

Review

Nutritional Countermeasures to Environmental Endocrine Disruption in Cardiovascular Disease

Yang Xu¹, Chongzhe Pei^{1,*}, Hongmei Zheng¹, Li Xue¹, Hongshi Li¹, Heng Cai^{1,*}¹Department of Cardiology, Tianjin Medical University General Hospital, 300052 Tianjin, China*Correspondence: chongzhepei@163.com (Chongzhe Pei); caihengch@163.com (Heng Cai)

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Abstract

Background: Patients remain at substantial residual cardiovascular risk despite standardized management of classical risk factors. These limitations in clinical practice have led to an exposome-based approach. Among environmental exposures, endocrine-disrupting chemicals (EDCs) have emerged as ubiquitous and insidious promoters of cardiometabolic disease. **Objectives:** This review critically examines chronic environmental exposure to EDCs and the role of these chemicals in cardiovascular injury. In addition, this review highlights how targeted dietary therapies can shift patient management from passive environmental avoidance toward active biological protections. **Methods and Results:** We review recent mechanistic advances and show that lipophilic EDCs can hijack host signaling networks even at very low exposure levels. These molecular alterations promote mitochondrial dysfunction and global epigenetic reprogramming, leading to proximal metabolic derangements, particularly adipose tissue inflammation, insulin resistance, and atherogenic dyslipidemia. The cardioprotective effects of dietary antioxidants and bioactive phytochemicals appear to arise from intracellular signaling crosstalk. These compounds activate the nuclear factor erythroid 2-related factor 2 (Nrf2) antioxidant pathway while inhibiting the nuclear factor kappa B (NF-κB) proinflammatory cascade, thereby reducing oxidative stress and endothelial inflammation. Bioactive compounds such as polyphenols, omega-3 fatty acids, and vitamin D may function as nutriepigenetic modulators that counter receptor toxicity and resolve vascular inflammation. Simultaneously, the gut microbiota–vascular axis may act as a biological filter. The Mediterranean diet provides one such holistic intervention by strengthening intestinal barrier function, improving short-chain fatty acid (SCFA) signaling, and reducing pro-atherogenic trimethylamine N-oxide (TMAO) production. **Conclusions:** EDC exposure disrupts metabolism and can lead to cardiovascular disease. Nutritional approaches targeting the vulnerable human–environment interface can become a proactive chemopreventive shield. Future preventive cardiology may require a significant shift toward precision dietary fortification with an exposome-level risk assessment.

Keywords: environmental endocrine disruptors; cardiovascular disease; endocrine homeostasis; metabolic regulation; nutritional intervention; metabolic syndrome

1. Introduction

Despite the widespread identification and standardized management of classical cardiovascular risk factors (hypertension, dyslipidemia, diabetes, and smoking), cardiovascular disease (CVD) remains a significant epidemiological challenge, and many patients continue to possess substantial residual cardiovascular risk [1,2]. This challenge has shifted attention in cardiovascular science toward the exposome, a concept that encompasses the cumulative impact of environmental exposures and their biological effects across the lifespan [3]. Within this broader landscape of non-traditional risks, endocrine-disrupting chemicals (EDCs) have emerged as a pervasive threat in modern industrialized life [4]. Unlike acutely toxic agents, synthetic compounds such as bisphenols, phthalates, and per- and polyfluoroalkyl substances (PFAS) exert their effects insidiously, mimicking endogenous signals or disrupting physiological pathways at very low, chronic exposure levels. Since many of these chemicals are lipophilic and environmentally persistent, they bioaccumulate in human adipose

tissue and can drive a lifelong burden of metabolic disturbance, often with a clinically silent latency [5]. The cascade of pathophysiological events extends from the inhibition of nuclear receptors and impaired mitochondrial bioenergetics to epigenetic reprogramming. Ultimately, these upstream molecular modifications contribute to irreversible endothelial injury, pathological immune–inflammatory dysregulation, and destabilization of atherosclerotic plaques [6,7]. Importantly, targeted nutrition represents a promising protective strategy. Accordingly, this review aims to examine the pathogenic continuum from environmental EDC exposure to cardiovascular damage. We also consider how nutritional interventions may strengthen physiological barriers and propose a framework informed by recent advances in nutritional epigenetics and microbiome–vascular crosstalk.

2. Environmental Endocrine Disruptors

Although classical cardiovascular risk factors are more commonly identified and managed, CVD—the leading cause of death worldwide—continues to undergo an



