Polyphenols for an Increased Ability to Cope with Environmental Toxicants

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Abstract

Human exposure to environmental toxicants is inevitable, but there is evidence that certain pollutants (e.g. heavy metals and air particulate matter) contribute to major diseases, such as neurodevelopmental and metabolic disorders, cardiovascular disease and some cancer types.

Nutrition can be a means of reducing the disease vulnerability associated with environmental exposures. In this work, the potential of dietary polyphenols to modify environmental and occupational toxicant-induced pathologies is discussed. Published data on the effects of flavonoids, hydroxycinnamic acids, resveratrol and other polyphenols in *in vitro* and *in vivo* models show that different compounds can modulate key pathological processes implicated in those diseases. Polyphenols can attenuate oxidative stress, inflammatory response, cell death and carcinogenesis, and modulate other specific mechanisms triggered by toxic pollutants, including by the persistent polychlorinated biphenyls and polycyclic aromatic hydrocarbons.

The critical analysis of the current knowledge in this subject at the interface of nutritional and environmental sciences encourages further research. A deeper understanding of toxicants chronic effects and polyphenol protective mechanisms is expected to advise future nutritional intervention studies.

Keywords: Antioxidants; Endothelial dysfunction; Metabolic disruptors; Neurotoxicity

Introduction

The importance of nutritional status and nutrients in the health effects of environmental toxicants has been recognized for some time [1-4]. However, the relation between environmental exposures and nutrition in health condition is complex and much still remains to uncover.

It is well accepted that nutritional deficiencies can influence the level of pollutant exposure and toxicity, and, in some circumstances, nutrient supplements may play a mitigating role [1,2]. Regarding exposure, some studies indicate that iron and calcium supplementation can reduce blood lead concentration in children, as well as, in pregnant and lactating women [2]. To better cope with toxicity, antioxidant vitamins C and E have traditionally received an exceptional attention as means to reinforce physiological defense systems against environmental stressors [1,3,5].

More recently, evidence is accumulating that dietary polyphenols may also provide an increased protection against toxic pollutants (references in next sections). Polyphenols are a diverse collection of bioactives, including flavonoids, hydroxycinnamic acids, stilbenes and other compounds widely

distributed in the human diet. Epidemiological data show an inverse association between the intake of several polyphenols and the risk of some chronic diseases. Besides the chemical antioxidant (free radical scavenging) activity, animal and *in vitro* studies strongly support the notion that some polyphenols can affect key physiological processes, and these actions can influence the sensitivity or resistance to toxic insults.

It was previously suggested that nutrition may represent a sensible prevention strategy for diseases associated with environmental exposures [1]. Understanding the ability of polyphenols or other bioactive nutrients to modify human vulnerability to environmental toxicants could pave the way for nutritional intervention strategies in higher risk individuals and populations.

Environmental Toxicants and Chronic Health Effects

Humans are exposed to numerous chemicals present in air, soil, water and food that can have specific toxic effects depending on the route of exposure, dose and individual susceptibilities. Many pathologies have been associated to environmental pollution, and significant evidences exist for the contribution of exposure to some particular pollutants to specific chronic pathological conditions, such as, neurodevelopmental disorders [6], obesity and related metabolic diseases [7,8], cardiovascular diseases [9-11], chronic pulmonary diseases [12] and various types of cancer.

Neurological and Metabolic Disorders

Exposure to environmental neurotoxicants can interfere with developing infant and children brain, giving rise to a spectrum of structural and functional deficits. Neurodevelopmental disabilities, including autism and attention-deficit hyperactivity disorder, have been strongly associated to environmental and occupational chemicals, such as, lead, methylmercury, Polychlorinated Biphenyls (PCBs), arsenic, manganese and chlorpyrifos (organophosphate pesticide) [2,6]. Also concerning neurotoxicity, it should be referred that epidemiological studies have linked pesticide exposure to increased risk of Parkinson's disease, and several pesticides, such as rotenone, paraquat or dieldrin (organochloride pesticide), induce pathological features of Parkinson's disease in cell and animal models of neurodegeneration.

