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The Environmental Pollutant, Polychlorinated Biphenyls, and Cardiovascular Disease: a Potential Target for Antioxidant Nanotherapeutics

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Abstract

Despite production having stopped in the 1970s, polychlorinated biphenyls (PCBs) represent persistent organic pollutants that continue to pose a serious human health risk. Exposure to PCBs has been linked to chronic inflammatory diseases, such as cardiovascular disease, type 2 diabetes, obesity, as well as hepatic disorders, endocrine dysfunction, neurological deficits and many others. This is further complicated by PCB's strong hydrophobicity, resulting in their ability to accumulate up the food chain and to be stored in fat deposits. This means that completely avoiding exposure is not possible, thus requiring the need to develop intervention strategies that can mitigate disease risks associated with exposure to PCBs. Currently, there is excitement in the use of nutritional compounds as a way of inhibiting the inflammation associated with PCBs, yet the suboptimal delivery and pharmacology of these compounds may not be sufficient in more acute exposures. In this review, we discuss the current state of knowledge of PCB toxicity and some of the antioxidant and anti-inflammatory nanocarrier systems that may be useful as an enhanced treatment modality for reducing PCB toxicity.

Keywords

Antioxidant; nanocarriers; PCBs; Toxicity

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Conflict of Interest Disclosure

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1. Polychlorinated biphenyls – history and health implications

Persistent organic environmental pollutants, such as polychlorinated biphenyls (PCBs), are a global health concern due to their negative impact on human health and the ecosystem. This negative impact largely hinges upon pathologies that include oxidative stress and inflammation at their root, and are linked to numerous non-communicable diseases. Therefore, this presents an interesting paradigm in which PCB-induced toxicity may be decreased through specific therapies that target oxidative stress and inflammatory pathways.

PCBs are a toxic class of chlorinated aromatic compounds that have been and continue to be an issue in environmental health since their introduction in the 1920s [1, 2]. At least 1.3 million tons of PCBs, comprising about 130 identified individual congeners, were manufactured worldwide prior to their banning [3]. PCB production was global with PCB mixtures being manufactured in the United States and overseas under different brand names including Aroclors (USA), Clophens (Germany), Phenoclors and Pyralenes (France), Fenclors (Italy), Fenochlors (Spain), Kanechlors (Japan) and Sovol (former USSR) [4]. Although PCBs were first synthesized in Germany during the late nineteenth century, commercial PCB production only started in 1929 with large scale production initiating in 1945, and were primarily used for industrial purposes, including as an insulator for capacitors and transformers due to their chemical and thermal stability [5].

PCB production ended in the United States (as part of the Toxic Substances Control Act in 1979) and western Europe during the 1970s but continued in eastern Europe until the 1990s and worldwide production was stopped after the Stockholm Convention in 2001. Currently, there is no known PCB production; however, PCBs may still be formed inadvertently during industrial processes such as pigment production [6]. Moreover, PCB pollution and contamination is worldwide with incidences of PCB exposure and detection in humans and the environment reported in numerous countries across the globe such as Belgium, Italy, Spain, Slovakia, Russia, Kenya, Egypt and Japan to name a few [7–11]. However, their resistance to chemical and thermal degradation translates to bioaccumulation in humans and marine life. Specifically, after sequestering in riverbeds and other hydrophobic environments, PCBs are consumed by bottom-dwelling organisms and are often not degraded, leading to biomagnification along trophic levels of the food chain and increased PCB concentrations and toxicity in animals and humans.

2. Polychlorinated biphenyl congeners and chemistry

PCBs are lipophilic compounds that still persist in the environment to this day, despite efforts of remediation and excavation. Due to their lipophilicity, PCBs are found in hydrophobic environments such as soil and riverbeds, and eventually bioaccumulate in adipose tissue of living organisms. However, the ability to sequester within humans and exert toxicity also depends on the physical structure and geometry of PCBs, which is largely dictated by their degree of chlorination.

Depending on the number and position of chlorine atom substitutions, there are 209 possible PCB congeners, all of which were manufactured commercially. This degree of chlorination

has a significant impact on PCB exposure, metabolism, and toxicity. Specifically, PCBs are metabolized via hydroxylation by cytochrome P450 enzymes. However, lower chlorine-containing congeners (*mono* and *di* substituted) have a higher propensity to be metabolized and excreted, while higher chlorine-containing congeners are less extensively metabolized and thus are more likely to be sequestered and display toxicity [12].

Structurally, PCBs are grouped into two major classes: non-coplanar PCBs and coplanar PCBs (Fig. 1). Non-coplanar PCB chlorine substitution is either *ortho*- or *di-ortho*-substituted, leading to steric pressure and a distorted geometry, and are described as "non-dioxin like PCBs," while coplanar PCB chlorine substitution lacks *ortho*- substitution, leading to a planar structure and a "dioxin-like" classification [13]. Some mono-*ortho* PCBs appear to possess both "non-dioxin like" as well as "dioxin-like" properties and are referred to as mixed congeners [14]. Notably, some PCBs (mixed congeners), with characteristics of both coplanar and non-coplanar congeners, have affinity to the pregnane-xenobiotic receptor (PXR) and constitutive androstane receptor (CAR), as well as the AhR, giving rise to pathologies such as non-alcoholic steatohepatitis (NASH), obesity, and diabetes [15]. While mechanisms of action of both non-coplanar and coplanar PCBs can result in inflammation, oxidative stress, and toxicity, non-coplanar PCBs tend to exert their toxic properties via endocrine disruption, neurotoxicity, and an immunotoxicity-related mechanism, whereas coplanar PCBs display toxicity via an aryl hydrocarbon receptor (AhR)-dependent mechanism.

In addition, PCBs were commercially manufactured as mixtures of congeners and not as a single entity. In North America, Monsanto Corporation produced and marketed these mixtures under the brand name "Aroclor". Older generation Aroclors such as Aroclor 1260 contained approximately 60% chlorine content by weight and were found to be toxic to occupational workers. They were later replaced by newer generation Aroclors such as 1016 that possessed lower chlorine content [16]. As such, the exact composition of contaminated sites can vary greatly, resulting in a varied health risk potential that these sites pose.

3. Exposure routes and disease risks

Historically, PCB exposure in humans were either occupational or accidental, however the most relevant route of PCB exposure today is through ingestion of PCB-contaminated food and water. In fact, studies have shown that PCBs are present in fish globally, which results in human exposure via the oral route [12, 17–19]. This chronic, low concentration exposure results in inflammation and toxicity, as well as the development and progression of chronic inflammatory diseases, such as obesity, cardiovascular disease, various cancers such as liver, stomach, intestinal, and thyroid cancers, as well as non-Hodgkin lymphoma, and diabetes. In contrast, acute toxicity has also been the subject of investigation, due to symptoms of skin lesions and immunocompromised individuals, resulting from immunosuppression [20–26].

Overall, PCB toxicity is a critical and central issue in environmental and human health, and it is an issue without a specific therapy. Interestingly, healthful nutrition, such as those enriched in polyphenols and antioxidants has been found to decrease the oxidative stress and inflammation induced via PCB exposure [24]. However, therapy through the consumption of

diet-derived bioactive compounds with antioxidants and anti-inflammatory properties has limitations that include a lack of bioavailability and stability [27]. These limitations may be overcome through employment of nanotherapy options that specifically treat PCB-induced oxidative stress and inflammation through targeted, controlled, and effective delivery of antioxidants and other protective bioactive compounds.

3.1 PCB exposure: Acute and chronic disorders

Health disorders associated with PCB exposure can be acute or chronic depending on the dose, duration of exposure, type of congener and degree of chlorination. Acute disorders occur as a result of accidental or occupational exposures that are associated with high doses and take place over a short period of time. Acute disorders were reported in accidental PCB poisonings such as the Yusho disease in 1968 that affected about 14,000 people in Japan and the Yu-cheng disease in 1979 that affected approximately 2,000 people in Taiwan [28–31]. During those incidences, mass PCB poisoning occurred in people consuming rice bran oil that was previously contaminated with PCBs and polychlorinated dibenzofurans (PCDFs) during production. Common symptoms included dermal and ocular effects such as chloracne, skin rashes and ocular lesions, irregular menstrual cycle and carcinogenesis [32–34]. High dose PCB exposure in occupational populations that worked at PCB manufacturing plants or dealt with PCB-containing equipment reportedly resulted in elevated liver enzymes levels consequently leading to hepatic effects, dermal effects such as chloracne characterized by acne-like eruptions on the face frequently on the cheeks and behind the ears, respiratory problems and cancer [35–38]. Although these may be considered acute effects, due to their severity and sudden onset, they persist over time considering that most PCB congeners are resistant to bio-degradation and can bioaccumulate. In fact, follow up studies on persons that had high dose PCB exposure demonstrated that these cohorts suffered from a range of health disorders including malignant neoplasms of the liver and stomach, as well as neoplasia in lymphatic and hematopoietic tissues affecting the immune response. Onset of diseases due to PCB exposure are also found in multiple organ systems such as the cardiovascular and circulatory system, gastrointestinal and digestive system, musculoskeletal and connective tissue systems and include neurological, cognitive development and reproductive defects [32, 39, 40].