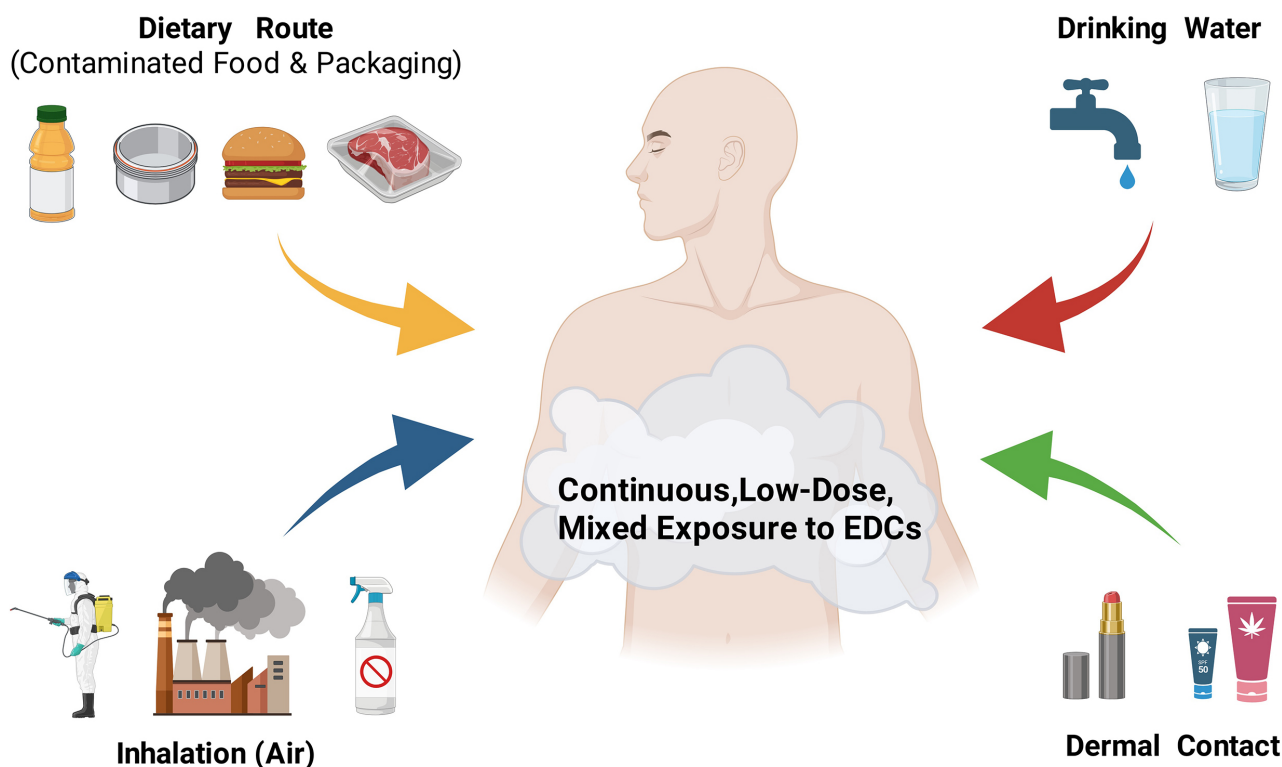


Fig. 1. Principal routes of human exposure to endocrine-disrupting chemicals (EDCs). People are constantly exposed to complex mixtures of EDCs through various routes, primarily through their diet (contaminated food and migration from packaging) and drinking water, as well as through airborne and dermal contact.

important epidemiological transition [1,2]. Control of traditional risk factors cannot fully eliminate most residual cardiovascular risk in many patients [8,9]. This limitation has intensified scientific interest in the exposome. Among environmental determinants, EDCs are of particular relevance. These ubiquitous external agents affect the endocrine system and are increasingly recognized as an important non-traditional risk factor in the pathogenesis of cardiometabolic disease [4]. EDCs comprise a broad range of synthetic exogenous compounds in the environment that interfere with normal endocrine function by altering hormone synthesis, metabolism, binding, or signal transduction. EDCs are further classified according to their chemical structure and origin and include bisphenols, phthalates, organic compounds, per- and polyfluoroalkyl substances (PFAS), and certain pesticides [10,11]. Human exposure occurs continuously at low levels through complex mixtures, mainly via pesticide residues in food, migration from food-contact materials, drinking water, inhalation, and dermal contact [12] (Fig. 1).

The endocrine system plays a central role in cardiovascular and metabolic regulation. In addition to the classic hypothalamus–pituitary–target gland axes (thyroid, adrenal, and gonadal), emerging endocrine organs such as adipose tissue, liver, and muscle actively participate in the regulation of glucose and lipid metabolism, as well as inflammation, through the secretion of bioactive mediators

such as leptin, adiponectin, and fibroblast growth factor 21 (FGF21). EDCs can disrupt multiple endocrine axes and signaling pathways, thereby promoting systemic metabolic dysfunction [10,13,14].

Two major toxicological features of EDCs are developmental programming and lifelong accumulation. Early life, particularly the fetal and infant periods, represents a critical window for organ development and metabolic programming. During this period, EDC-induced epigenetic alterations, including changes in DNA methylation, can modify metabolic phenotypes and increase the risk of obesity, insulin resistance, and CVD in adulthood [15,16]. In addition, many EDCs are lipophilic and environmentally persistent, which facilitates adipose tissue accumulation and biomagnification [17]. Therefore, prolonged exposure results in bioaccumulation and continuous internal exposure to low doses, sustaining cardiovascular risk over time with a latent and insidious course [18].

Accordingly, this review systematically examines the pathogenic cascade linking exposure to EDCs, endocrine disruption, metabolic disorder, and cardiovascular damage. Building on this framework, we also discuss the protective role of nutrition as both a preventive and interventional strategy and consider contributions from an integrative medicine perspective to precision prevention and the comprehensive management of cardiovascular disease.