Environmental obesogens or metabolic disruptors such as bisphenol A, some pesticides, tributyltin (organotin), PCBs and phthalates, can alter the susceptibility to obesity, diabetes and related metabolic disorders [7,8,11,13]. Exposure to these compounds during development and/or other sensitive time periods alters adipose tissue development and/or food intake and metabolism by specific effects in brain and other organs/tissues. The increased risk may be most apparent when the developmental exposure is combined with consumption of a high-calorie, high-carbohydrate, or high-fat diet later in life. In this regard, several environmental chemicals were found to affect adipocyte differentiation, physiology, metabolism and adipokine secretion [13], functions that may be modulated by polyphenols [14,15].

Cardiorespiratory Complications and Cancer

Exposure to particulate matter air pollution contributes to cardiovascular morbidity and mortality. Ambient particulate matter, especially fine and ultrafine particles, including those from motor vehicle exhaust emissions in urban areas, have been consistently linked with increased risk for ischemic heart disease, stroke, heart failure and arrhythmias. Air particles contain transition metals such as iron, vanadium, chromium and nickel, as well as Polycyclic Aromatic Hydrocarbons (PAHs) among other compounds, which can trigger pulmonary and systemic inflammatory responses, in addition to imbalance of the autonomous nervous system. Pro-oxidative and pro-inflammatory mediators released from the lungs into the circulation, and ultrafine particles passing into the systemic circulation, can act on the heart and vasculature causing oxidative stress and endothelial dysfunction, favoring the development and progression of atherosclerotic lesions [9,10,16].
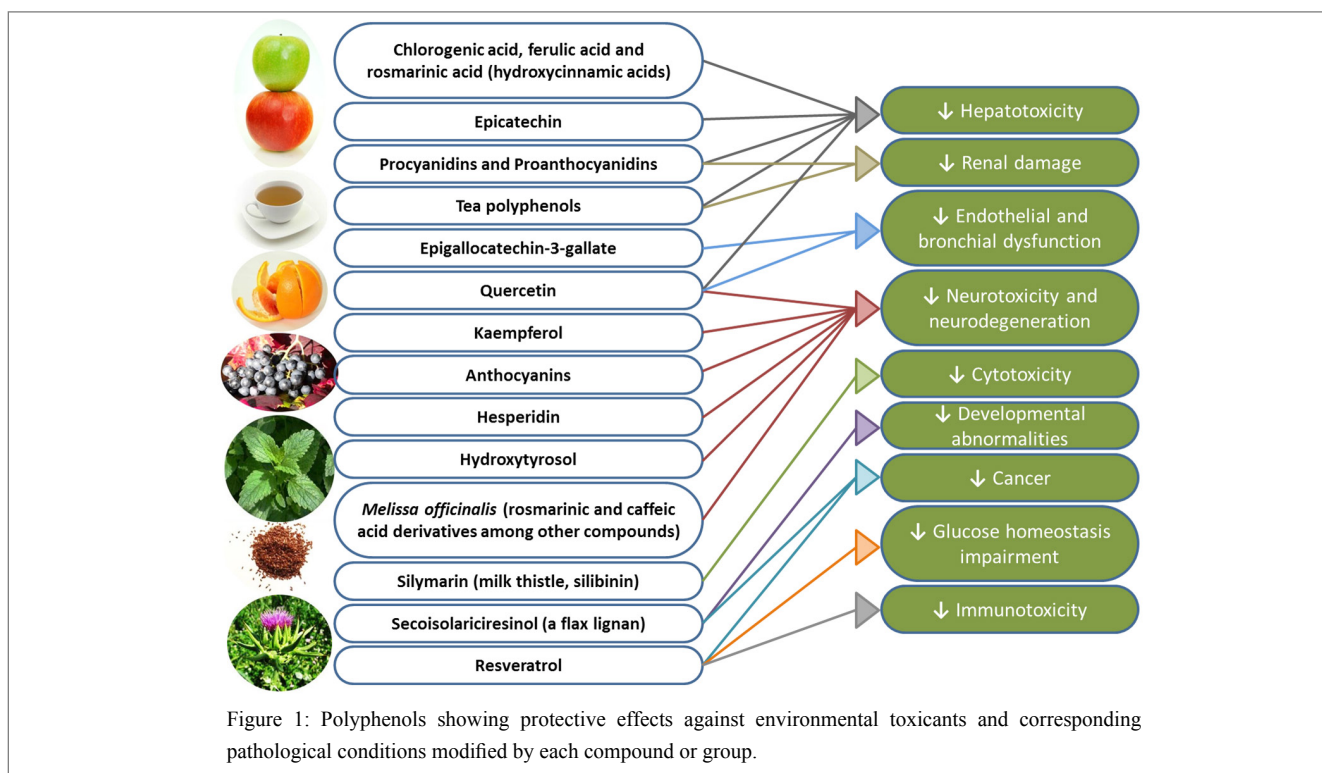
Oxidative modifications of Low-density Lipoproteins (LDL), and homeostasis of cholesterol and lipid antioxidants participate in pathogenic features common to diabetes, cardiovascular and other degenerative diseases. α-Tocopherol is the main form of vitamin E and the main lipid-soluble antioxidant in blood and tissues, and low concentrations of vitamin E are associated with cardiovascular complications [17,18]. Supplementation with vitamin E decreases lipid peroxidation markers in diabetic patients, and reaching higher levels of this antioxidant in blood yields substantial decreases in lipid peroxidation in diabetic, cystic fibrosis and hypercholesterolemia patients [18]. So, it is very relevant that polyphenols such as quercetin and catechins protect α-Tocopherol from oxidative degradation in human LDL and inhibit the production of oxidized-LDL that has increased atherogenicity [17,19]. Moreover, dietary supplementation with those flavonoids increased the level of α-Tocopherol in blood plasma and liver of rats [17].

