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Review Article

A Phytochemicals Approach towards the Role of Dioxins in Disease Progression Targeting Various Pathways: Insights

Saba Beigh*

Department of Public Health, Faculty of Applied Medical Sciences, Al Baha University, Al-Baha, SAUDI ARABIA.

ABSTRACT

Introduction: Dioxins represent a category of enduring environmental contaminants that possess the capability to elicit endocrine disruptions and a spectrum of ailments, most notably encompassing malignancies, immunological impairments, and nervous system impairments. These chemical compounds incite the generation of Reactive Oxygen Species (ROS), consequently instigating cellular toxicity through the activation of the Aryl Hydrocarbon Receptor (AHR). Given the significant noxiousness associated with dioxins, it is imperative to implement decisive actions aimed at mitigating ongoing ambient exposure. In spite of advancements in comprehending the origin and fundamental mechanisms of persistent environmental pollutants, the development of efficacious interventions has remained an elusive endeavor. **Objectives:** This investigation focuses on the distinct pharmacological mechanisms inherent in polyphenolic constituents that have been hitherto explored in relation to various dioxin-induced toxicities, both in *in vivo* and *in vitro* models. **Materials and Methods:** Preclinical studies were identified through systematic searches of PubMed, Embase, and the Cochrane Library, while clinical trials were retrieved from ClinicalTrials.gov and PubMed databases. **Results:** Preclinical research unveils the significant efficacy of phytochemicals in mitigating dioxin toxicity. Conversely, clinical findings exhibit a mixed spectrum of outcomes, but hold promise for the use of phytochemicals as adjuncts to conventional therapies for diverse dioxin-induced toxicities. These outcomes suggest that polyphenols may exert substantial influence on disease-related mechanisms such as oxidative stress, inflammation, apoptosis, and gene regulation. **Conclusion:** In our assessment, this represents the inaugural comprehensive review encompassing *in vitro* and *in vivo* investigations concerning the molecular-level interactions between various environmental contaminants and polyphenols. Furthermore, additional clinical investigations are warranted, with a focus on the appropriate patient populations, identification of relevant toxicity biomarkers, and elucidation of the impact of phytochemicals on these parameters.

Keywords: Phytochemicals, Reactive oxygen species, Chronic disorders, Persistent organic pollutants, Aryl hydrocarbon receptor.

Correspondence:
Dr. Saba Beigh
Department of Public Health, Faculty of Applied Medical Sciences, Al Baha University, Al-Baha-65431, SAUDI ARABIA.
Email: beigh.sabba@gmail.com, sbeigh@bu.edu.sa

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INTRODUCTION

Dioxins are undesirable environmental pollutants primarily originating from industrial activities, notably such as incineration and the production of particular pesticides, herbicides, and fungicides. In scientific research endeavors, only minuscule quantities of dioxins are intentionally generated.[1] Dioxins, along with related chemical compounds known as dibenzo-*p* compounds, constitute a substantial family of chemically similar complexes that persist in both the human body and the environment. They elicit a diverse range of responses and exert their effects through comparable mechanisms. This chemical class encompasses Polychlorinated Dibenzo-*p*-Dioxins (PCDDs), Polychlorinated Dibenzofurans (PCDFs), Polychlorinated Biphenyls (PCBs), and other related substances.[2] Dioxins were virtually absent in the environment prior to the advent of human civilization, primarily arising from natural events such as wildfires and seismic activity.[3] Nonetheless, these compounds are now pervasive within the human population, with elevated levels detected in individuals residing in more industrialized areas. This prevalent distribution gives rise to concerns among both public health specialists and medical professionals, owing to the comprehensive array of manifest and latent health conditions associated with these substances.[1] Figure 1 illustrates a variety of mechanisms through which dioxins enter an ecosystem.

Human exposure to dioxins can emanate from diverse origins, encompassing environmental factors, occupational activities, or inadvertent contamination. The broader populace mainly encounters dioxins through ambient environmental exposure. Although dioxins may be generated from specific localized origins,

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their ecological influence transcends geographical boundaries. The global presence of dioxins in the environment underscores their capacity for extensive dissemination and endurance.[4] The highest concentrations of these substances are often detected in a diverse array of foods, encompassing dairy products, meat, fish, and shellfish, as well as in sediments and soils. In contrast, there is very limited presence of dioxins in water, air, and plant life. [4] Substantial quantities of industrial oils containing PCBs (Polychlorinated Biphenyls) are present worldwide, with some of these oils containing significant levels of PCDFs (Polychlorinated Dibenzofurans). The long-term storage and improper disposal of these materials pose a significant risk of dioxin release into the environment, potentially contaminating food sources for both humans and animals.[5] PCB-based garbage is difficult to dispose of without endangering the environment and humans. Such materials must be handled as hazardous waste and are best eliminated by high-temperature burning in specialized facilities.