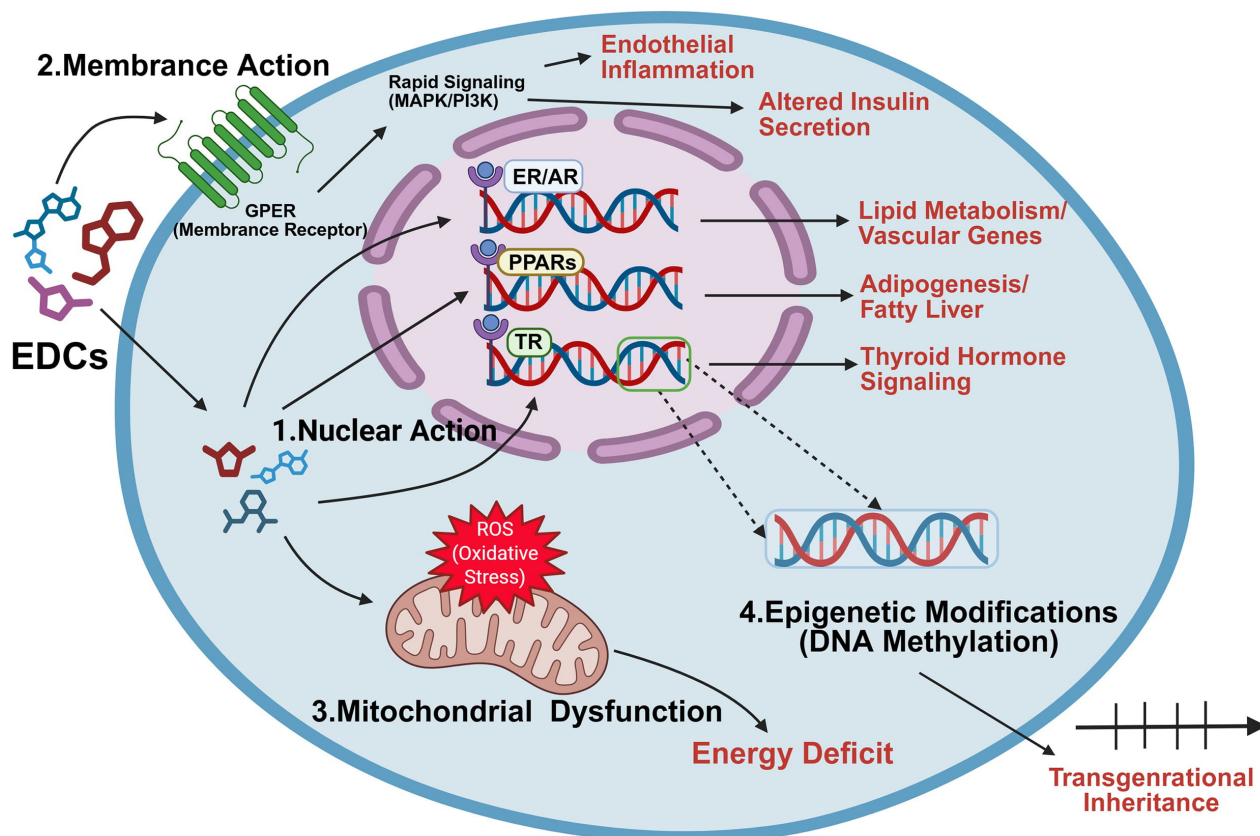


Fig. 2. EDCs disrupt cellular homeostasis through four interconnected mechanisms. (1) Interference with nuclear receptors (e.g., ER, AR, PPARs, TR). (2) Activation of rapid non-genomic signaling via membrane receptors (e.g., GPER). (3) Induction of oxidative stress and mitochondrial dysfunction. (4) Induction of epigenetic changes (e.g., DNA methylation) that may contribute to transgenerational inheritance. ER, Estrogen Receptor; AR, Androgen Receptor; PPARs, Peroxisome Proliferator-Activated Receptors; TR, Thyroid Hormone Receptor; GPER, G protein-coupled estrogen receptor.

3. Core Mechanisms of EDC-Induced Endocrine Disruption and Metabolic Dysregulation

EDC-mediated disruption can perturb metabolic and cardiovascular homeostasis through multiple molecular pathways, including nuclear receptor signaling (e.g., ER, AR, and PPARs) and mitochondrial bioenergetic impairment, oxidative stress, and epigenetic reprogramming (Fig. 2).

3.1 Nuclear Receptor-Mediated Signaling Interference

EDCs primarily induce metabolic toxicity through interference with nuclear receptor signaling. EDCs that mimic or block natural hormones by binding to the corresponding receptors can upset metabolic equilibrium.

3.1.1 Estrogen Receptor (ER) and Androgen Receptor (AR) Signaling Axes

A range of chemicals, including bisphenol A (BPA) and some phthalates, exhibit strong estrogenic activity. ERs regulate transcriptional programs involved in lipid metabolism, vasodilation, and inflammation. BPA expo-

sure can impair vasodilation by downregulating endothelial nitric oxide synthase (eNOS) expression and function [19]. In contrast, vinclozolin is a pesticide that can act as an AR antagonist. Vinclozolin disrupts hormone-mediated fat distribution, contributing to central obesity and dyslipidemia, both alone and in mixtures at low doses [20]. In addition, studies have shown that mono-phthalate esters (mPAEs) and hydroxylated polycyclic aromatic hydrocarbons (OH-PAHs) disrupt ER signaling while promoting abnormal hepatic triglyceride (TG) uptake and synthesis. Aryl hydrocarbon receptor (AhR)-mediated CD36 activation can also promote marked hepatic lipid accumulation and steatosis [21].

3.1.2 Dysregulation of Peroxisome Proliferator-Activated Receptors (PPARs)

Members of the PPAR nuclear receptor family have emerged as key transcriptional regulators of lipid homeostasis and glucose metabolism. PPAR- γ is widely regarded as the “master regulator” of adipocyte differentiation and insulin sensitivity. TBT, TPT, and BPA might act as PPAR- γ ligands and promote receptor activation within an EDC-specific signaling context. This can enhance adipocyte

differentiation and fat deposition, ultimately contributing to systemic insulin resistance [22,23]. PPAR- α regulates hepatic fatty acid β -oxidation. Meanwhile, phenolic compounds can interfere with PPAR- α signaling, impairing the natural ability of the liver to degrade fat and thereby increasing TG levels [24,25]. Research further suggests that PFAS, bisphenols, mPAEs, and OH-PAHs can activate PPAR- α or PPAR- γ [26,27]. Indeed, these compounds disrupt lipid homeostasis and promote abnormal adipocyte differentiation by disturbing the balance between fatty acid production and degradation.