Chronic or long-term PCB exposure in humans can lead to health effects including disorders of the hepatic system, cardiovascular complications, endocrine dysfunction, reproductive and developmental abnormalities, neurological defects and effects on the immune system. These chronic effects are becoming increasingly relevant to human health research because they reflect the effects of exposure levels in the general population and are not restricted to electrical capacitor workers or victims of PCB poisonings. Furthermore, identifying a particular disease pathology and elucidating the mechanistic evidence that link PCB exposure to such disorders can prove challenging, given the span of chemicals pertaining to the human exposome. Nonetheless, evidence from epidemiologic studies suggest strong correlations of various disease risks with PCB exposure, and numerous experimental studies on animal models have validated such reported findings as discussed below.

PCB effects on the liver include liver cancer, non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) that are correlated with elevation of liver enzymes including gamma-glutamyltransferase (GGT), alanine transaminase (ALT) and aspartate transaminase (AST). Studies on human populations have shown positive associations between serum PCB concentrations and elevated liver enzymes, indicative of liver injury [41–43]. Non-coplanar PCBs such as PCB 153 and Aroclor mixtures such as Aroclor 1260 that are heavily non-coplanar in composition have been shown to worsen NAFLD and promote hepatic inflammation in the presence of diet-induced obesity [16, 44]. Coplanar PCBs such as PCB 126 have also been shown to promote fatty liver or steatosis similar to other dioxin-like chemicals [45]. Additionally, studies by the National Toxicology Program (NTP) and other groups have shown that both PCB 153 and PCB 126 can induce liver cancer in rats [46, 47]. The liver functions as a site for both xenobiotic metabolism and maintenance of energy homeostasis through regulation of multiple key metabolic pathways. Since PCBs are xenobiotics, the liver becomes the first target organ of PCB toxicity provided that PCB exposure occurs through the oral route. Given the liver's role in metabolic regulation, hepatic dysfunction caused by PCB exposure can escalate into associated metabolic disorders such as insulin resistance and diabetes, obesity, dyslipidemia and the metabolic syndrome [48–50].

PCB effects on the cardiovascular system include associations of PCBs with incidences of hypertension in residents of Anniston, Alabama where the Monsanto Corporation plant was located, as well as in a PCB-exposed Spanish cohort and in the NHANES population [51–53]. However, PCB effects on the cardiovascular system encompasses other complications such as myocardial infarction, stroke and vascular injury [54, 55]. Rodent studies have also reported PCB-induced vascular inflammation and injury, consequently leading to undesirable cardiovascular aftermaths such as inflamed vascular pathology indicative of endothelial cell dysfunction and atherosclerosis [56]. Interestingly, PCBs indirectly act as a risk factor for cardiovascular diseases through hepatic disrupting effects such as increased synthesis of cholesterol and triglycerides and dyslipidemia [57]. Indeed, NAFLD/NASH has been proposed as a risk factor for cardiovascular disease, further adding complexity to PCB-induced multi-organ toxicity.

PCB impact on the endocrine system is majorly perturbed thyroid function due to reduced circulating thyroid hormone levels with PCB exposure, eventually affecting thyroid hormone-associated neurodevelopment and neurological defects [58–60]. PCBs are also viewed as endocrine disruptors with another relevant endocrine effect being association with type 2 diabetes mellitus due to PCB toxicity on pancreatic beta cells and compromised insulin secretion [61, 62]. Other PCB effects include alterations in immunological responses particularly deficient immune function in humans [63] and demonstrated immunosuppression in rodent studies [64] and adverse effects in the reproductive system [65, 66].

4. Mechanisms of toxicity: Metabolic pathways and oxidative stress

The well-studied mechanisms of PCB toxicity depending on their structural classification is demonstrated in Fig. 2. For most of the observable effects, major PCB-mechanisms of action

have been attributed to AhR-activation and upregulation of AhR target genes that precedes unwanted effects such as inflammatory response and oxidative stress. The AhR is a ligand-activated transcription factor primarily expressed in the liver but also found in extra-hepatic tissues. PCB binding to this hepatic receptor causes its nuclear translocation and induction of xenobiotic genes such as cytochrome P450 enzymes such as CYP1A1 and CYP1A2 [67]. However, AhR activation is not restricted to xenobiotic metabolism, but it also plays an important role in many developmental pathways, such as hematopoiesis and differentiation. Hence, its activation is also linked to cell cycle pathways, cell proliferation and cancer [68]. There are also cross-talks between AhR activation and inflammation-related pathways such as the nuclear factor kappa B (NFκB) and nuclear factor (erythroid-derived 2) -like 2 (Nrf2) activation pathways; hence PCB activation of the AhR can result in upregulation of inflammatory cytokines, including interleukins (IL-6, IL-2) and tumor necrosis factor alpha (TNFα), formation of reactive oxygen species (ROS), and induction of antioxidant enzymes [69–71]. The imbalance that ensues due to the amount of ROS produced and the body's inability to eliminate such reactive intermediates results in oxidative stress and tissue damage. Additional mechanistic studies have shown that PCBs can induce inflammation and oxidative stress through epigenetic modification [72, 73].

Coplanar PCBs often referred to as "dioxin-like" PCBs elicit their toxicity through AhR induction; however, multiple non-coplanar PCBs are "phenobarbital-like" and activate other hepatic, xenobiotic receptors namely the pregnane-xenobiotic receptor (PXR) and the constitutive androstane receptor (CAR) [13, 15]. Outcomes of CAR and PXR activation are associated with metabolic effects such as NAFLD/NASH, dysregulated energy metabolism and obesity. Nonetheless, and because PCBs occur as mixtures of both congener classes, outcomes of PCB exposure therefore can result in pro-inflammatory and cardio-metabolic disorders. Notably, other mechanisms of PCB-induced toxicity include microRNA alterations, interference with epidermal growth factor receptor (EGFR) signaling and direct effects on vascular endothelium that can promote oxidative stress responses [24, 74, 75].

5. Antioxidant therapy as a possible pathway to combat PCB derived toxicity

Given the critical role that chronic oxidative stress plays in PCB toxicity, it is reasonable to assume that treatments, which can directly counter this pathology, could be a potential antidote to PCB exposure. Since oxidative stress is a state of excess production of oxidants/ROS/free radicals, increasing the antioxidant concentration via external supplementation could counter excess ROS production, and thereby alleviate the oxidative stress condition. Indeed, to maintain red/ox balance, dietary antioxidants, either as a part of fruits and vegetable consumption or vitamin supplementation, have been considered a part of a healthy life style. For example, long term and moderate intake of red wine, a source of resveratrol, has been linked to decreased cardiovascular and cerebrovascular ischemic occurrence [76]. Yet, despite these intended goals, to date, clinical studies evaluating the use of dietary antioxidants for chronic disorders, including diabetes, cardiovascular diseases and neurological as well, have failed to demonstrate significant benefits. For example, antioxidants, such as curcumin, have failed to show significant protective effects against

Alzheimer's disease in a clinical trial with oral intake of the antioxidant over 48 weeks, although pre-clinical trials showed protection in neurodegenerative disorders in mice or rat model [77–80]. Nevertheless, longitudinal and observational human studies support the health promoting benefits of diet-derived bioactive compounds that have antioxidant and/or anti-inflammatory properties [81–83]. As such, along with proper nutrition, there remains a need for treatments that can provide interventional therapy for environmental toxic exposure. To understand the source of the inconsistency between observational studies and clinical trials and identify potential solutions, a brief overview of cellular oxidative stress and a summary of strategies attempted to date are presented.

5.1 Antioxidant action pathway in the vascular endothelium

During cellular oxidative stress, especially vascular oxidative stress, a host of cellular pathways are activated that directly result in the enzymatic formation of ROS and reactive nitrogen species (RNS), (Fig. 3). The terms ROS/RNS are general terms used for the reactive species derived from oxygen or nitrogen atoms. As such, it is difficult to imagine a scenario where all of the species formed result in a unified physiological outcome. However, given their short half-lives, it is still challenging to decouple the specific action of individual ROS/RNS molecules in each pathway. In the case of PCB induced toxicity, uncoupling cytochrome P450 1A1 (CYP1A1) and activation of AhR is thought to play a major role of ROS generation, which in turn results in the excess production of free radicals, leading to chronic inflammation and disease [84, 85]. Another mechanism common to oxidative stress induction that has been identified in PCB toxicity is the formation of superoxide anions via the NADPH oxidase enzyme that results in the oxidation of NADPH to $NADP^+$ [86]. Within the cytosol, this superoxide anion is subsequently converted to hydrogen peroxide in the presence of superoxide dismutase (SOD). In turn, hydrogen peroxide in the presence of transition metal ions (Cu, Fe) can form the highly reactive, hydroxyl radicals [87].