Predominantly, dioxin exposures primarily arise through secondary pathways, such as animal-derived food items or other products that incorporate dioxins. Reports substantiated by the World Health Organization (WHO) have identified various animal-based foods, including meat, fish, and eggs, as the principal sources of dioxin in organisms.[6] Acquaintance can occur by ingesting of soil, inhaling, drinking water, and skin absorption. The most widely recognized biochemical signs include steadily increasing overproduction of Reactive Oxygen Species (ROS), bioactive prostaglandins, pro-inflammatory cytokines, and a variety of oxidative metabolic enzymes.[7] Nuclear Factor-Kappa B (NF-κB), a pivotal transcription factor in the inflammatory cascade, and an array of other proteins engaged in oxidative and antioxidative pathways, can be stimulated by Reactive Oxygen Species. Cyclooxygenase enzymes (COX-1 and COX-2) generate prostaglandins, which have been recognized as a principal category of inflammatory mediators induced by TCDD. Moreover, one autocrine mechanism that seems to play a significant role in the adverse effects of TCDD in mice is its capacity to stimulate the production of Tumor Necrosis Factor-alpha (TNF-α).[8] TNF-α may activate NF-κB by attaching to its particular receptor, which is known to further promote the production of pro-inflammatory cytokines and chemokines, including IL-8.POPs are widely present, which has led to a renewed interest in natural compounds that could be able to defend against their hazardous components.[9]

Polyphenols constitute one of the most abundant and ubiquitously distributed classes of chemical compounds in the plant kingdom. This category encompasses a vast array of over 8000 distinct compounds, of which flavonoids make up more than half of this diverse group.[10]

Polyphenolic compounds represent significant components of the standard human diet and are found in various consumable forms, including packaged food products like beverages, spices, and preserved items, as well as fresh edible plants. The suggested capacity of polyphenols to reduce susceptibility to diseases primarily stems from their ability to lower the levels of ROS within cellular environments. Moreover, the anti-inflammatory properties of polyphenols are closely linked to their potential to prevent cardiovascular diseases, and they exhibit pleiotropic effects in this context.[11] The anti-inflammatory effects of polyphenols can be partly attributed to their antioxidative characteristics, which impede the initiation of inflammatory cascades by reducing the overall levels of ROS. Furthermore, they exert a regulatory influence on the production and activities of pro-inflammatory enzymes, including Cyclooxygenase (COX), Lipoxygenase (LOX), and inducible Nitric Oxide Synthase (iNOS), as well as signaling pathways such as NF-kB, a pivotal mediator of inflammation. Additionally, polyphenolic compounds inhibit the adhesion of immune cells and promote the restoration of damaged epithelial tissues.[12] As per research findings, polyphenols have been observed to elicit several physiological effects. These include an enhancement of catabolic metabolism within adipocytes, a reduction in the absorption of dietary

