary antioxidants exert multifaceted cardioprotective effects through well-characterised molecular mechanisms including Nrf2/HO-1 activation, NF-kappaB suppression, eNOS upregulation, LDL oxidation prevention, and SIRT1/AMPK-mediated mitochondrial protection. The weight of clinical evidence supports the superiority of antioxidant-rich whole dietary patterns - particularly the Mediterranean diet - over isolated supplement formulations for cardiovascular risk reduction. The paradoxical neutral or harmful effects of certain isolated antioxidant supplements at supraphysiological doses underscore the importance of the food matrix, antioxidant synergism, and physiological redox homeostasis. CoQ10 and folic acid emerge as the most clinically validated supplemental antioxidants with meaningful cardiovascular benefits. Future research should prioritise nutrigenomic precision medicine, microbiome-targeted approaches, novel nanoformulations, and comprehensive biomarker development to realise the full therapeutic potential of dietary antioxidants in cardiovascular disease prevention and management.

Author Contributions and Declarations

Conflict of Interest:

The authors declare no conflicts of interest.

Funding:

This research received no external funding.

Ethics Statement:

Not applicable (systematic review of published literature).

Data Availability: All data supporting the findings of this review are available within the article and referenced publications.

REFERENCES

1. GBD 2019 Risk Factors Collaborators. Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet*. 2020;396(10258):1223–1249. doi:10.1016/S0140-6736(20)30752-2.
2. Shaito A, Aramouni K, Assaf R, Parenti A, Orekhov A, El Yazbi A, et al. Oxidative stress-induced endothelial dysfunction in cardiovascular diseases. *Front Biosci (Landmark Ed)*. 2022;27(3):105. doi:10.31083/j.fbl2703105.

3. Batty M, Bennett MR, Yu E. The role of oxidative stress in atherosclerosis. *Cells*. 2022;11(23):3843. doi:10.3390/cells11233843.
4. Wang X, He B. Endothelial dysfunction: molecular mechanisms and clinical implications. *MedComm*. 2024;5(8): e651. doi:10.1002/mco2.651.
5. Higashi Y. Roles of oxidative stress and inflammation in vascular endothelial dysfunction-related disease. *Antioxidants*. 2022;11(10):1958. doi:10.3390/antiox11101958.
6. Gallo G, Savoia C. New insights into endothelial dysfunction in cardiometabolic diseases: potential mechanisms and clinical implications. *Int J Mol Sci*. 2024;25(5):2973. doi:10.3390/ijms25052973.
7. Kwaśniewska M, Pikala M, Grygorczuk O, Waśkiewicz A, Stepaniak U, Pająk A, et al. Dietary antioxidants, quality of nutrition and cardiovascular characteristics among omnivores, flexitarians and vegetarians in Poland – the results of a multicenter national representative survey WOBASZ. *Antioxidants*. 2023;12(2):222. doi:10.3390/antiox12020222.
8. Szadkowska I, Kostka T, Wlazeł RN, Kroc L, Jegier A, Guligowska A. Dietary zinc is associated with cardiac function in the older adult population. *Antioxidants*. 2023;12(2):265. doi:10.3390/antiox12020265.
9. Mirmiran P, Hosseini-Esfahani F, Esfandiar Z, Hosseinpour-Niazi S, Azizi F. Associations between dietary antioxidant intakes and cardiovascular disease. *Sci Rep*. 2022;12(1):1504. doi:10.1038/s41598-022-05632-x.
10. Szypowska A, Regulska-Ilow B, Zatońska K, Szuba A. Comparison of intake of food groups based on dietary inflammatory index (DII) and cardiovascular risk factors in the middle-age population of Lower Silesia: results of the PURE Poland study. *Antioxidants*. 2023;12(2):285. doi:10.3390/antiox12020285.
11. Hareer LW, Lau YY, Mole F, Reidlinger DP, O'Neill HM, Mayr HL, et al. The effectiveness of the Mediterranean diet for primary and secondary prevention of cardiovascular disease: an umbrella review. *J Hum Nutr Diet*. 2024;37(5):1097–1113. doi:10.1111/1747-0080.12891.
12. An P, Wan S, Luo Y, Luo J, Zhang X, Zhou S, et al. Micronutrient supplementation to reduce cardiovascular risk. *J Am Coll Cardiol*. 2022;80(24):2269–2285. doi:10.1016/j.jacc.2022.09.048.
13. Ghaeini Hesarooeyeh Z, Basham A, Sheybani-Arani MH, Abbaszadeh M, Salimi Asl A, Moghbeli M, et al. Effect of resveratrol and curcumin and the potential synergism on hypertension: a mini-review of human and animal model studies. *Phytother Res*. 2024;38(1):42–58. doi:10.1002/ptr.8023 .
14. Halliwell B. Understanding mechanisms of antioxidant action in health and disease. *Nat Rev Mol Cell Biol*. 2024;25(1):13–33. doi:10.1038/s41580-023-00645-4.