3.1.3 Thyroid Hormone Receptor (TR) Interference

Polybrominated diphenyl ethers are EDCs that can alter thyroid homeostasis by changing circulating thyroid hormone levels. Sheikh [28] conducted molecular docking studies and reported that environmental pollutants such as 4-tert-octylphenol and 4-nonylphenol bind to human thyroid hormone-binding globulin (TBG) and thyroid hormone receptors (THR). Moreover, 4-nonylphenol and MBP, a BPA metabolite, were found to interact with amino acid residues at ligand-binding sites. Therefore, such interference with thyroid hormone transport and receptor binding is likely. Meanwhile, since thyroid hormones are essential for basal metabolic rate, lipid homeostasis, and cardiac function, disruption of this signaling axis may contribute to CVD both directly and indirectly [29].

3.2 Membrane Receptor-Mediated Rapid Non-Genomic Effects

In addition to classical nuclear receptor pathways, EDCs can induce rapid biological effects. These effects may occur through activation of membrane-associated receptors, such as the G protein-coupled estrogen receptor (GPER), or through direct interference with intracellular signal transduction networks. BPA acts as a ligand for GPER and can rapidly activate downstream MAPK/ERK and PI3K/Akt signaling cascades. This rapid signaling may trigger abnormal insulin secretion or endothelial inflammation within minutes to hours, thereby affecting metabolic homeostasis before transcriptional responses are activated [30,31].

3.3 Oxidative Stress-Driven Mitochondrial Bioenergetic Crisis

Many EDCs damage mitochondria and disrupt mitochondrial function. These chemicals induce excessive reactive oxygen species (ROS) production and alter intracellular redox balance. ROS overload directly damages mtDNA and respiratory chain proteins, causing loss of mitochondrial membrane potential and impairing electron transport chain function, as well as ATP production [32]. According to Grossini et al. [33], the vascular endothelial damage of such an injury is not limited to mitochondrial damage; it also activates inflammatory and apoptotic cascades that

contribute to multi-organ pathology. Persistent oxidative stress in vascular endothelial cells and cardiomyocytes promotes mitochondrion-mediated apoptosis and NLRP3 inflammasome activation, culminating in endothelial and myocardial dysfunction and remodeling [32,34]. Guo et al. [35], utilizing *in vivo* and *in vitro* models, showed that BPA increases ROS production, reduces ATP generation, and disrupts mitochondrial membrane potential, leading to cardiomyocyte apoptosis and impaired cardiac development. According to animal studies [36], even 15 days of exposure to low-dose TBT at the acceptable daily intake (ADI) level caused severe hypoestrogenism through ovarian dysfunction. The resulting loss of hormonal homeostasis removed vascular protection, induced marked oxidative stress, including excess superoxide anion, and promoted structural remodeling, including collagen deposition and medial atrophy, in the vessel wall. Thus, vasodilatory capacity was impaired.

3.4 Epigenetic Modifications and Transgenerational Inheritance

EDCs can alter DNA methylation, histone modifications, and non-coding RNA expression. These epigenetic modifications can remain stable through cell division and may also be transmitted to subsequent generations [37,38]. DNA methylation occurs predominantly at cytosine residues within CpG dinucleotides. Meanwhile, changes in DNA methylation can alter chromatin structure, leading to gene silencing or aberrant gene activation. Usually, recruitment of complexes involved in chromatin remodeling produces gene silencing through promoter hypermethylation, whereas hypomethylation increases chromatin accessibility and may drive aberrant gene expression or overexpression [39,40]. In a series of experiments, Anway et al. [41,42] reported that transient gestational exposure of female animals to anti-androgenic pesticides (vinclozolin) and/or estrogenic pesticides (methoxychlor) resulted in decreased sperm output, reduced motility, and increased germ cell apoptosis in male offspring. These reproductive defects were not due to DNA sequence changes; instead, the phenotypes were stably inherited to the F4 generation and beyond, likely through epigenetic imprinting of the male germline. Thus, transient embryonic exposure can induce multigenerational phenotypes.

4. From Endocrine–Metabolic Disruption to Cardiovascular Injury

EDCs can disrupt metabolic processes through multiple molecular mechanisms, creating a major pathophysiological substrate for CVD.

4.1 EDC-Driven Metabolic Disorders

4.1.1 Central Obesity and Adipose Tissue Dysfunction

Notably, BPA and phthalates act as obesogens by promoting the differentiation of preadipocytes into mature

adipocytes, which can also inhibit lipolysis and disrupt cellular lipid redox homeostasis, ultimately leading to ectopic lipid accumulation. Chronic low-grade inflammation in adipose tissue promotes M1 macrophage polarization, which increases TNF- α and IL-6 secretion [43,44]. Meanwhile, adiponectin secretion declines and leptin resistance develops. Adipose tissue inflammation is strongly implicated in insulin resistance [45,46]. Francis et al. [47] reported that EDCs can directly disrupt adipose tissue energy metabolism and brown and beige fat thermogenesis, thereby promoting obesity. Epidemiological studies [48] indicate that PFAS are also obesogens that may impair adipogenesis and energy metabolism, increasing the risk of overweight and obesity. PFAS exposure may further lead to endocrine complications. Moreover, an adult population study in the United States [49] found that mixed exposure to polycyclic aromatic hydrocarbons (PAHs) was significantly and positively associated with metabolic syndrome and its components, including abdominal obesity and elevated TGs. This risk is further increased by adverse lifestyle factors.

4.1.2 Insulin Resistance and Dysregulation of Glucose Homeostasis

EDCs disrupt insulin signaling cascades by inducing oxidative stress and inflammation in peripheral tissues, thereby impairing glucose uptake in skeletal muscle. EDCs also exacerbate fasting hyperglycemia by increasing hepatic glucose production. Prolonged exposure to toxic and glucolipotoxic environments damages the pancreatic β -cells through a dual-hit mechanism that progressively impairs their function [50,51,52]. A cross-sectional assessment with the NHANES data [53] found that adolescents with high PAH metabolite levels (2-naphthol) had a two-fold higher odds of metabolic syndrome and hyperglycemia. In animal models, a high-fat diet combined with BPA exposure exerts synergistic effects that worsen prediabetic phenotypes [54]. Similarly, a study in the United States of non-obese pregnant women found that higher early pregnancy plasma concentrations of highly chlorinated polychlorinated biphenyls (PCBs) were associated with an increased risk of gestational diabetes mellitus (GDM) [55]. Moreover, PFAS and PBDEs have been linked to a higher risk of diabetes.