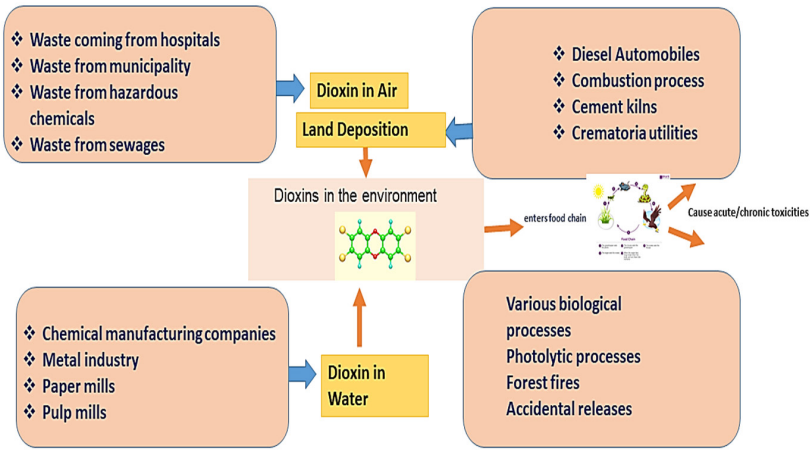
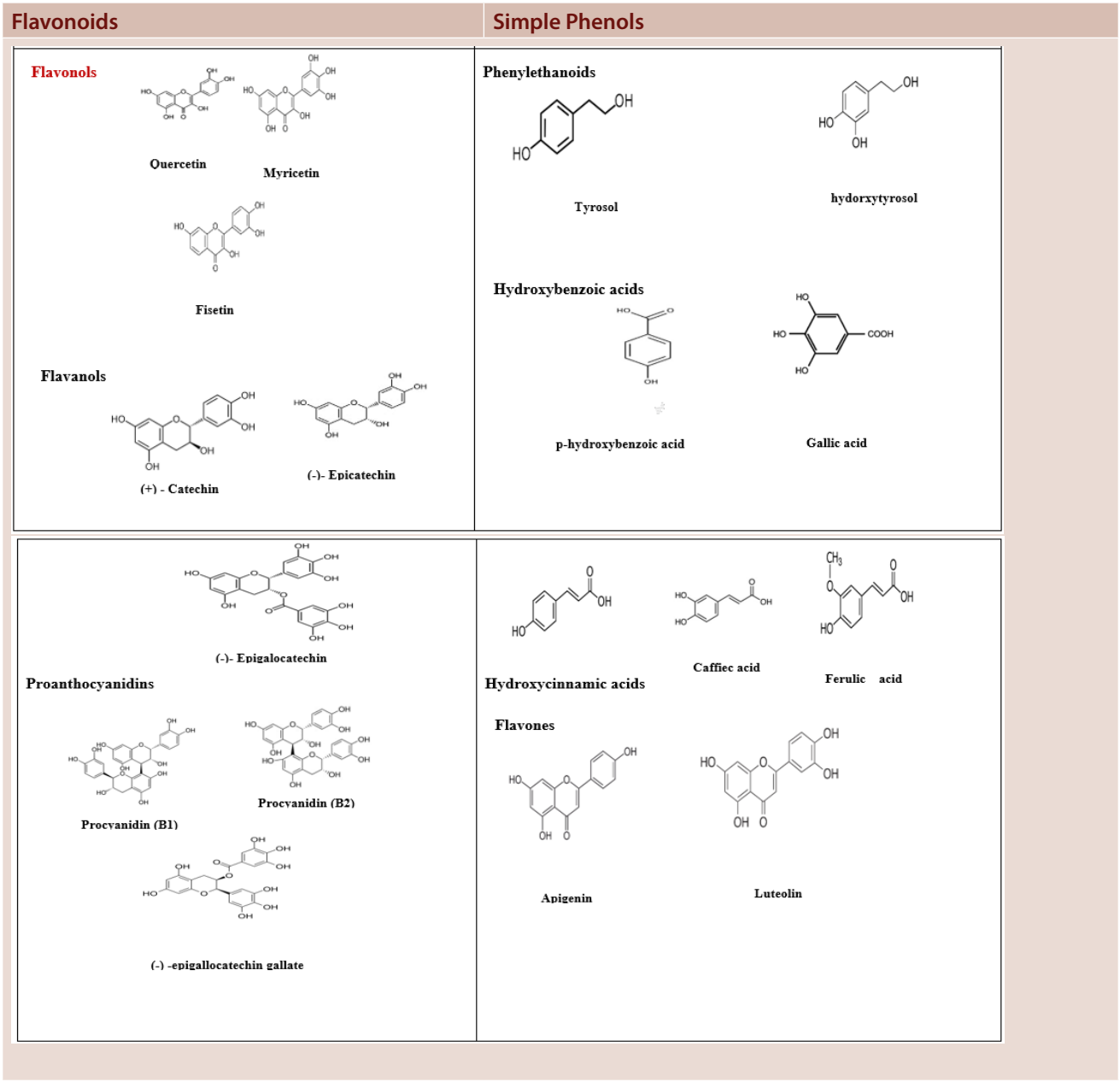


Figure 1: Contributors to Dioxin pollution.

Table 1: Structure of various polyphenolics showing therapeutic potential against various toxicities induced by persistent organic pollutants.



fats in the intestines, a mitigation of Low-Density Lipoprotein (LDL) oxidation, and the facilitation of cholesterol transfer from macrophages, predominantly mediated by High-Density Lipoprotein (HDL). Furthermore, the neuroprotective properties of polyphenols are underpinned by their ability to initiate distinct signaling pathways that regulate neurogenesis and synaptic plasticity, thereby exerting an influence on cerebral function and resilience.[12]

In this manner, polyphenolic compounds have the potential to enhance memory and cognitive faculties. Furthermore, these chemicals contribute to the prevention of neurodegenerative conditions by diminishing inflammatory responses within the nervous system and promoting the survival of neurons. Additionally, polyphenols exhibit the ability to counteract the neurotoxic effects associated with amyloid plaques, a hallmark feature observed in neurodegenerative diseases like Alzheimer's disease.[13] Polyphenols are abundant in plant-based dietary sources and possess notable biological and chemical properties. They exhibit a suppressive effect on various xenobiotic compounds, including dioxins.[14] Further investigation into the efficacy of these compounds in mitigating the consequences of persistent organic pollutants, particularly compounds related to dioxins, is imperative. The primary goal of the aforementioned research is to assess recent advancements in understanding various diseases associated with Persistent Organic Pollutants (POPs) and explore potential mechanisms of action related to these disorders through