Yet, despite these radical generating mechanisms, cells also possess endogenous antioxidant defense systems to counteract ROS production. For instance, hydrogen peroxide can be "inactivated" by enzymes, including catalase, which converts hydrogen peroxide into water and oxygen [88, 89], and the peroxiredoxins that can reduce peroxide molecules [90]. In reducing peroxides, the peroxiredoxins oxidize glutathione (GSH) into the oxidized disulfide, GSSG [91]. Glutathione is a highly abundant cytosolic molecule that serves to maintain a reducing environment in the cytosol. The level of glutathione is maintained by the conversion of GSSG back to GSH, catalyzed by glutathione reductase. This natural cellular redox cycle continues until disrupted by external factors, leading to accumulation of ROS and oxidized lipids, proteins and DNA, which can stimulate inflammation, apoptosis and cell death.

Based upon these pathways, antioxidant therapy could potentially serve as an intervention for PCB induced oxidative stress related toxicity. It has been theorized and published multiple times that external supplementation of antioxidants (i.e., enzymes, synthetic antioxidant or natural nutritional antioxidants) can counter the excess radical production, restoring natural cellular function. These externally supplemented antioxidants can act in multiple ways, 1) through the downregulation of ROS generating enzymes and upregulating

the natural antioxidant defense system, 2) by metal ion chelation, reducing the production of hydroxyl radicals and/or 3) direct scavenging of radical electrons, thereby inactivating ROS [92, 93]. The following section summarizes some of the attempts at controlling oxidative stress through antioxidants and the observations or limitations noted.

5.2 Current antioxidant therapies

5.2.1 Direct Antioxidant Treatment—Antioxidants can be broadly divided into two main categories: antioxidant enzymes and small molecule antioxidants. Antioxidant enzymes have the advantage of high specificity of action. Some of the most common antioxidant enzymes for oxidative stress defense are superoxide dismutase (SOD), catalase, glutathione peroxidase, glutathione reductase, and peroxiredoxins. SOD is capable of converting superoxide radical to hydrogen peroxide (H_2O_2). H_2O_2 can further be reduced to water and oxygen via catalase action. Therefore, combined therapy of SOD/ catalase might be suitable for suppression of ROS derived oxidative stress. Glutathione peroxidase helps in detoxification of H_2O_2, hydroperoxides, lipid peroxides, by utilizing the glutathione redox cycle. Through this high specificity, tailored approaches to treatment can be obtained. In addition, these enzymes function through a catalytic pathway, allowing for multiple copies of ROS (often millions of copies) to be scavenged for each enzyme molecule introduced, leading to a highly potent function. However, antioxidant enzymes are not without their drawbacks, including limited stability *in vivo*, the challenge to formulate delivery strategies, and the requirement of parenteral routes of administration.

Alternatively, small molecule antioxidants typically have a broad mechanism of action, as they are able to scavenge a variety of ROS/RNS, and potentially provide a robust protection strategy. There are numerous small molecule antioxidants, typically derived from dietary sources, that have been studied for suppression of cellular oxidative stress or used for clinical and pre-clinical testing of vascular oxidative stress, including natural dietary antioxidants like vitamin C and E. Curcumin, quercetin, epigallocatechin gallate (EGCG), from the flavonoid class of molecules, are characterized by the presence of at least one phenolic group in their molecular structure, and also have been found to mitigate cellular oxidative stress [94].

For instance, curcumin, a yellow pigment from curcumin longa, with two phenoxy groups, has been shown to have anti-inflammatory properties and possess an antioxidant potential of about 2.5–2.8 times more potent than Trolox, a common reference standard [95]. Because of its free radical scavenging properties, it has been shown to suppress induced oxidative stress in various *in vitro* models [96]. It is also known to show its anti-inflammatory effect through inhibition of clooxygenase-2 (COX-2), lipoxygenase (LOX), and inducible nitric oxide synthase (iNOS). The upregulation of these enzymes has been associated with the pathogenesis of tumor progression and other inflammatory disorders [97]. Curcumin in *in vitro* models has shown to possess a protective effect against diabetes. For instance, curcumin treatment slows the formation of advanced glycation end products and to inhibit activation of hepatic stellate cells, which is linked to hyperglycemia in diabetic cases [98]. In the case of tumor cell growth, Perry et al. showed that administration of curcumin to athymic mice, xenografted with glioma U-87 cells resulted in slower tumor growth subcutaneously

and in the intracerebral regions, inhibiting the glioma induced angiogenesis [99]. In another study conducted by Niu et al., 2μM curcumin was able to achieve 80% cell death of melanoma A375 cells, when coupled with light photosensitization, as opposed to only 20% with curcumin alone [100].

Another polyphenolic flavonoid, quercetin, has been shown to be highly effective at suppressing cellular oxidative stress. In a study conducted with retinal pigment epithelial cells (RPE), quercetin demonstrated a dose dependent protective effect against hydrogen peroxide generated cellular oxidative stress, showing its potential towards treatment of retinal degeneration [101, 102]. Damage of RPE cells is associated with age related macular degeneration resulting in loss of vision and oxidative stress, which is considered to be one of the major underlying cause for its pathogenesis. In the case of PCB induced toxicity, quercetin has also been used *in vitro* and *in vivo* to suppress toxicity, suggesting a promising approach to therapeutic use. For instance, during *in vitro* studies with vascular endothelial cells, quercetin inhibited PCB 77 induced CYP1A1 expression and suppressed with AhR activation, which is responsible for excess ROS production [85]. Quercetin was also shown to inhibit PCB induced phosphorylation of caveolin-1, which plays a significant role in pathogenesis of atherosclerosis [103],[104]. In another study conducted by Selvakumar et. al., quercetin was shown to have a neuroprotective effect against PCB induced oxidative stress and hippocampal apoptosis in rats, where decreased levels hydrogen peroxide, lipid peroxidation and protein carbonyl content were experienced 30 days after the simultaneous treatment of quercetin along with Aroclor 1254 as compared to only Aroclor exposure [105]. Although, quercetin is a direct scavenger of ROS/RNS and *in vitro* studies have shown this action at treatment concentrations of 5–50 μM [106], it is found to be only in nanomolar concentrations in the brain upon administration. This concentration is not likely sufficient to show neuroprotective effect by direct antioxidant action, but is rather acting as a pro-oxidant creating a mild oxidative stress state to stimulate cellular antioxidant defense mechanisms [107–109]. One of the proposed pathways of such stimulation self-defense is activation Nrf2-ARE (nuclear factor (erythroid-derived 2)-like 2- antioxidant response elements) pathway, which controls the various proteins including heme-oxygenase-1, GPX, SOD etc. [110, 111]. Induction of PON2, (a gene from paroxonase family, known to exert antioxidant effect) is another suggested mechanism of self-antioxidant stimulation upon quercetin exposure to neuronal cells at low concentrations [112–114].

Apart from flavonoids, carotenoids have also been explored showing protective effect on RPE cells, acting as blue light filters and ROS intermediate quenchers, help suppressing oxidative stress [115]. The alpha-tocopherol form of Vitamin E has also shown superior antioxidant properties, demonstrating the benefits of vitamin E supplementation towards cardiovascular diseases. For example, dietary supplementation of Vitamin E (specifically α-tocopherol form) significantly reduced aortic lesions in mice over 4–10 weeks, reduced restenosis after angioplasty in rabbits [116]. Table 1 lists some antioxidants and possible mechanism of action pathways and functions.