4.1.3 Dyslipidemia

EDCs are known to alter hepatic lipid metabolism, thereby increasing circulating TG levels. Meanwhile, EDCs can also impair two key high-density lipoprotein (HDL) functions: anti-inflammatory activity and reverse cholesterol (C) transport. A high TG/low HDL-C profile can significantly increase the risk of atherosclerosis and cardiovascular disease [43,56]. Kim et al. [57] reported that ApoE-knockout mice exposed to BPA (50 $\mu\text{g/kg/d}$) and a high-fat diet for 12 weeks developed a 1.7-fold increase in

aortic atherosclerotic lesion area, along with elevated non-HDL-C levels. These findings suggest that long-term BPA exposure promotes atherogenesis by increasing atherogenic lipid burden. In a human cohort study, maternal phthalate exposure during pregnancy was associated with elevated TG levels in male offspring, indicating that this environmental exposure can affect subsequent generations and that susceptibility to lipid dysregulation may differ by sex [27].

4.2 The Terminal Pathways to CVD

The metabolic and molecular alterations described above act together in the cardiovascular system, contributing to organ damage through five main pathways.

4.2.1 Endothelial Dysfunction

According to researchers, EDC triggers oxidative stress, which directly damages vascular endothelial cells and reduces the bioavailability of nitric oxide (NO), a vasodilator [32,58]. According to assessments, heavy metal EDCs, such as cadmium (Cd), are strongly associated with atherosclerosis and endothelial damage [59]. Cohort studies conducted in Europe [60] show that higher prenatal and postnatal PFAS concentrations are significantly associated with HGF and other markers of endothelial injury. Accordingly, the risk of vascular injury from environmental exposure may begin in childhood.

4.2.2 Immune-Inflammatory Dysregulation

EDCs exert complex effects on inflammation rather than simple linear immunomodulation. Low doses may promote inflammation, whereas higher doses or specific mixtures may deplete or suppress immune cells. This non-monotonic dose-response pattern is a key feature of EDC toxicology [61,62]. Evidence indicates that EDCs interact with both proinflammatory NF- κB pathways and anti-inflammatory PPAR-mediated pathways, thereby disturbing immune homeostasis [63]. One study found that IL-8 and MCP-1 levels were inversely associated with mixed PFAS exposure [60]. Thus, certain EDCs may drive immune imbalance through complex mechanisms involving immunosuppression or depletion.

4.2.3 Atherosclerotic Plaque Formation and Destabilization

Following endothelial activation, EDCs work with substances that produce proinflammatory factors to significantly increase adhesion molecules such as ICAM-1 and VCAM-1, thereby facilitating monocyte adhesion and migration through the endothelium into the intima. Under the dyslipidemic microenvironment, EDCs also promote the phagocytosis of oxidized-low-density lipoprotein (ox-LDL) by upregulating CD36 and other scavenger receptors in macrophages, leading to foam cell formation and lipid core development. Chronic inflammation is characterized by the overproduction of matrix metallopro-

teinas (MMPs). Ultimately, chronic inflammation further increases matrix metalloproteinase (MMP) production, weakening the fibrous cap and increasing plaque rupture risk and the likelihood of acute coronary syndrome (ACS) [10,64,65].

4.2.4 Renin–Angiotensin–Aldosterone System (RAAS) Activation

Potent and stably acting EDCs cause non-homeostatic pathological activation of the RAAS. Meanwhile, elevated angiotensin II (Ang II) levels promote systemic vasoconstriction and sodium–water retention, while also significantly increasing cardiac afterload through vascular smooth muscle proliferation and myocardial fibrosis. These alterations accelerate remodeling in target organs [2,10]. Birth cohort studies suggest that sex-specific effects exist on blood pressure (BP) following BPA exposure [66]: elevated BP appears more likely in girls, whereas disturbances in glucose metabolism appear more likely in boys, highlighting a sex-specific window of susceptibility in cardiovascular development.

4.2.5 Direct Cardiotoxicity

According to research findings, EDCs can also exert direct toxicity on cardiac tissue. Moreover, EDCs can directly alter the gating properties of calcium channels, such as L-type, and potassium channels, causing repolarization abnormalities and increasing the risk of lethal arrhythmias [67]. Additionally, EDCs disrupt excitation–contraction coupling systems by inhibiting sarcoplasmic reticulum calcium uptake via SERCA2a inhibition, which reduces myocardial contractile reserve [68]. Research using a zebrafish model has shown that fluorene-9-bisphenol (BHPF) is a major cardiac developmental toxicant because of its impact on cardiac looping and contractility [69]. BHPF also exhibits strong teratogenic and lethal effects in mammals, underscoring the serious threat to early cardiac development from BHPF exposure.

5. Nutritional Interventions as a Countermeasure to EDC-Induced Cardiovascular Toxicity

5.1 Defending Against Environmental Endocrine Disruption

The connection between environmental exposure and cardiovascular health is increasingly recognized as a consequence of disrupted endocrine balance. Environmental chemicals, including bisphenols and phthalates, act as potent metabolic disruptors by mimicking or competing with physiological hormones. These toxicants interfere with ER and PPAR signaling pathways, altering the function and metabolism of endothelial and myocardial cells [70,71]. Counteracting the cardiovascular burden of ubiquitous environmental pollutants requires proactive dietary strategies. This shift from passive avoidance to active nutritional for-

tification represents a paradigm shift in managing environmental CVD risks.