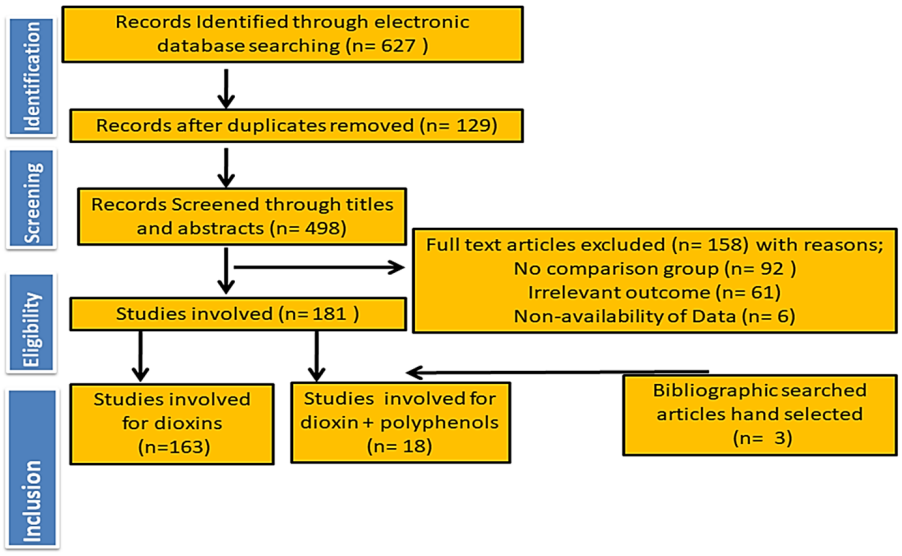


Figure 2: Prisma flow diagram showing the steps and retrieval steps of the study.

the utilization of diverse phytochemicals. Our emphasis is on the role of phytochemicals in preventing various forms of toxicities associated with dioxins, along with the pertinent mechanistic pathways and recovery mechanisms, underscoring their significance. A depiction of the chemical structures of various phytochemicals is provided in Table 1 for reference.

MATERIALS AND METHODS

Up until July 2023, an extensive collection of high-quality references pertinent to the present research focus was meticulously curated. A systematic and well-structured search of existing data was conducted, utilizing keywords such as "persistent organic pollutants, cancer, hormonal imbalance, pharmacological therapy, polyphenols," within the databases Medline/PubMed, Cochrane, and Embase. Exclusion criteria were applied to filter out redundant data points, invalidated articles, studies focused on specific diseases, statistically unreliable analyses, articles published in languages other than English, publications that did not constitute scientific studies (such as commentaries, letters, editorials, reviews, and meta-analyses), and any other articles that did not align with the scope of this review. Additionally, references cited in the selected articles were scrutinized for supplementary information. Employing the aforementioned keywords, an initial pool of 627 results was acquired and subjected to rigorous evaluation. Subsequently, 181 articles were chosen for qualitative analysis (see Figure 2). Among these, 163 studies delved into the toxicological aspects of dioxin, while 18 investigations examined the effects of various polyphenolic compounds on dioxin.

Chemistry of Dioxin

An expanding body of environmental research underscores the concerning repercussions of human activities linked to rapid industrialization on the fundamental ecological processes that underpin life on Earth. It is worth noting that, despite the existence of policies and regulations in numerous countries designed to mitigate these undesirable outcomes, the scale of these effects persists as a substantial menace to the ecosystems and critical resources of the planet.[14] The release of a wide array of intermediates and industrial byproducts stemming from common contaminants used in commercial and daily activities can lead to the inadvertent discharge of substantial quantities of these substances into the environment. This unintentional discharge can result in adverse consequences, including immune system impairment, disruptions in the reproductive processes of both animals and humans, an elevated cancer risk, and potential impacts on behavioral and neurodevelopmental patterns. A multitude of compounds, numbering in the dozens, have demonstrated similar harmful properties, representing a significant threat to public health due to their potential contamination of the food supply. Among these substances, dioxins and Polychlorinated Biphenyls (PCBs) emerge as particularly concerning contributors to this health hazard.[15-16]

Dioxins and their related compounds, collectively known as DLCs, have a widespread presence in the environment. These substances belong to a category of molecules possessing intrinsic hazardous properties, defined by their common chemical structures and biological characteristics. While specific natural events such as volcanism and wildfires do emit dioxins and related compounds, the primary source of these substances is human activities. Dioxins, in particular, are notably released through the incineration of various materials, including plastics, pesticide-contaminated waste, pentachlorophenol-treated wood, and other polychlorinated compounds.[16-17]

Dioxins are also emitted in small quantities from sources such as residential heating systems, vehicle exhaust emissions, and cigarette smoke. DLCs encompass a diverse array of compounds,