5.2.2 Known limitations of antioxidant therapy and oxidative stress management—Despite much of the promise of antioxidant therapy, there has been limited clinical evidence to suggest that oral antioxidant delivery can be an effective treatment for

oxidative stress related diseases. Indeed, recent reports have continued to emerge as highly critical of this approach. At the core of all these findings, the data suggests that poor pharmacology prevents these compounds from functioning as hypothesized. For instance, many antioxidant compounds are plagued by short half-lives due to fast renal clearance, inactivation of activity before reaching the site of treatment as a result of first pass metabolism, poor solubility, lack of natural accumulation at sites of interest and hepatic uptake. The bioavailability, site of absorption (gastro-intestinal tract or intestines), chemical metabolite formation (glycosides, esters etc) and antioxidant capacity of polyphenols are different from each other [145, 146]. During metabolism, polyphenols serve as substrates for several enzymes in the small intestine and colon, resulting in their biotransformation through esterase, glucosidase, decarboxylation, and demethylation [147, 148]. Hence, the therapeutic activity of the antioxidant polyphenols is also dictated by their metabolic state and not only the plasma concentration. Resveratrol, with anti-microbial and anti-inflammatory properties, has reduced bioavailability upon oral administration due to its metabolization into glucuronides and sulfates [149]. Curcumin bioavailability is reduced by several factors including its instability at neutral and alkaline pH, inability to permeate through the intestinal lumen to the blood stream, and its rapid conversion into metabolites within the body. Some of these curcumin metabolite forms such as tetra-, and hexahydrocurcumin show significant antioxidant activity, while other forms of sulfo- or octahydrocurcumin have shown minimal to no anti-inflammatory properties. Hence, it becomes important which form of metabolite is formed upon administration [95, 150–152].

PCB induced toxicity and vascular oxidative stress often go hand-in-hand and there is *in vitro* evidence showing the protective effect of antioxidants like quercetin and EGCG against PCB 77 induced inflammation. In addition, vitamin C and E have been reported to be protective against oxidative stress caused by PCB mixtures[153]. These examples of antioxidant protection are usually successful in *in vitro* models but *in vivo* administration of antioxidants often fail to be effective due to their fragile structural properties under systemic environment. As such, in order to determine if these antioxidant compounds can provide an effective treatment against PCB toxicity, it becomes important to control the method of delivery to ensure intact compounds reach their intended site of action for the required duration of action.

5.3 Antioxidant Therapy through Payloads for Controlled and Effective Delivery

As antioxidants possess promising effective properties, but also possess significant pharmacological limitations, they represent ideal candidates for nanocarrier drug delivery systems. Figure 4 illustrates some of the design factors in nanocarrier design for drug delivery systems and their synthesis processes. Nanoparticles have been considered for many years as a way of modifying the inherent pharmacokinetics of the drug, by stabilizing the compound, enhancing accumulation at sites of action, controlling release and thereby widening the duration of efficacy [154]. The advantages of these systems are their physiochemical properties, including surface chemistry, charge, size and shape, dictate the ultimate fate of the loaded drug (Fig. 4, Fig. 5). For instance, the size of nanocarriers determines the ultimate transport in the circulatory and transcellular systems, with 30–100 nm diameter particles being effective for transcellular and pericellular transport; 50–500 nm

particle systems are ideal for long bloodstream circulation [155]; 200–800 nm are best for targeting of sinusoidal cells in liver and spleen [156], while greater than 5 μm being used for organ delivery via mechanical retention [157]. However, these trends are also related to the surface chemistry of materials as well. While nanocarriers in the 50–500nm can provide long circulation, this is only possible when the surface of the particles are of neutral charge and highly hydrophilic, as is the case of poly(ethylene glycol) PEG coated particles [158–160]. When hydrophobic particles in this size range are i.v. injected, they are rapidly cleared by the hepatic system, which provides a unique passively targeted system for fast hepatic uptake, serving as an effective treatment for acute liver disorders [161, 162]. Alternatively, long circulating particles of sizes that can pass through leaky vasculature can result in local particle accumulation, a process that known as the enhanced permeation and retention (EPR) effect [163]. In addition to these considerations, one must also be mindful of the drug loading and associated release rate. To date, there have been many systems pursued to enhance the delivery and efficacy of antioxidant systems, including, liposomal encapsulation systems, polymeric nanoparticles (encapsulated or polymeric pro-drug forms), magnetic nanocarriers, polyplex complexes, and exosomes. In this section, a review of these approaches is provided along with discussion of the potential impact these systems could have on PCB related toxicity.

5.3.1 Liposomes—Liposomes are spherical vesicles comprising of one or more phospholipid bilayers, containing an internal aqueous core that is isolated from the external aqueous space. They are artificially synthesized analogs of natural cellular vesicles, including endosomes and exosomes. They are well known for their biocompatibility, low toxicity, and bioabsorbable nature [164]. The major advantage of such systems lies in their ability to load both hydrophilic and lipophilic drugs, due to presence of aqueous core and lipid bilayer in their structure [165]. With its versatile properties, many liposomal systems have been designed with the aim to encapsulate unstable, fragile drugs to get long circulation times and increased bioavailability. They can be internalized by cells via lipid bilayer fusion and are able to facilitate delivery by diffusion or temperature dependent unfolding of the vesicles. Hence, liposomes have been explored extensively for delivery of small molecule antioxidants and antioxidant enzymes to the organs and tissues with oxidative insults.

N-acetylcysteine (NAC), curcumin, quercetin, resveratrol, alpha-tocopherol (Vitamin E), coenzyme Q, enzymes such as GSH, SOD, and catalase are several antioxidants and antioxidant enzymes delivered through liposomes [166]. Liposomal NAC has shown protection against liver injury in a rat sepsis model and better potency against acute respiratory-distress in a rat model [167–169]. While combination of NAC with tocopherol showed protection against mustard gas induced lung damage in guinea pigs [170]. In another study by Alipour et. al., liposomal NAC was able to inhibit acetaminophen induced hepatotoxicity in rats [171].

In the flavonoids category, the use of liposomal curcumin has shown to increase curcumin plasma concentration upon oral administration [172], which demonstrated better inhibition of pancreatic carcinoma cell growth and anticancer properties both *in vitro* and *in vivo* [164, 173–176]. In a similar manner, in a pre-clinical study, liposomal quercetin formulations have

also shown protective effects against carbon tetrachloride induced hepatotoxicity [177]. Quercetin loaded liposome delivery also helped reduce the peroxynitrite induced myocardial injury [178], while PEGylated quercetin liposomes enhanced anti-tumor activity towards lung and colon cancer in mice [179]. These PEGylated quercetin liposomes not only increased the half-life of quercetin from a few minutes to 2 hours, they also demonstrated higher accumulation and retention in organs.

As a therapy against environmental toxicity, quercetin has also been explored in fighting oxidative stress due to environmental toxicants such as arsenic, which is normally found in contaminated water. In a study conducted by Ghosh et al., quercetin encapsulated liposomes were to inhibit arsenic toxicity by preventing hepatic oxidative stress, decreased arsenic accumulation in liver while free quercetin administration failed to show any significant effect upon sodium arsenite exposure [180]. Resveratrol is another flavonoid that has been loaded into liposomal systems, and has shown the ability to inhibit vascular intimal thickening in rats upon intraperitoneal injection [181], while combination of curcumin-resveratrol encapsulated liposomal delivery showed highest antioxidant serum concentration, longest retention time and demonstrated reduced prostate cancer incidence in mice [182]. These studies strongly suggest the impact antioxidant nanocarriers could have as an intervention to PCB exposure.

In the case of antioxidant enzymes, SOD and catalase encapsulated liposomes resulted in 90% of the survival of newborn rat pups upon exposure to lethal 95% oxygen exposure, while placebo treated newborns resulted in 60% mortality [183]. CuZn-SOD loaded liposomes also showed their protective effect against cerebral ischemia-reperfusion injury in rats. Longer circulation times and ability to cross the blood brain barrier aided longer retention and higher accumulation of CuZn-SOD (upto 2 hours) via liposomal delivery when compared with CuZn-SOD delivered in its free form (30 minutes of retention time). [184, 185]. Another observation made was that enzyme activity was always higher in the injured brain than in the non-injured control at any given time-point, suggesting the activation of natural antioxidant enzyme defense mechanisms upon sufficient antioxidant delivery. In the case of cardiac disorders, one of the pre-clinical trials conducted by Laursen et al. demonstrated that the delivery of SOD resulted in the reduction of blood pressure by 50 mmHg in angiotensin II induced hypertension and enhanced hypotensive response to acetylcholine [186]. Liposome-encapsulated SOD has also demonstrated enhanced efficacy in topical application in a pre-clinical study, where a reduction in post-burn edema and wound size was observed due to enhanced antioxidant effect of SOD against neutrophil mediated injury [187]. In a clinical trial, Cu/Zn SOD-liposome systems showed regression in radiation induced fibrosis by the third week of treatment [188]. They have also shown complete regression with the prophylactic action, in the cases where fibrosis development was certain [189] .