5.2 Nutritional Epigenetics and Receptor Antagonism

Bioactive phytochemicals, especially polyphenols, resveratrol, and quercetin, as well as the isothiocyanate sulforaphane, can effectively counter the cardiovascular toxicity of EDCs [72]. These nutrients act as antioxidants and serve as nutri-epigenetic modulators [73]. For instance, sulforaphane activates Nrf2 signaling, which enhances hepatic clearance of EDCs and reduces the proinflammatory vascular cascade induced by dioxin-like compounds [74,75].

5.2.1 Dual Modulation by Phytochemicals and Antioxidants Through Nrf2–NF-κB Crosstalk

Dietary antioxidants and bioactive phytochemicals, including polyphenols, resveratrol, and quercetin, act as signaling modulators and help restore EDC-induced intracellular homeostasis [76,77]. EDCs induce cardiovascular toxicity, largely through a pathological increase in ROS, which acts as an important molecular trigger for the NF-κB proinflammatory cascade and subsequently leads to endothelial dysfunction, adhesion molecule expression, and accelerated atherogenesis [78,79].

Phytochemicals inhibit this pathogenic progression through a complex dual mechanism. To a large extent, these compounds activate Nrf2, the master transcriptional regulator of cellular antioxidant defense. The Nrf2 pathway is activated, leading to the upregulation of important endogenous enzymes, such as superoxide dismutase (SOD) and heme oxygenase-1 (HO-1), which can scavenge the ROS generated by EDCs and help restore mitochondrial redox balance [80,81,82]. Meanwhile, these bioactive agents prevent the phosphorylation and nuclear translocation of NF-κB, reducing transcription of the proinflammatory cytokines (TNF-α and IL-6) and limiting chronic vascular wall inflammation. Crosstalk between Nrf2-mediated cytoprotection and NF-κB-targeted anti-inflammation provides an important biological rationale for using nutrition to prevent environmentally toxicant-associated cardiometabolic risks [83,84].

5.2.2 Omega-3 Polyunsaturated Fatty Acids (PUFAs) and Inflammation Resolution

Extensive evidence demonstrates that omega-3 polyunsaturated fatty acids, particularly EPA and DHA, mitigate atherogenesis by directly suppressing the arachidonic acid (AA) cascade and resolving vascular inflammation [85,86]. According to a study, EPA and DHA can also alter the lipid mediator profile that EDCs often disrupt. In the context of cardiovascular risks, this helps address both EDC exposure and LDL-associated damage. By competing with EDC-induced AA metabolites, omega-3 fatty acids reduce prothrombotic and proinflammatory eicosanoid synthesis [87,88,89].

Omega-3 fatty acids also act as natural ligands for PPAR- α and PPAR- γ . Thus, omega-3 PUFAs can help reverse the metabolic-disrupting effects of phthalates by activating numerous nuclear receptors, many of which disrupt lipid metabolism. Activation of this pathway enhances fatty acid oxidation and inhibits the NF- κ B pathway, thereby reducing EDC-induced vascular inflammation. Moreover, a new mechanism called specialized pro-resolving mediators (SPMs) can convert omega-3 intake into protection [90]. These molecules help to actively promote resolution of vascular wall inflammation and reverse chronic low-grade inflammation associated with persistent organic pollutants.

5.2.3 Vitamin D as a Genomic and Endocrine Shield

Vitamin D intake is important because this micronutrient acts as a hormone and serves as a cofactor in insulin signaling pathways that are key targets of phthalate metabolic interference. Vitamin D also directly antagonizes many EDCs that target the vitamin D receptor (VDR) or disrupt calcium signaling [91,92]. Certain EDCs, such as cadmium and some pesticides, promote the overactivation of the renin-angiotensin system (RAS), which may explain their association with hypertension. Vitamin D has a strong and negative impact on renin transcription. However, maintaining adequate vitamin D status can mitigate the hypertensive effects of EDCs and help preserve endocrine homeostasis in the cardiovascular system [93,94].

EDCs also promote aberrant DNA methylation patterns of genes involved in cholesterol transport, such as *ABCA1* [95]. Nonetheless, vitamin D can influence DNA methyltransferase activity through the VDR and help protect the cardiovascular genome [96,97]. Furthermore, vitamin D has been shown to upregulate antioxidant enzymes (e.g., SOD) to mitigate BPA-induced oxidative stress in target organs such as the liver [98]. Importantly, this general protective effect extends to the cardiovascular system, where vitamin D administration preserves heart architecture and reduces apoptotic indices after BPA exposure [98,99].

5.3 The Gut–Microbiota–Vascular Axis: A Dynamic Biofilter

EDCs can switch metabolic regulation to favor adipogenesis and insulin resistance, thereby enhancing the risk of atherosclerosis [100,101]. The gastrointestinal tract represents the main route through which ingested EDCs enter the host circulatory system [102]. The gut microbiota acts as a dynamic biofilter, and some bacteria use enzymes (e.g., β -glucuronidases) to deconjugate EDC metabolites (e.g., BPA-glucuronide) back into active forms that may re-enter the liver through enterohepatic recirculation [103,104]. Integrating nutritional interventions can modulate this axis through several mechanisms.

5.3.1 Sequestration and Barrier Integrity

The diet can be fortified with high-viscosity dietary fibers and selected probiotics. Physical binding of

lipophilic EDCs in the intestinal lumen reduces their systemic absorption. According to a nutritional definition, intake of fermentable dietary fiber and polyphenols (the “prebiotic effect”) can support the growth of beneficial genera such as *Bifidobacterium* and *Akkermansia muciniphila* [105,106]. As shown previously [107,108], these microbes strengthen the gut barrier by increasing tight junction proteins, including occludin and zonula occludens-1, thereby limiting systemic absorption of lipophilic EDCs that contribute to cardiovascular toxicity.