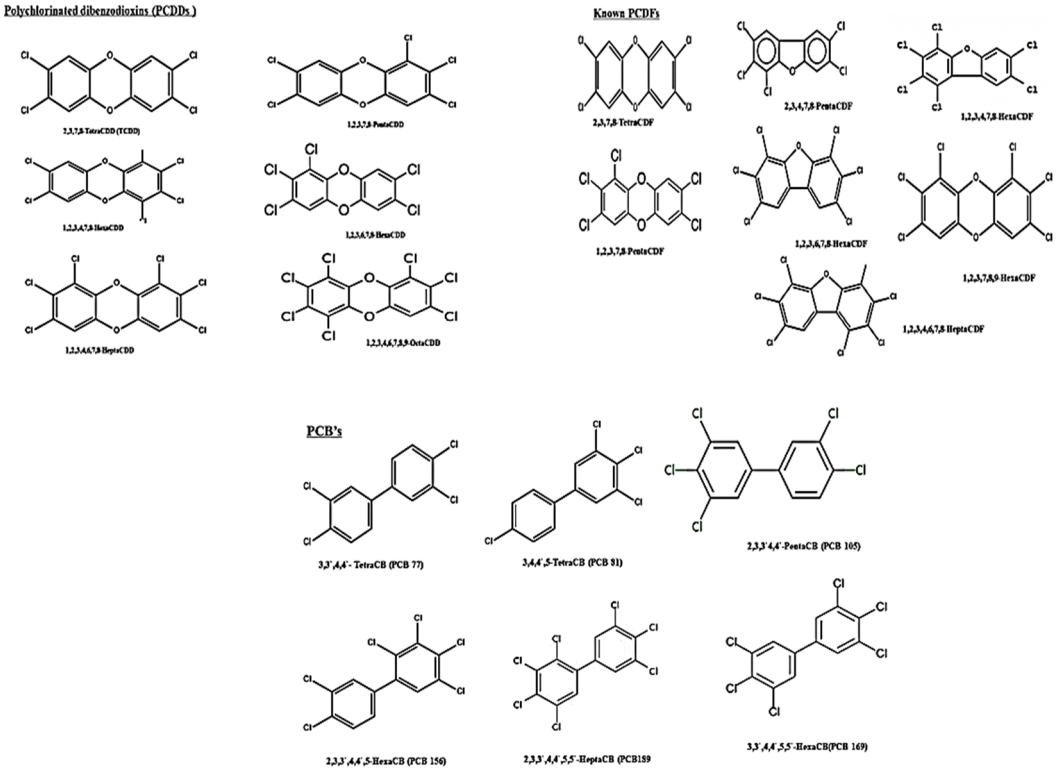


Figure 3a: Dioxins and dioxin like compounds.

typically classified into three groups: Polychlorinated Biphenyls (PCBs), Chlorinated Dibenzo-p-Dioxins (CDDs), and Chlorinated Dibenzofurans (CDFs). The prevalence of CDDs and CDFs in the environment can be attributed primarily to a combination of natural processes and human activities.[18] Dioxins can potentially trigger a range of health issues, and the number and arrangement of chlorine atoms in these compounds determine their level of toxicity. Dioxins are designated as Persistent Organic Pollutants (POPs) because they endure in the environment for extended periods and are slow to degrade.[19]

Dioxin-Like Compounds (DLCs) can be categorized into eight distinct groups based on the number and location of chlorine atoms in their chemical structure. These categories include mono-Chlorinated Dioxin (CDD), Di-Chlorinated Dioxin (DCDD), Tri-Chlorinated Dioxin (TrCDD), tetra-chlorinated dioxin (TCDD), Penta-Chlorinated Dioxin (PeCDD), and Hexa-Chlorinated Dioxin (HxOCDD). Among these, 2,3,7,8-TCDD, which possesses four chlorine atoms, is recognized as the most lethal and is more widely known due to its extreme toxicity. The CDDs family, alternatively known as polychlorinated dioxins, encompasses a total of 75 distinct chemicals. In their purest form, these compounds appear as colorless solids or crystals. Figure 3 (a) displays some of the recognized classes of dioxins, and Table 2 provides the nomenclature for various DLCs.

Source of Exposure

Indeed, natural events such as volcanic eruptions and certain human activities like municipal waste incineration, cigarette smoke, the release of fly ash, and various industrial processes collectively contribute to the release of dioxins and chemically analogous compounds into the environment. These sources, in combination, introduce these substances into the ecosystem.[1] The sources of dioxins have indeed evolved significantly over the past four decades, primarily due to the stringent regulations imposed by government authorities. The strict adherence to these regulations, designed to minimize the release of these harmful substances into the environment, has led to a substantial reduction in sources, particularly those originating from industrial activities. As outlined in the study, Polychlorinated Dibenzo-*p*-Dioxins (PCDDs) often emerge as by-products during the industrial or small-scale production of certain compounds, including Polychlorinated Biphenyls (PCBs), specific herbicides, and fungicides based on chlorophenol.[20] PCDDs have been identified in several historical sediment core samples, and the primary sources of these compounds are incineration and combustion activities. Notably, the levels observed in the oldest samples are approximately 10-20% lower than those recorded in samples from the 1990s.[21] The chlorine-based industry significantly contributes to dioxin emissions, accounting for approximately 80-90% of the current emissions. An important development occurred in the post-1940s period with the introduction of pentachlorophenol

Table 2: Dioxin and related compounds nomenclature.