5.3.2 Polymeric nanocarriers—Liposomes were one of the first nanocarrier systems to have been developed, with initial research dating back to the 1960s. Since then, other nanocarrier systems have been explored, with polymer nanoparticles representing one of the most versatile and promising systems in terms of controlled release, tunable shape, and the shear variety of chemistries available, all relying on the mechanism of bulk degradation

and/or diffusion for drug release, tuned most commonly by pH and temperature. Most of these systems have focused on the formulation and design of biodegradable systems that provide sustainable and controlled release of fragile small molecule antioxidants or enzymes.

Poly(lactic acid) (PLA) and poly(lactic-co-glycolic acid) (PLGA) nanospheres for antioxidant encapsulation have been studied extensively for controlled delivery. PLA/PLGA is a biodegradable polymer that breaks down into lactic acid and glycolic acid and has been FDA approved for various implantable and injectable drug delivery applications. Antioxidant enzyme PLGA encapsulated microspheres have been formulated as a means of overcoming the short-lived stability issues associated with enzyme delivery, especially where delivered enzymes ultimately are shuttled to the lysosomes, as is the case with delivery of SOD or catalase [190]. Quercetin loaded nanocarriers composed of PLA backbone have been shown to reduce arsenic induced oxidative stress and associated gene expression in liver. In fact, the PLA carriers were found to be more effective at reducing oxidative stress and inhibiting fibrosis compared to liposomal quercetin administration [180]. Curcumin loaded into PLGA nanoparticles was also able to reduce arsenic toxicity in a rat model through the inhibition of oxidative damage in rat kidney and brain. A significant reduction in the levels of lipid peroxides and a revival of the natural antioxidant enzyme defense system were some of the important observations made with curcumin nanoparticles [191]. Co-enzyme Q10 (CoQ10) loaded PLGA nanoparticles administered orally have also demonstrated enhanced ejection fraction over the span of three months in rats induced with myocardial ischemia [192]. In another pre-clinical study with renal hypertensive rat model, CoQ10 encapsulated PLGA nanoparticles showed improved blood pressure (30 and 15 mmHg decrease in systolic and diastolic pressure respectively) at 60% lower dosage frequency than the rats treated with just CoQ10 suspension (23 and 10mmHg pressure reduction) [193] Yet, one limitation of PLA/PLGA is the potential local accumulation of acid byproducts that can lead to a decrease in pH, resulting in acidic protein inactivation and local inflammation [194]. As an alternative, polyketal polymers have also been studied. The advantage of polyketal polymers is that their degradation products are neutral, forming diols and acetone. Polyketal SOD microspheres were shown to alleviate muscular ischemic reperfusion injury and bleomycin induced pulmonary injury upon intratracheal administration. These microparticle systems, in a rat model, also showed sustained scavenging of excess superoxide oxide production after ischemia-reperfusion injury up to at least 3 days after infarction [195, 196].

While these microsphere systems were able to show some activity locally, in order to promote systemic delivery, catalase was loaded into PEG-PLA nanoparticles in the size range of 200–300 nm. These carrier systems demonstrated the ability to possess prolonged activity for over 24 hours, even when residing in proteolytic environments, such as lysosomes [197]. Further exploring the PEG chemistry in nanoparticle formulation, chung et al. formulated micellar nanocomplexes comprising PEG-EGCG-herceptin shell and core system. The combination of antioxidant EGCG and anticancer protein Herceptin in these micellar systems demonstrated better tumor selectivity, growth reduction and longer half-life of Herceptin than the direct treatment in mice [198].

Most of these nanoparticle systems are synthesized through a simple single or double emulsion technique, where a solution of polymer and antioxidant are placed into an organic solvent, which is then added to an aqueous solution, allowing the organic solvent to either evaporate or extract out, leaving behind nanoparticles. This physically loaded system typically results in low drug loading efficiency, and a high burst release once purified and placed back into an aqueous environment [199–202]. An alternative method that has been developed is to conjugate the drug to the polymer or to actually polymerize the antioxidant into a degradable polymeric form. The idea is derived from the growing market of pro-drugs of pharmaceutically active yet structurally fragile drugs, where any selected functional group of the drug molecule is modified to protect from deactivation and upon systemic administration, are converted back to the original compound [203]. Carboxylic, hydroxyl, amino, carbonyl groups present in active drug molecules are a few groups explored for transformation into esters, carbonates, carbamates, amides, phosphates and oximes [204]. Ester forms are one of the most common used form of pro-drugs due to its ability to be hydrolyzed systemically into an active molecule [205, 206].

Based on this concept, pro-drug polymeric nanocarriers have also been synthesized and explored for antioxidant delivery. Since most of the small molecule antioxidant possess one or more hydroxy or thiol groups, they can be functionalized and formulated into polyester, polyanhydride or poly(β-amino ester). For example, Wattamwar et al. were able to polymerize trolox (synthetic analogue of Vitamin E) into poly(trolox ester) via Steglich esterification[207]. Nanoparticles composed of poly(trolox ester) were formed via a single emulsion nanoprecipitation method, resulting in particles of 200 nm. Importantly, these particles were able protect pulmonary microvascular endothelial cells against nanocobalt toxicity, suppressing ROS formation [207, 208]. In addition to these findings, the particles possessed a unique ability to inhibit protein oxidation, an effect that was not observed with the native antioxidant, emphasizing the importance of the mode of delivery and how it can augment the observed outcome.

Poly(beta-amino ester) (PBAE) chemistry was further employed by our group for the conjugation of quercetin and curcumin into crosslinked polymers films, microparticles, nanoparticles or nanogel systems [209]. The single-phase reaction-precipitation method was versatile enough to render nanogels in the range of 50 to 800 nm, with uniform release over 24–36 hours by bulk hydrolytic degradation. Both curcumin and quercetin conjugated systems demonstrated protection against induced oxidative stress in endothelial cells [210, 211]. Curcumin PBAE nanogels were specifically explored for their action on mitochondrial oxidative stress, since mitochondria are considered to be a major source of ROS production once triggered. It was shown that free curcumin at low dosage did not show any potential towards OS while at higher concentration resulted in pro-oxidant damage. Importantly, curcumin PBAE nanogels demonstrated an overall higher TC_{50} value of 100 μg/ml as compared to free curcumin (TC_{50} 5 μg/ml) and was able to effectively suppressed mitochondrial oxidative stress over 24 hours. This widening of the therapeutic window for curcumin represents a critical feature and benefit of nanocarrier delivery.

5.3.3 Targeted Antioxidant Nanocarriers—As mentioned, PCB exposure can lead to acute liver, skin, ocular inflammation and induce/ aid carcinogenesis, while its

bioaccumulation in multiple organs results in chronic effects leading to cardiovascular disease and the development of carcinogenic malignancies. While antioxidant nanocarriers have shown benefit in liver organ injury, as nanoparticles do not naturally accumulate in the vascular endothelium, a targeting method must be employed in the nanocarrier design. By coating nanoparticles in affinity molecules directed against cell surface epitopes of the vascular endothelium, it becomes possible to turn antioxidant nanoparticles into vascular specific treatments. One such example is coupling the stealth properties of catalase encapsulated into biotinylated PEG-PLGA polymer nanocarrier with streptavidin modified PECAM-1 antibody. These immunotargeted nanoparticles resulted in 12% of the injected dose binding to the pulmonary vasculature, as compared to only 2% with the non-targeted (IgG coated) nanoparticles. Additionally, by loading the enzyme within the nanocarrier, it was able to elicit its function for at least 20 hours against oxidative stress in endothelial cells, where unloaded enzyme resulted in only a 3 hour function duration due to lysosomal trafficking and protein degradation [212]. In another study, nanoparticles synthesized via interaction of tocopherol phosphate and manganese porphyrin SOD-mimetic, with controlled release profile was conjugated with anti-PECAM, which demonstrated endothelial targeting and reduced expression of pro-inflammatory VCAM, E-selectin, IL-8 [213]. Excitingly, this group demonstrated SOD/catalase loaded anti-PECAM coated nanoparticles were able to accumulate up to 30% of the injected dose in the mouse pulmonary endothelium. Interestingly catalase targeted particles reduced pulmonary edema and leukocyte infiltration after exposure to endotoxin induced lung injury, while SOD loaded particles alleviated the associated lung inflammation [214]. In a preclinical study with mice, it was demonstrated that SOD-loaded, NR-1 PEGylated liposomes, polybutylcyanoacrylate (PBCA), as well as PLGA nanoparticles, showed protection against cerebral ischemia-reperfusion injury, due to localized accumulation in the hippocampus and significantly reduced the observed infarct volume [215]. Surface modifying poly(trolox ester) nanoparticles with anti-PECAM-1 was also able to target endothelial cells. These targeted particles were able to suppress iron oxide induced oxidative stress better than non-targeted, IgG-coated nanoparticles [216]. In case of curcumin, about 100 nm sized nanoparticles conjugated with poly(butylcyanocylate), poly(lactide-co-glycolide), chitosan, albumin or acrylamide polymers have also shown higher peak serum levels and hence enhanced bioavailability [217–219].