Air pollution is also intimately related with the progression and exacerbation of chronic airway diseases, such as asthma. Elevated concentrations of air particles and gaseous pollutants can prompt a range of respiratory symptoms, including bronchoconstriction, bronchial reactivity and airway inflammation, and are consistently associated with increased hospital admissions for respiratory causes [5,12]. Although the response to environmental factors is complex, exposure to ambient air pollution can damage lung function, especially in children. Lung inflammation is connected to cardiovascular responses and, furthermore, is being related to the progression of human CNS inflammation by licensing pathogenic immune cells to migrate towards the CNS [20].

PAHs and dioxins are well-known carcinogenic compounds present in environmental (and food) samples, such as vehicle exhaust, air particulate matter, particulates from coal combustion or cigarette smoke. Another environmentally relevant human carcinogen is the heavy metal cadmium. It is well documented that long-term exposures to environmental and occupational toxicants are associated with elevated risks of cancer in various organs. Numerous studies have been examining the potential of polyphenols for cancer prevention and therapy, and this subject can be followed in other published works [21].

Dietary Polyphenols and Protective Actions

Oxidative stress and dysregulated inflammation are common conditions in chronic and environmental exposure-associated pathologies [1,4,9,12,22]. Since flavonoids have recognized antioxidant and anti-inflammatory actions, their potential for counteracting environmental toxicants has been explored [4,23]. Figure 1 lists the flavonoids and other polyphenols being studied with this aim.

Figure 1: Polyphenols showing protective effects against environmental toxicants and corresponding pathological conditions modified by each compound or group.

Protection against Heavy Metals Toxicity and Neurodegeneration

Arsenic, lead and mercury are classical metal poisons in environmental and occupational toxicology. Epicatechin and proanthocyanidins (and lycopene) were found to protect rats against lead and mercuric chloride (hepato)toxicity, avoiding the loss of antioxidant enzymes, inhibiting production of reactive oxygen species (ROS) and, therefore, antagonizing oxidative stress [24,25]. Similar results were observed with tea polyphenols (and schisandrin B), and moderate antiapoptotic action of procyanidins, against mercuric chloride renal damage [26,27].

The olive oil hydroxytyrosol also prevented ROS production and apoptosis induced by mercury in human erythrocytes and neuroblastoma cells [28], which has a critical importance if we remember the metal accumulates in erythrocytes and, in autism, brain nitrosative stress correlates with mercury concentration. Different studies have supported the protective ability of antioxidants and polyphenols, including silymarin, against arsenic-induced toxicity in cellular, rodent and rabbit models [3].

Other recent works with animal models point out that quercetin and hesperidin can attenuate aluminum neurotoxicity [29,30]. Chronic intragastric administration of quercetin simultaneous to aluminum alleviated mitochondrial abnormalities and apoptosis caused by the metal, decreasing degeneration of CA2 pyramidal neurons, in hippocampus of rat brain [29]. Moreover, in the work by Thenmozhi et al. the protective action of hesperidin reflected in reduction of aluminum-induced cognitive deficits [30]. Although some studies have indicated that flavonoids may reduce absorption of metal ions, namely iron [23], the above effects of quercetin seem unrelated to any interference with the absorption of the aluminum, as the metal concentration in the serum of the animals was not altered by quercetin administration.