Term	Definition
Congener	Chlorinated dibenzo-p-dioxins have 75 congeners, all of which belong to the same chemical family.
Homologue	A set of molecules with the same amount of chlorination and comparable structural properties. Eight CDD homologues exist, ranging in chlorination from monochlorinated to Octo chlorinated.
Isomer	Elements that are analogous to one another. The homologues of TCDDs, for example, are made up of 22 isomers.
Specific congener	Unique chemical notation is used to identify it. 2,4,8,9-tetr achlorodibenzofuran, for example, is denoted to as 2,4,8,9-TCDF.
D	Homologous class symbol: dibenzo-p-dioxin.
F	Homologous class symbol: dibenzofuran.
M	Mono represents a single halogen substitution.
D	di is a representation for two halogen substitutions.
Tr	Three halogen substitutions are denoted by the symbol tri.
T	Tetra is a symbol signifying four halogen substitutions.
Pe	Penta is a symbol indicating five halogen substitutions.
Hx	Hexa is a symbol signifying six halogen substitutions.
Hp	Hepta is a symbol indicating seven halogen substitutions.
O	The symbol for octa, which stands for eight halogen substitutions.
CDD	Halogens swapped at any position in chlorinated dibenzo-p-dioxins.
CDF	Halogens in chlorinated dibenzofurans can be substituted at any position.
PCB	Polychlorinated biphenyls.

Source: EPA, 1989.

into the market. This introduction was linked to a notable rise in the presence of hepta- and octa-Polychlorinated Dibenzo-p-Dioxins (PCDDs) in the environment.[22] The European Dioxin Air Emission Inventory analyzed the emission scenarios from 1993 to 1995 and found that solid waste from municipal incinerators remained the major source of overall dioxin emissions.[23] Substantial quantities of dioxin are also released during the annealing of iron. Supplementary nonferrous metal production and healthcare wastes incinerator have both been acknowledged as important emission sources. Concentrations in the surrounding emaciated in the 1960s and early 1970s and are presently declining. In the nearest future, it is projected that emission from non-industrial sectors will outweigh those from industrial plants. For several major industrial source types, a 90% decrease in emissions will be realized.[24]

Scientific research indicates that dioxin exhibits an affinity for binding to carbon-based substances found in sediments and soils. Furthermore, dioxins tend to accumulate in fatty tissues and possess the capability to disperse over significant distances from their emission sources, even when present in trace amounts in adjacent environmental matrices.[25]

Dioxins can undergo effective long-distance transport in the environment through processes involving evaporation and condensation cycles. Remarkably, dioxins have a propensity to accumulate in Arctic regions, influenced by global circulation patterns and reduced evaporation rates related to freezing temperatures. In these Arctic areas, dioxins undergo bio-accumulation in various species within the ecosystem, and as they progress up the food chain, they eventually reach human populations.[26] In mammals, dioxins exhibit a relatively long half-life, typically ranging from 7 to 15 years. Exposure to dioxins, even at low doses, has been associated with various adverse health effects, including carcinogenesis, neurological abnormalities, immune system dysfunction, and reproductive disorders. Dioxins appear to function like synthetic hormones, given their extended half-life in the body. They bind to specific Aryl hydrocarbon Receptors (AhR) within living cells, initiating a series of molecular events that result in biochemical and cellular alterations.[27]

Studies have confirmed that among sources of dioxin emissions stemming from incineration and combustion processes, the chemical sector constitutes a minor contributor in comparison to other sectors.[17] Considerable knowledge has been amassed regarding the causes of air emissions, and the European Dioxin Air Emission Inventory Project has provided valuable insights. According to their estimates, by the year 2005, air emissions of dioxins had substantially decreased, achieving a remarkable 90% reduction compared to the emission levels recorded in 1985. This