5.3.4 Routes of administration and features of acute vs chronic care—A final consideration to be made in the use of antioxidant therapies is that of the route of administration. Given their size and use, most studies have focused upon i.v. injection of nanocarrier systems. Yet, such intervention strategies are likely to be limited to acute and sub-acute exposures, as prolonged i.v. administration is highly undesirable. As such, exploration of alternative delivery methods, including inhalation, intratracheal, intraperitoneal, and topical administration are needed. All of these methods have been tried for the delivery of antioxidant in free form. Clinical trials employing oral delivery of antioxidants such as curcumin in free form have been conducted several times, with variable dosage towards suppression of oxidative stress induced inflammation. Curcumin as such has shown to reduce the inflammation in chronic diseases upon long term daily dosage such as in case of diabetes, by inhibiting the progression of type 2 diabetes. But, oral administration

comes with very low bio-distribution of the antioxidant, because of which even doses as high as 4–8 g per day resulted in maximum of 3.6 μM after 1 hour [220]. Intraperitoneal administration on the other hand increased the curcumin plasma levels 10 fold as compared to oral route [221], while curcumin liposomes administered intraperitoneally to obese mice showed improved insulin resistance [222].

Antioxidant encapsulated nanoparticles, comprising resveratrol, resveratrol-curcumin co-delivery, quercetin, and CoQ10 have been explored for skin disorders, with the goal of treating UV radiation induced oxidative stress and skin cancer. Indeed, resveratrol loaded solid lipid nanoparticles showed rapid diffusion and retention in cell membranes [223] There has also been some evidence showing effectiveness of antioxidant NPs towards acute renal failure, where CoQ10 encapsulated NPs when administered intravenously helped in reducing the blood pressure of mice induced with renovascular hypertension [224]. In another example, intratracheally administered SOD/catalase loaded liposomes resulted in protection from acute lung injury by increasing the antioxidant activity of alveolar type II cells [225, 226]. Aerosolization of liposomal encapsulated Cu/Zn SOD has also demonstrated long systemic circulation of antioxidant enzymes [226]. Yet, despite these studies, there still remains a significant need for the evaluation of the impact alternative routes of administration have nanocarrier therapeutic potential.

6. Conclusions

Chronic exposure of environmental pollutants remains a significant health concern. Even now, PCBs pose a continuous threat to the health and safety of our population. As a result, we need a wide array of tools and strategies to counteract these potential risks. While effective and healthful nutrition is likely to be a major player in our strategies to minimize health hazards, as seen by clinical trials of antioxidant interventions, it is unlikely that nutrition alone is enough to treat or prevent all PCB exposure-induced disorders. As such, strategies that can reduce body burden, enhance antioxidant delivery to target cells, and capture PCBs before entering the body can potentially be used to provide defense against PCB toxicity. Furthermore, we know from other treatments, such as NAC for acetaminophen toxicity, where antioxidant therapy can be an effective antidote. In order to enhance antioxidant therapy, strategies for effectively delivering antioxidants, such as nanocarriers, are likely required. Further studies for ideal candidates will be needed to best assess which compounds will be most effective at countering the toxicity of co-planar and non-coplanar PCBs. Finally, while studies with injectable nanocarriers provide some promising results, such routes of administration are not likely acceptable for chronic delivery systems. Thus, research into inhalation, intranasal, buccal or oral drug delivery systems are likely to be a fruitful area of research to determine if they can provide the needed exposure to treat PCB toxicity.

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Classification of PCBs

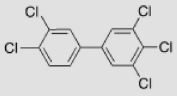
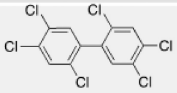
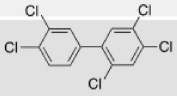
Congener Example	Structure	Geometry	Classification	Receptor Activation
PCB 77, 126		Coplanar	Dioxin like	AhR
PCB 153, 187		Non-coplanar	Non-dioxin like	PXR/CAR
PCB 156, 189		Mixed Coplanar	Dioxin and non-dioxin like	AhR/PXR/CAR

Figure 1.

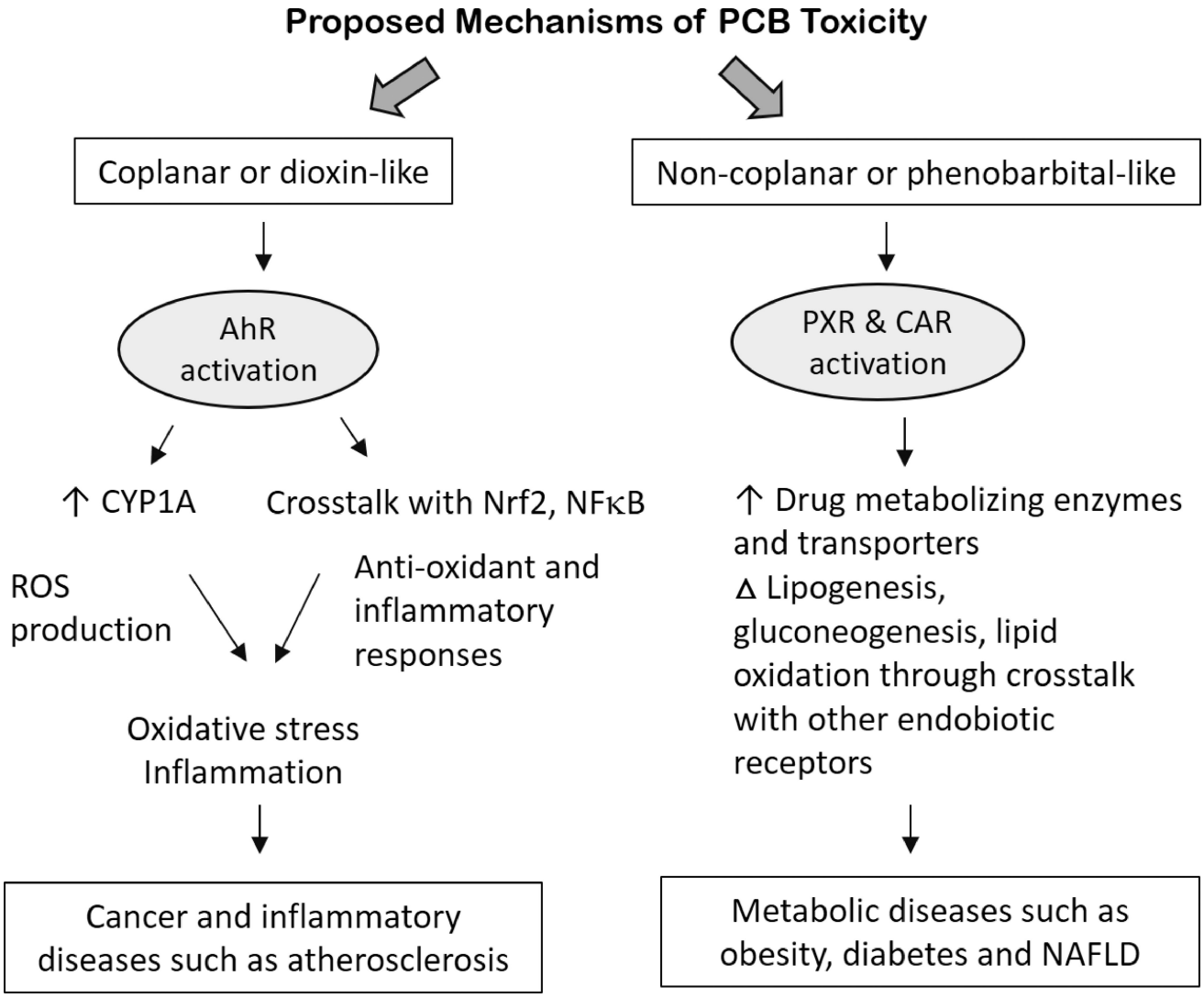


Figure 2.