Concerning the neurotoxic risks of manganese, an anthocyanin-rich extract of açaí was found to reduce oxidative stress and cell death induced by the metal in astrocytes, even at low concentration [31], and, in vivo, the aqueous extract of *Melissa officinalis* (Figure 1) showed an antioxidant effect in different brain areas of mice chronically intoxicated with manganese [32].

The neuromodulator potential of anthocyanins has been emphasized in recent years and, as well as kaempferol, it was observed to protect neurons in rotenone models of Parkinson´s disease [33-35]. It is also to be recalled that reduced risk of Parkinson´s disease was associated with consumption of black tea, with no relation to caffeine [23].

Modulation of Persistent Organic Pollutants and Particulate Matter Toxicities

Important efforts are being done to understand endothelial dysfunction induced by PCBs and ambient particulate matter, which may play a major role on the cardiovascular complications associated with exposure to environmental pollutants. Epigallocatechin-3-gallate (EGCG) and quercetin are able to inhibit oxidative stress caused by PCBs in vascular endothelial cells, decreasing ROS production and inducing Nrf2-regulated antioxidant enzymes [36,37]. Diminished levels of oxidative stress and DNA damage markers and increased expression of liver antioxidant enzymes, associated with reduced liver injury, were also observed in PCB-exposed animals when treated with a green tea extract (source of epicatechin and EGCG) or quercetin [38,39]. Critical to prevent vascular inflammation and atherosclerosis, EGCG and quercetin significantly attenuated PCB-induced expression of inflammatory markers via modulation of NF-κB signaling in endothelial cells [37,40,41].

The toxic effects of PCBs (dioxin-like), dioxin and PAHs have been primarily associated to the activation of the Aryl hydrocarbon Receptor (AhR) and subsequent induction of responsive genes, such as cytochrome P450 CYP1A1 [40,42,43]. In endothelial cells, EGCG and quercetin reduced PCB-mediated increase in AhR-DNA binding activity and expression of CYP1A1 [36,37,40], whereas in the liver of mice fed with green tea and subsequently exposed to PCB an upregulation of AhR was observed [38]. In a work using rats treated with the potent AhR agonist PCB-169, feeding caffeic acid derivatives (chlorogenic acid, ferulic acid and rosmarinic acid) increased the level of hepatic glutathione and antioxidant enzyme activities, and protective effects were observed in reducing CYP1A1 activity and oxidative damage markers [43]. The anti-cancer potential of dietary flaxseed (linseed) has been underlined and secoisolariciresinol, a phytoestrogen flax lignan, was recently reported to suppress morphological abnormalities in zebrafish embryos exposed to PCB-126 [44,45].

Resveratrol is another AhR antagonist and showed beneficial effects against PCB and dioxin (2,3,7,8-tetrachlorodibenzo-p-dioxin) toxic effects in adipocytes and murine models [14,46,47]. Administration of the stilbene to pregnant and nonpregnant mice protected mothers and their fetuses from dioxin immunotoxicity, and reduced the expression of CYP1A1 in thymus of both the mother and the fetus [46]. Highly relevant, dietary antagonists of the AhR may alter the susceptibility to carcinogenesis in offspring of mothers exposed to AhR activators during gestation [47].

Martino et al. investigated dioxin toxicity in pancreatic beta cells and observed that nM concentrations of the toxicant rapidly increased intracellular calcium, caused several ultrastructural alterations and cell death [42]. In an apparently AhR-independent manner, mitochondria revealed as an early target of dioxin cytotoxicity and EGCG was able to alleviate dioxin-induced cell death, impairment of glucose-stimulated insulin secretion and mitochondrial depolarization.

Mitochondria and membrane NAD(P)H oxidases also participate in oxidative stress induced by particulate matter in human bronchial epithelial and pulmonary artery endothelial cells, as in other conditions of endothelial dysfunction, and a protective action can be expected from some flavonoids

that inhibit production of ROS by those redox systems [5,16,23,33,48-50]. In this line, quercetin was found to reduce ROS production and mitochondrial changes elicited by fine particulate matter in bronchial epithelial cells [5]. Additionally, activation of cell signaling pathways such as extracellular signal-regulated kinases1/2 by particulate matter was linked to ROS production in human endothelial cells, and may be modulated by EGCG and eventually other polyphenols [16,42]. These results have high interest for prevention of lung oxidative damage and inflammation implicated in the cardiorespiratory consequences of air pollution.