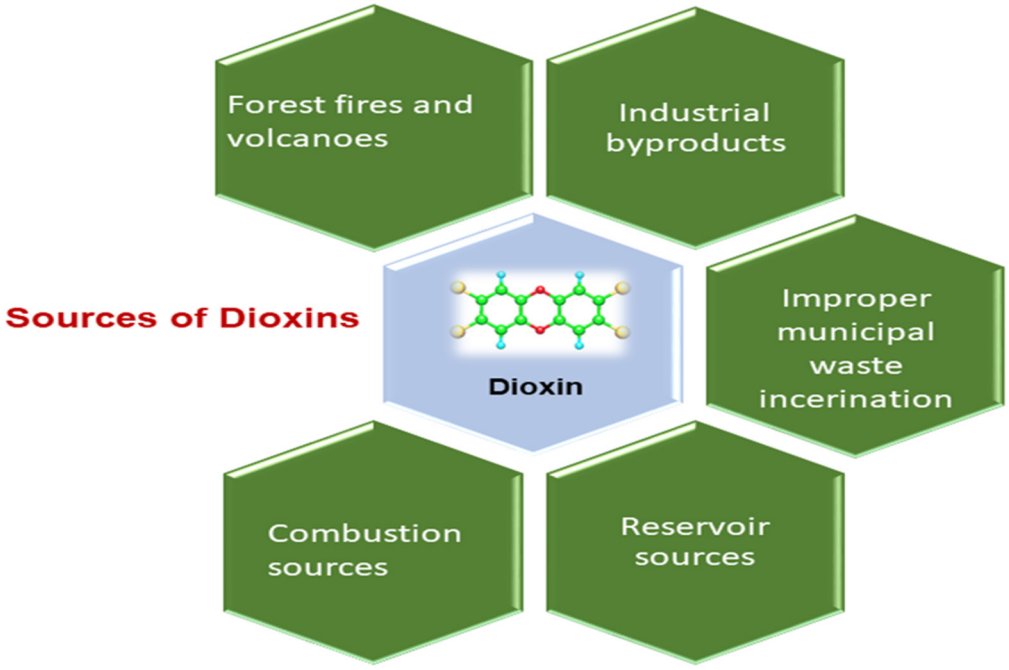


Figure 3b: Various sources of dioxin.

reduction reflects the successful efforts and regulations put in place to mitigate dioxin emissions over the years.[17] Figure 3 (b) shows various sources of dioxin.

Although there has been a decrease in recognized anthropogenic emissions, in-depth analysis has revealed that emissions from sources such as residential wood and coal burning, accidental fires, emissions from transportation, and the release of dioxins from wood treated with Pentachlorophenol (PCP) remain substantial contributors to dioxin emissions in the environment. This underscores the necessity for ongoing vigilance and regulatory measures to address these diverse sources of dioxin contamination.[4] A variety of prospective and significant dioxin emission sources and pathways, particularly non-atmospheric emission mechanisms, have not been explored. In the near term, it is projected that emissions starting from non-industrial source will surpass those from commercialized sources. For several major industrial source types, a 90% decrease in emissions will be realized. When compared to dioxin emissions from incineration and combustion sources, the chemical sector is a minor contributor. Very little is known about the dioxin releases from synthetic chemicals, effluents, processing byproducts, and landfills. Dioxins are produced during the manufacture of dyes and colorants, a source that has not garnered much consideration.[3]

Certainly, numerous studies have pointed out that colorants can contain significant amounts of dioxins. Furthermore, dioxins from textiles can be transferred to sewage sludge during the laundering of garments, and this sludge is frequently employed as agricultural fertilizer. As a result, sewage sludge can potentially become a source of dioxins in the food chain, emphasizing the intricate nature of dioxin exposure routes and the requirement for comprehensive management strategies.[23] Dioxins are produced during the manufacture of dyes and pigments, a source that has not garnered much attention. A little portion of the material may be transported straight via a person's skin. Textiles may be a precursor chemical for dioxin and other POP production during incineration.[28] However, Information on dioxin and other POP emissions from textile dyes and the pigment industry is limited due to the absence of comprehensive and trustworthy emission data.

Dioxin Remediation Measures

Phytoremediation has been recognized as a viable approach for removing environmental contaminants from soils, water, and sediments that is suitable towards the ecosystem. Plant-mediated bioremediation is the phytoremediation method that is the most exact.[29] Toxic compounds in groundwater or the soil are biologically broken down, absorbed into plant cells via its roots, and then transformed by plant enzymes into the environment may be summed up as two phases in the phytoremediation process.[29]

Due to a very big Kow, microorganisms have a substantial impact on PCB biodegradation throughout the rhizoremediation process. Previous studies displayed that a discrete complex of herbal roots might trigger microbial processes called "rhizodegradation" or "rhizoremediation" that can break down PCBs in polluted soils.[30] On the other hand, plant roots can produce extracellular enzymes, microbial growth factors, and organic acids that can