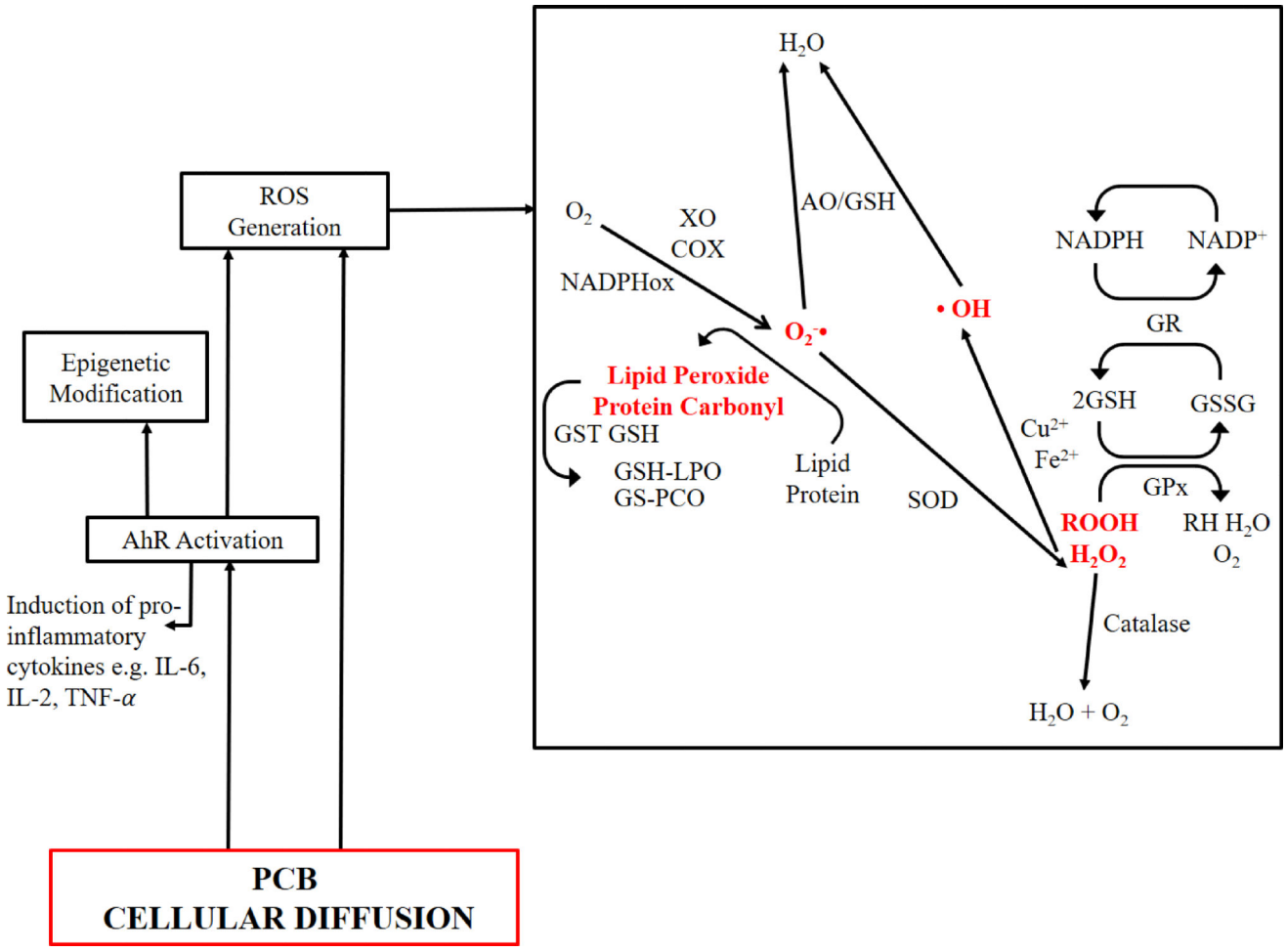


Figure 3.

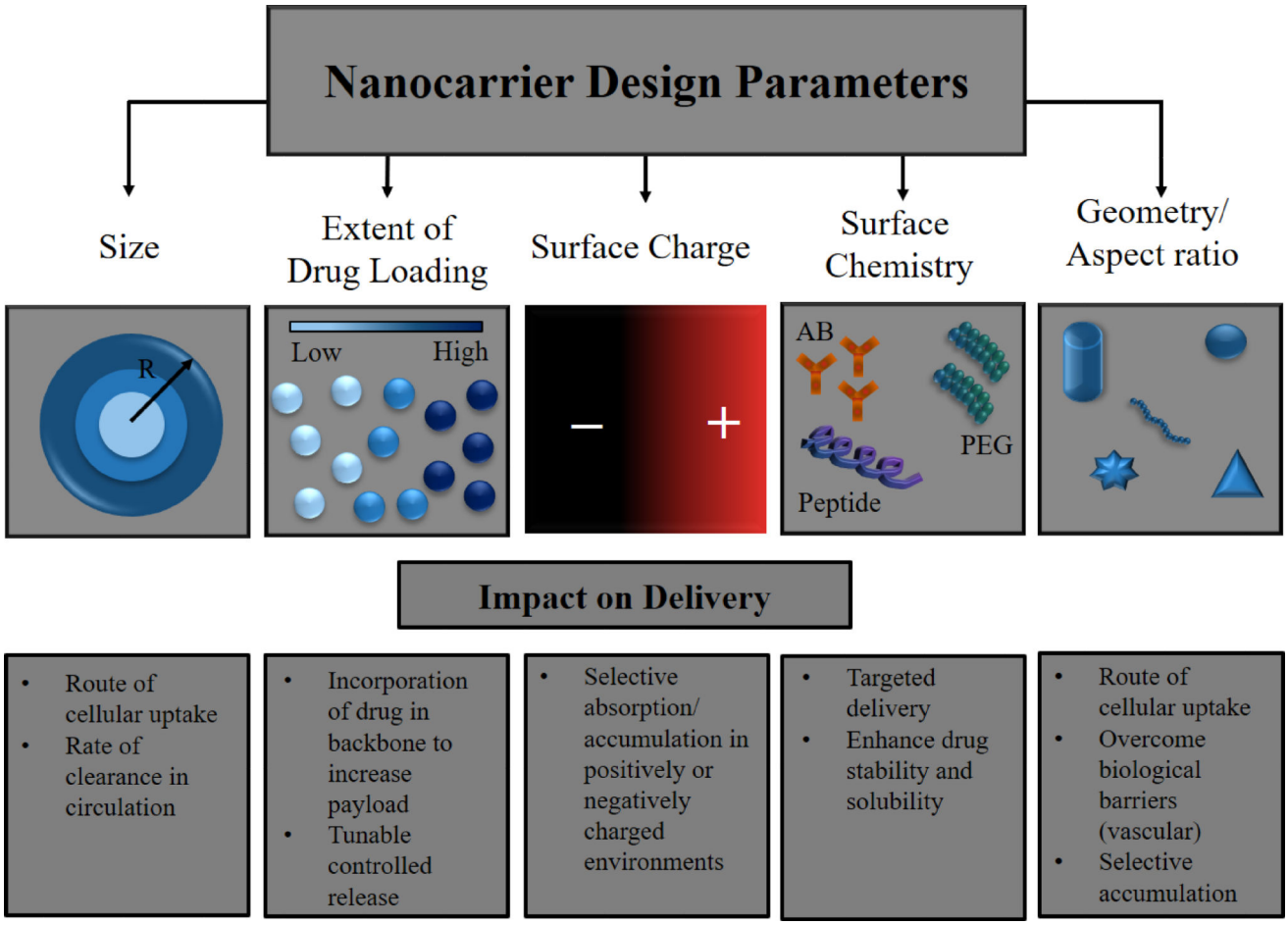


Figure 4.