5.3.2 Metabolic Reprogramming

The interaction between nutrition and the microbiota generates bioactive metabolites that directly regulate endocrine homeostasis and vascular health [109]. Fermentation of fiber materials produces the short-chain fatty acids (SCFAs) butyrate, a source of energy for the gut epithelium, and propionate, which signal through the G-protein coupled receptors GPR41 and GPR43 [110]. Notably, these SCFAs help prevent glucose impairment and vascular wall injury following EDC exposure. SCFAs have also been found to counteract EDC-induced inflammation of adipose tissue, improve insulin sensitivity, alleviate obesogenic effects, and ultimately attenuate atherosclerosis [100,102].

5.3.3 TMAO Suppression

Recent evidence indicates that some EDCs may alter microbial composition toward an atherogenic profile and raise TMAO (trimethylamine N-oxide) levels [111,112]. Adopting a high-quality nutritional pattern, mainly one rich in Mediterranean-style extra virgin olive oil and the associated trimethylamine (TMA) analog DMB, can prevent TMA produced by the microbiota, thereby protecting the vascular endothelium from the combined effects of EDCs and dysbiosis [113,114].

5.3.4 Hormonal Stabilization

EDCs often impair the release of incretins such as GLP-1, which are vital for glucose metabolic regulation and endothelial function. Dietary modifications that alter the composition of the microbiota, especially with probiotics, can restore the rhythmicity of the hormones [115,116]. Nutrition can buffer the endocrine system against disruptive oscillations due to environmental toxins by stabilizing the microbial milieu and preserving endocrine homeostasis, thereby protecting against myocardial remodeling and hypertension [117,118].

5.4 Holistic Dietary Patterns in the Exposome Era

Given the complexity of the human exposome, which involves simultaneous exposure to multiple EDCs, supplements should be considered as part of dietary patterns rather than in isolation. The protective effects of the Mediterranean diet (MedDiet), enriched in omega-3 fatty acids and antioxidants, against cardiovascular diseases are synergis-

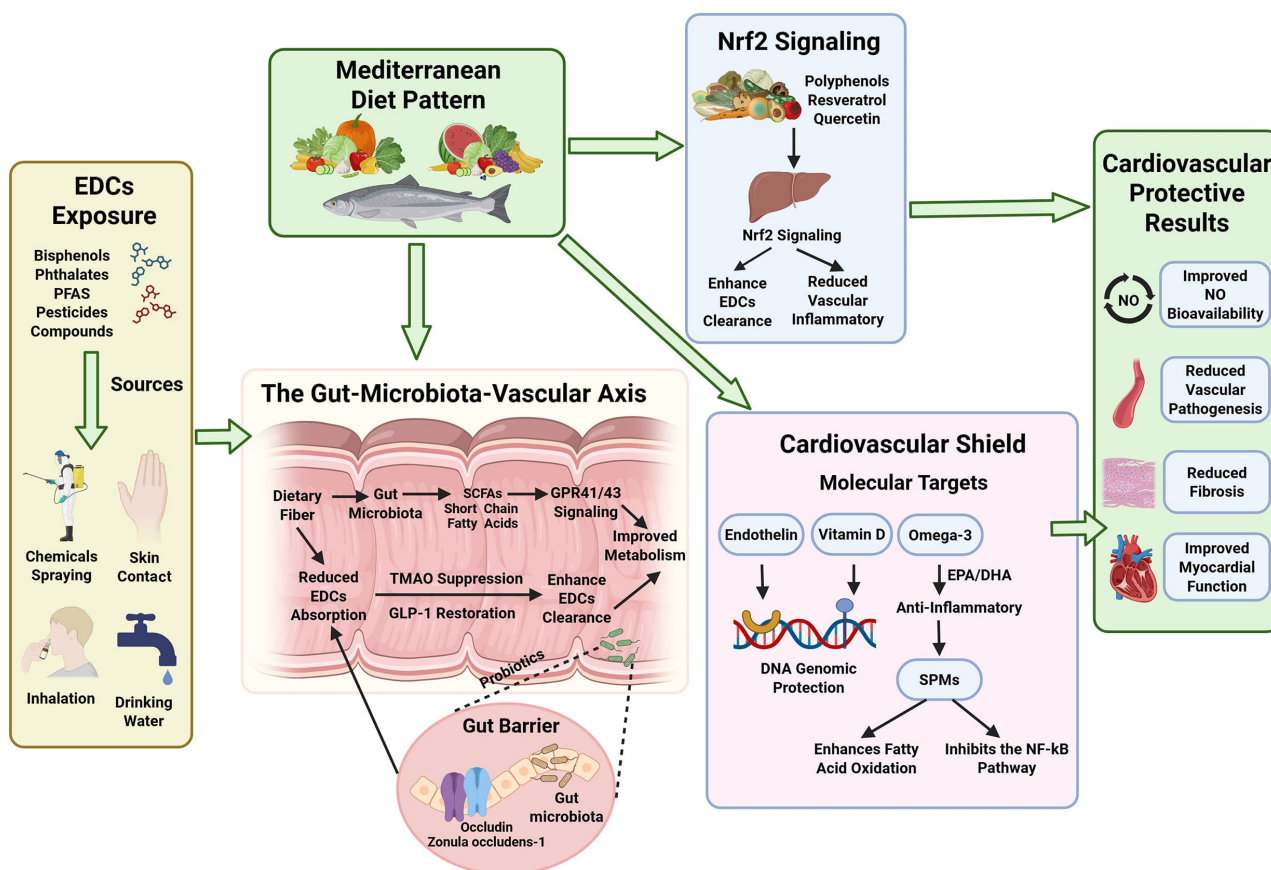


Fig. 3. Nutritional defense mechanisms that counteract EDC-induced cardiovascular toxicity. Targeted dietary strategies may synergistically neutralize toxicant effects by modulating the gut–microbiota–vascular axis, enhancing hepatic clearance, and providing direct molecular protection to preserve vascular homeostasis.

tic. Notably, protecting endothelial NO is a key therapeutic target in cardiovascular prevention. The MedDiet plays an essential role in preventing cardiovascular disease by improving NO bioavailability and reducing endothelial reactivity [119]. Recent clinical evidence [120] suggests that high adherence to the MedDiet is associated with lower urinary EDC metabolites and better endothelial function, indicating that nutritional excellence can partially mitigate the toxic burden of modern urban living (Fig. 3).