Perspectives

Nutrition in Environmental and Occupational Health

There is an increasing awareness and evidences supporting the health risks of exposition to environmental pollution. Diet can be a source of nutrients essential or auxiliary to our physiological detoxification processes, but food can simultaneously be a dangerous vehicle of toxic pollutants [2,51]. A recent review identified arsenic, lead and cadmium among the more problematic metal contaminants in drinking water in several parts of the word, affecting large populations where important nutritional deficiencies may exist [52,53]. In other cases, the consequences of environmental toxicants can combine with high-fat diets, sedentary lifestyles and low fruits and vegetables consumption in the etiology of "modern age" diseases [1].

Despite that nutritional or pharmacological therapies may give (some) protection against toxic chemicals, we cannot fail to point out that prevention through the use of adequate agricultural practices, hygienic practices in food handling and the definition and implementation of environmental, food and health policies are crucial to minimize the risk of developing diseases. Preventing and treating the sources of toxicants in food production, water supplies, indoor and ambient air, industrial and other workplaces, must always be the first line of action in environmental health. However, potentially toxic chemicals will never be completely avoided and the possibility that nutritional factors modify the toxic outcomes of pollutants should be considered in the complex interaction of Environment (including nutrition) and Health (Figure 2).
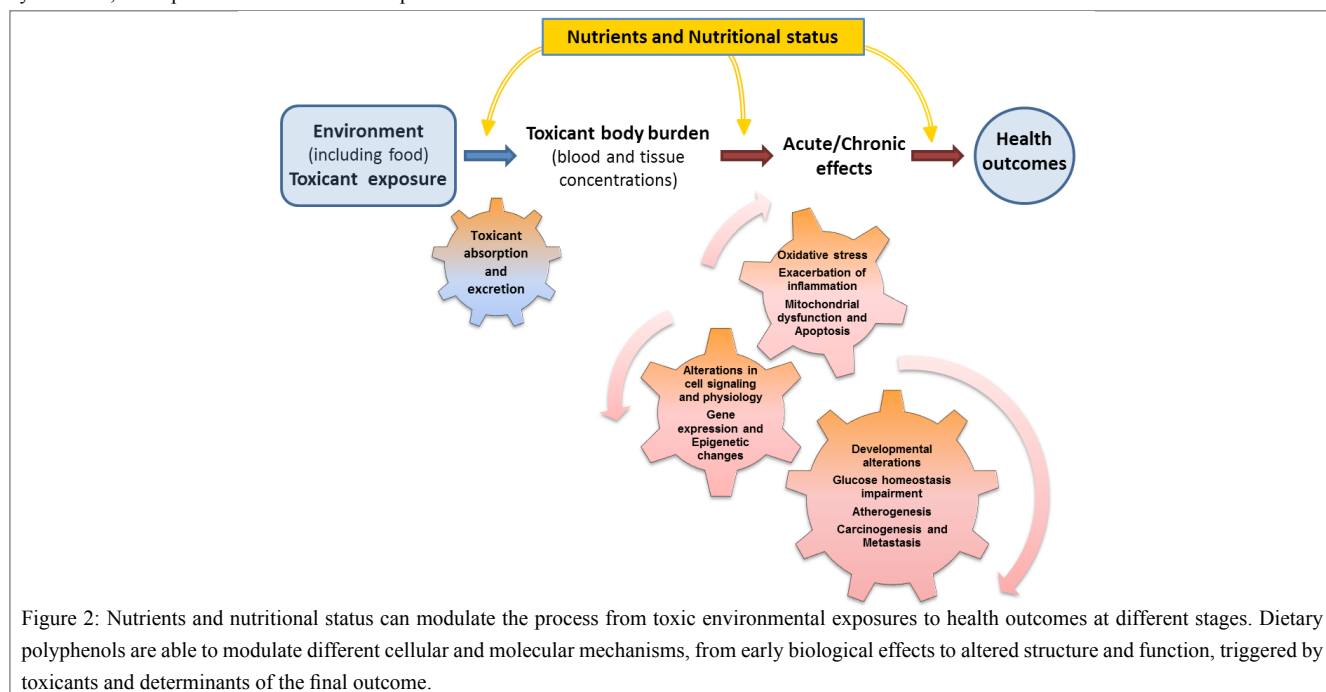

Figure 2: Nutrients and nutritional status can modulate the process from toxic environmental exposures to health outcomes at different stages. Dietary polyphenols are able to modulate different cellular and molecular mechanisms, from early biological effects to altered structure and function, triggered by toxicants and determinants of the final outcome.