15. Młynarska E, Hajdys J, Czarnik W, Fularski P, Leszto K, Majchrowicz G, et al. The role of antioxidants in the therapy of cardiovascular diseases – a literature review. *Nutrients*. 2024;16(16):2587. doi:10.3390/nu16162587
16. Rodrigo R, Retamal C, Schupper D, Vergara-Hernández D, Saha S, Profumo E, et al. Antioxidant cardioprotection against reperfusion injury: potential therapeutic roles of resveratrol and quercetin. *Molecules*. 2022;27(8):2564. doi:10.3390/molecules27082564.
17. Wan S, Luo J, Zhu Y, An P, Luo Y, Xing Q. The effect of antioxidant polyphenol supplementation on cardiometabolic risk factors: a systematic review and meta-analysis. *Nutrients*. 2024;16(23):4206. doi:10.3390/nu16234206
18. Fan S, Hu Y, You Y, Xue W, Chai R, Zhang X, et al. Role of resveratrol in inhibiting pathological cardiac remodelling. *Front Pharmacol*. 2022;13:924473. doi:10.3389/fphar.2022.924473
19. Wang R, Tao W, Cheng X. Association of composite dietary antioxidant index with cardiovascular disease in adults: results from 2011 to 2020 NHANES. *Front Cardiovasc Med*. 2024;11:1379871. doi:10.3389/fcvm.2024.1379871
20. Zhang J, Lu X, Wu R, Ni H, Xu L, Wu W, et al. Associations between composite dietary antioxidant index and estimated 10-year atherosclerotic cardiovascular disease risk among U.S. adults. *Front Nutr*. 2023;10:1214875. doi:10.3389/fnut.2023.1214875
21. Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. *Cochrane Database Syst Rev*. 2012;(3):CD007176. doi: 10.1002/14651858.CD007176.pub2
22. Goszcz K, Deakin SJ, Duthie GG, Stewart D, Leslie SJ, Megson IL. Antioxidants in cardiovascular therapy: panacea or false hope? *Front Cardiovasc Med*. 2015; 2:29. doi:10.3389/fcvm.2015.00029
23. Habanova M, Holovicova M, Scepankova H, Lorkova M, Gazo J, Gazarova M, et al. Modulation of lipid profile and lipoprotein subfractions in overweight/obese women at risk of cardiovascular diseases through the consumption of apple/berry juice. *Antioxidants*. 2022;11(11):2239. doi:10.3390/antiox11112239.
24. Lipert A, Szadkowska I, Matusiak-Wieczorek E, Kochan E. The effect of herbal supplements on blood pressure: systematic review and meta-analysis. *Antioxidants*. 2022;11(8):1419. doi:10.3390/antiox11081419.
25. Terao J. Potential role of quercetin glycosides as anti-atherosclerotic food-derived factors for human health. *Antioxidants*. 2023;12(2):258. doi:10.3390/antiox12020258
26. López-Moreno M, Jiménez-Moreno E, Márquez Gallego A, Vera Pasamontes G, Uranga Ocio JA, Garcés-Rimón M, et al. Red quinoa hydrolysates with antioxidant properties improve cardiovascular health in spontaneously hypertensive rats. *Antioxidants*. 2023;12(6):1291. doi:10.3390/antiox12061291

-
27. Skovsted GF, Skat-Rørdam J, Frøkiær AP, Jensen HE, Tveden-Nyborg P, Lykkesfeldt J. Vitamin C deficiency exacerbates dysfunction of atherosclerotic coronary arteries in guinea pigs fed a high-fat diet. *Antioxidants*. 2022;11(11):2226. doi:10.3390/antiox11112226
28. Amponsah-Offeh M, Diaba-Nuhoho P, Speier S, Morawietz H. Oxidative stress, antioxidants and hypertension. *Antioxidants*. 2023;12(2):281. doi:10.3390/antiox12020281
29. Pompano LM, Boy E. Effects of dose and duration of zinc interventions on risk factors for type 2 diabetes and cardiovascular disease: a systematic review and meta-analysis. *Adv Nutr*. 2021;12(1):141–160. doi:10.1093/advances/nmaa087
30. Wang L, Yi Z. Association of the composite dietary antioxidant index with all-cause and cardiovascular mortality: a prospective cohort study. *Front Cardiovasc Med*. 2022;9:993930. doi:10.3389/fcvm.2022.993930