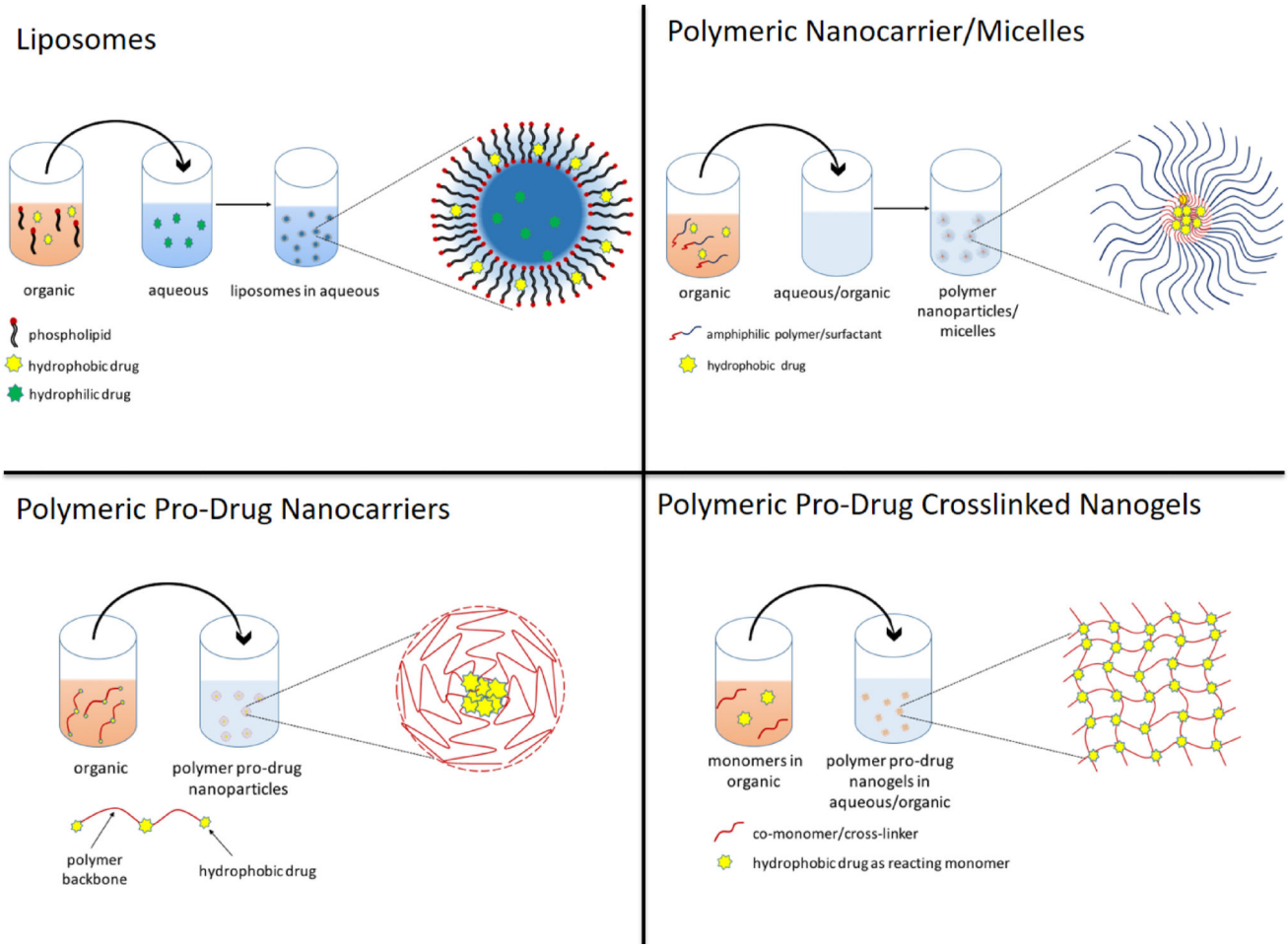


Figure 5.

Table 1

Known antioxidants/ antioxidant enzymes and their mechanism of action towards suppression of oxidative stress

Antioxidants	Mechanism of action/ functions
Enzymes	
Superoxide dismutase (CuZn-SOD, Mn-SOD found in mitochondria	• Superoxide reduction to oxygen and hydrogen peroxide [117, 118]
Catalase	• Hydrogen peroxide reduction to water and oxygen [119]
Glutathione peroxidase	• Hydrogen peroxide reduction to water and oxygen • Lipid peroxide reduction [120, 121]
Thioredoxin reductase (bronchial, alveolar epithelium)	• Antioxidant defense via disulfide reductase action to regulate the dithiol/disulfide balance • Role in electron transfer to thiol-dependent peroxidase, contributes indirectly removing oxidants [122]
Glutathione peroxidase (GPX)	• Detoxifies hydrogen peroxide and lipid peroxide [123]
Glutathione s-transferase	• Inactivates secondary metabolites such as unsaturated aldehydes, epoxides, hydroperoxides [124, 125]
Non-Enzymatic Systemic Antioxidants	
Vitamin E (α-tocopherol) (cell membrane-bound antioxidant)	• Oxidative defense against lipid peroxidation via donation of electron to peroxyl radical • Triggers apoptosis in cancer cells[126]
Vitamin C (ascorbic acid) (water soluble)	• Intra and extracellular antioxidant capacity, scavenges oxygen free radical • Converts of Vitamin E radical back to Vitamin E [127, 128]
Glutathione (abundant in cell compartments)	• Detoxifies hydrogen peroxide and lipid peroxide with the help of GPX by donating proton to membrane lipids • Converts oxidized Vitamin C and E back to original active form; regulates transcription factors (AP-1, NF-κB and Sp-1) [129]
Retinoic acid	• Inhibits NF-κB, interleukin IL-6m tumor necrosis factor-α production • Cancer cells anti-proliferative action via retinoic acid receptors • Induces cell cycle arrest and/or apoptosis [130, 131]
Melatonin (N-acetyl-5-methoxytryptamine) (hormone in animals, algae)	• Can cross blood-brain barrier easily • Once oxidized, cannot convert back to its original active form due to formation of stable end products (suicidal antioxidant) • Stimulates antioxidant enzymes, enhancing mitochondrial phosphorylation efficiency [132, 133]
Dietary Antioxidants	
Carotenoids (β-carotene) (pigment found in plants)	• Reduces peroxyl, hydroxyl and superoxide anion radicals • Antioxidant effects in low oxygen partial pressure while pro-oxidant effects in high oxygen concentration environment [134, 135]

Antioxidants	Mechanism of action/ functions
Epigallocatechin gallate (EGCG)	• Free radical scavenging • Blocks the tumor growth receptors during carcinogenesis • Inhibits lipopolysaccharide induced nitric oxide production [136, 137]
Quercetin	• Scavenges free radicals and chelates with metal ions • Prevents oxidation of low density lipoproteins [138]
Curcumin	• Scavenges free radical and chelates with metal ions • Reduces lipid peroxidation • Upregulates TGF-β1 and uPA levels • Anti-inflammatory properties - suppressed H2O2 and TNF-α induced release of NF-κβ, AP-1, IL-8 • Increases GSH biosynthesis [139, 140]
Resveratrol	• Trans-resveratrol as the active form • Similar scavenging potential as quercetin and EGCG in reducing lipid peroxides [141]
Synthetic antioxidant molecules	
N-acetyl cysteine (glutathione precursor)	• Scavenges hypochlorus acid (k= 1.36×10^10 $M^{-1}s^{-1}$) • Slowly reacts with H2O2, safe with oral administration but risks reported with intravenous administration [142, 143]
Trolox	• Direct scavenging of the free radicals
MitoQ	• Mitochondrial targeted with quinone antioxidant moiety • Cationic Triphenylphosphonium entity able to cross the lipid bilayer and accumulate in mitochondria • Reduces superoxide, peroxynitrite, and inhibits lipid peroxidation • Negligible reaction rate with hydrogen peroxides [144]

Table 2

Antioxidant nanocarriers and drug delivery applications

Antioxidant	Payload/ drug delivery system	Application
Resveratrol	Targeted solid lipid nanoparticles with Apolipoprotein E, 150–200 nm	*In* vitro: controlled release, higher permeability across blood brain barrier, hCMEC/D3 cells [227]
Curcumin	Curcusomes (curcumin liposomal nanoparticles)	*In vivo*: improved peripheral insulin resistance in genetically obese and high fat diet obese mice [228]
	Hepatocyte-targeted galactosylated chitosan-polycaprolactone curcumin nanoparticles	*In vitro*: 6-fold increase in apoptosis and necrosis of cancerous HepG2 cells as compared to curcumin [229]
	Curcumin loaded nanoparticle hydrogels, 140 nm	*In vivo*: Aflatoxin B1-induced liver damage in rats [230]
	Poly(beta-amino ester) nanogels (50–400 nm)	*In vitro*: inhibition of hydrogen peroxide induced mitochondrial oxidative stress in endothelial cells [211]
	Curcumin Liposomes	*Phase I clinical trial*: Intravenous delivery safe up to 120mg/m^2 in healthy subjects [231] *Phase 1 clinical trial*: intravenous infusion in patients with locally advanced or metastatic cancer to analyze the dose safety, on-going [232]
(−)-Epigallocatechin-3-O-gallate (EGCG)	EGCG-folic acid0PEG nanoparticles, 140 – 180 nm	*In vitro*: inhibition of MCF-7 cell proliferation [233]
	Bioactive peptide/chitosan-EGCG encapsulated nanoparticle for oral delivery, 150nm	*In vitro*: increased permeability in Caco-2 cells for Nano chemoprevention via oral route [234]
Quercetin	Hyaluronic acid-quercetin complexed micelles	*In vitro*: increased cytotoxicity inMCF-7 cell *in vivo*: inhibition of tumor growth in H22 tumor-bearing mice [235]
	PEGylated Poly (beta amino ester) nanogels (250–600 nm)	*In vitro*: decreased hydrogen peroxide induced toxicity in HUVECs cells [210]
N-acetyl cysteine	Pro-drug polymeric nanoparticles conjugated through disulfide bond	Inhibition of activation of microglia stimulated by lipopolysaccharide [236]