A great attention is being paid to dietary polyphenols for their beneficial effects in human health. The present experimental data strongly suggest that (at least some) polyphenols can ameliorate the adverse health outcomes of serious environmental and occupational exposures to both metal and organic toxicants. Protective capacities are being studied mainly for traditional polyphenols, such as tea catechins and quercetin, not excluding that others less studied might have similar or superior efficacies in specific conditions. The use of alternative sources, eventually in the form of nutraceuticals, deserves more investigation, for example *Cotoneaster* species rich in catechins and hydroxycinnamic acids [54].

Current Status and Research Needs

In coherence with other mechanistic analysis of the action of polyphenols, more extensively studied in the cardiovascular and nervous systems [23,55], the protection against environmental toxicants seems to result from multiple actions: inhibition of ROS production, induction of antioxidant enzymes, regulation of signal transduction pathways, mitochondrial rescue, prevention of cell death and anti-inflammatory activity. However, it is clear we don't have yet a full picture of the toxic effects of many pollutants and mechanism of action of polyphenols. In addition to traditional toxic mechanisms (e.g. AhR activation), new signaling routes and targets of environmental chemicals are being unveiled, such as, calcium homeostasis, membrane lipid rafts (caveolae) or dysfunctional redox systems [16,40,42]. Approaching the cellular and molecular details of polyphenol actions is essential for a comprehensive understanding and exploration of the beneficial compounds.

Several studies demonstrate polyphenols can alleviate acute effects, following short-term toxic exposures, and there is increasing data suggesting a significant role in modulation of chronic or delayed effects associated to long-term (sub-clinical) exposures or to toxic events at critical time windows, including transgenerational effects [29,32,46,47]. The potential to modify the chronic effects of toxic exposures is strengthened in the case of some cancers, cardiovascular and neurodegenerative complications for which environmental chemicals give a contribution and, by other side, a decreased risk is associated to polyphenol consumption, according to distinct epidemiological studies. More recent research on the epigenetic actions of polyphenols [41,47] should be highlighted and will surely be further investigated.

Future efforts are needed to study the protective capacities of polyphenols in humans. The data presently available is from *in vitro*, in some cases with human cells, or from animal models. Properly controlled studies of nutritional assessment and interventions in populations exposed to environmental toxicants would be highly useful [2,11,56]. It is possible that (only) individuals with high levels of oxidative stress or with chronic sub-clinical conditions for a long time benefit mostly from an antioxidant/polyphenol therapy, requiring the use of well-defined biomarkers to select individuals and doses [18].

Nutritional interventions may aim to reduce pollutant absorption, increase excretion of previously absorbed (stored) chemicals or modulate their toxic mechanism (Figure 2). The studies with polyphenols have been exploring this last option, but the possibility to modify toxicant absorption should not be disregarded since polyphenols reduce intestinal uptake of lipids and other dietary components [21,23]. In this context, it is worth mentioning a previous trial showed consumption of the non absorbable lipid olestra can accelerate PCBs removal from the body of exposed individuals [11].

To our knowledge, there are no reported clinical trials at the moment on the safety and efficacy of polyphenols in protection against specific environmental toxicants. However, studying a population with elevated concentrations of PCBs, fruit and vegetable intake was found associated with a reduced risk of developing type 2 diabetes [56]. In different toxicity intervention trials, dietary supplementation with silibinin [57] and green tea polyphenol extract [58] returned positive results, as did decaffeinated green tea in smokers [59]. Uncertainties still remain whether a single component from the diet or a combination of nutrients and dietary habits are more effective for a protective outcome [18]. Importantly, the safety and tolerability of polyphenols in humans is generally very good [23,60], asking for specific trials that can translate the preclinical data with environmental toxicants into new nutritional and therapeutic interventions.

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