6. Conclusions and Future Directions

Although standard lipid-lowering, antihypertensive, and hypoglycemic therapies have made substantial contributions to clinical care, the persistence of unmitigated residual cardiovascular risk calls for a shift in focus toward an exposome-based approach [9]. Thus, terms such as EDCs and environmental threats in non-traditional settings have gained increasing attention. Lipid-soluble EDCs can hijack host signaling networks at very low, chronic exposure levels, leading to bioaccumulation and initiation of a life-long trajectory of metabolic dysfunction [121]. The cascade that begins with interference in nuclear receptors, including ER, AR, and PPARs, and progresses through mitochondrial

oxidative stress and ultimately systemic epigenetic reprogramming may contribute to adverse CVD outcomes [122]. Importantly, the modern diet is both a major vehicle for these synthetic toxicants and a powerful therapeutic agent. Targeted nutritional strategies can strengthen biological defenses through nutriepigenetic modulation and the biofiltering capacity of the gut–microbiota–vascular axis [123,124]. Bioactive compounds and holistic dietary approaches, including the Mediterranean diet, attenuate EDC-induced toxicity by resolving inflammation, stabilizing endocrine oscillations, and limiting the translocation of lipophilic xenobiotics. Ultimately, nutrition plays an important role in the cardiometabolic continuum, transforming the vulnerable interface between humans and environmental contaminants into a barrier against exposure [87,125].

The transition from identifying environmental threats to delivering precise cardiovascular care is not without important challenges. Future research should focus on the following areas.

6.1 Examination of Multiple Omics

Future studies should move beyond single toxicants. Human exposure is typically characterized by complex low-

dose mixtures of EDCs rather than isolated compounds. Therefore, future longitudinal cohort studies should incorporate multi-omic platforms, including epigenomics, metabolomics, and microbiomics, to clarify the combined toxicity of mixed exposures. Establishing appropriate cut-off values for risk assessment will also require advanced computational models capable of characterizing non-monotonic dose–response relationships (NMDRs).

6.2 Decoding Cardiometabolic Imprinting Across Generations

The capacity of EDCs to induce developmental programming and stable transgenerational inheritance through epigenetic modifications represents a major public health concern. Further mechanistic research is needed to determine how transient embryonic exposure shapes adult cardiovascular trajectories. A key objective is to identify epigenetic markers with an early temporal window that may remain reversible in potentially affected populations.

6.3 Precision Nutritional Therapeutics and the Microbiome

Precision interventions should advance beyond broad dietary recommendations. Indeed, clinical trials are needed to determine whether specific nutritional protocols, such as prebiotic and probiotic supplementation [102,116] or SCFA-enhancing diets [106,109], can be tailored to the specific environmental toxicant burden and baseline microbiome of individuals [103,120]. Such approaches may help safely enhance the enterohepatic clearance of bioaccumulated persistent organic pollutants.

6.4 Incorporation Into Guidelines and Policy

A major translational objective is to integrate environmental risk assessment into standard cardiovascular clinical practice. Meanwhile, global regulators should also revise acceptable exposure limits based on chronic cardiovascular endpoints rather than acute toxicity alone. Moreover, acknowledging the exposome is no longer only an environmental issue; it is central to the future of preventive cardiology.

7. Strengths and Limitations

This review has several strengths. First, this review systematically maps the disease-causing pathways linking EDC exposure to cardiovascular harm, including nuclear receptor interference and mitochondrial oxidative stress, as well as epigenetic reprogramming and gut microbiota dysbiosis. Second, this review changes the cardiovascular prevention paradigm from passive avoidance to active nutriepigenetic strengthening. Indeed, by highlighting selective dietary compounds such as polyphenols, omega-3 PUFAs and vitamin D as targeted signaling modulators, this work provides a strong biological rationale for dietary countermeasures. In addition, the inclusion of the gut–microbiota–

vascular axis as a dynamic biofilter offers a translational perspective on how diet may limit systemic EDC bioavailability.

Despite these strengths, several limitations should be acknowledged. First, most mechanistic evidence regarding EDC-induced vascular damage [19,36,57,68] and the protective effects of nutrients [78,98,99] derives from *in vitro* and animal models, including murine and zebrafish studies. Therefore, extrapolating these findings directly to complex human pathophysiology should be performed with caution. Second, although epidemiological data suggest that holistic dietary patterns, such as the Mediterranean diet, confer cardioprotective benefits, large-scale randomized controlled trials remain limited. Moreover, such trials are urgently needed to define the optimal dosing, efficacy, and long-term clinical outcomes of specific phytochemicals and antioxidants against chronic, low-dose mixed EDC exposures in human populations. Finally, publication bias may also influence the overall synthesis.

Availability of Data and Materials

No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Author Contributions

YX, HC and CP conceptualized and designed the review. YX, CP, HZ, LX and HL performed the literature search and data extraction. YX drafted the original manuscript. HC, CP and HZ critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

The authors declare no conflicts of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work the authors used ChatGPT-3.5 in order to check spell and grammar. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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