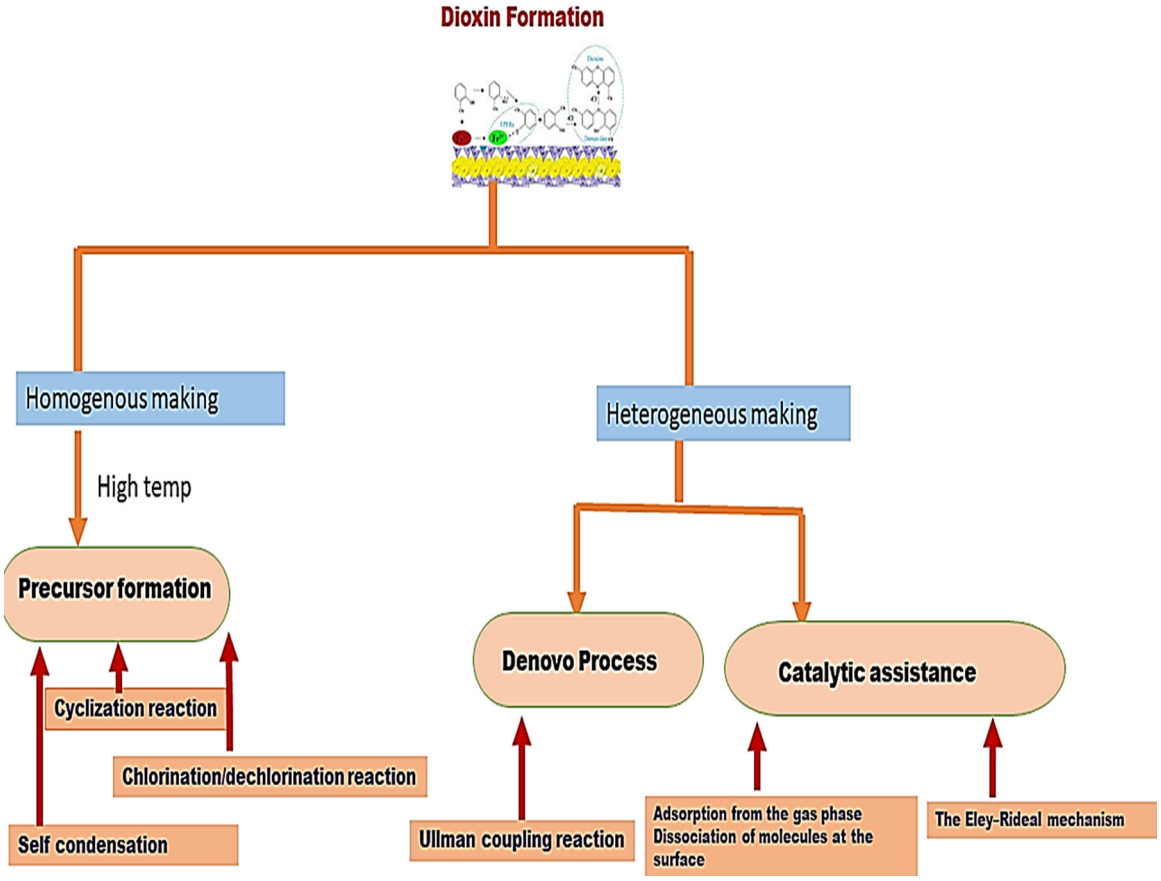


Figure 3c: Representation of bioremediation process in dioxin.

serve as electron donors.[30] Dioxins were found to primarily infiltrate the environment through flue gases from combustion and incineration activities, slag production from burning and incinerator activities and Dioxin-contaminated soil from industrial and reservoir sources.[30] As a result, it was decided to highlight an extensive, cutting-edge study on the cleanup, mitigation, and avoidance of these environmental threats. Due to their extensive release during combustion and incineration, flue gases are one of the main sources of dioxin emissions into the environment.[31] Dioxins are created in the incinerator system's flue gases by de novo synthesis and precursors at temperatures between 300 and 500°C. Dioxin concentrations in vent gases range from 1-500 ng ITEQ/m3.[28] Consequently, before the flue gas is released into the environment, it must be treated to diminish its content to a tolerable concentration (0.1 ng I-TEQ/Nm3). A low-tech, green remediation technique with little influence on the environment is phytoremediation.[32]

To be suitable for phytoremediation, a plant must possess significant biomass production, extensive root system dispersion, and the capacity to tolerate and accumulate contaminants. This technique is cost-effective due to the absence of energy-intensive machinery.[33] Furthermore, despite adding a plant may enhance the topsoil general quality because the vegetation and miniscule creatures add micronutrients, phytoremediation has minimal to no negative impacts on soil quality and morphology.[34] It is worth emphasizing that the absorption and translocation processes are primarily responsible for plants taking up PCBs. Furthermore, plants have the capability to metabolize PCBs in addition to reducing PCB concentrations in sediment and soil. Some studies have shown that plant cell cultures of Rosa spp. can metabolize dichloro, trichloro, and tetrachlorobiphenyl congeners.[35] Rosa species-specific plants cell lines may oxidize 3,4-dihydroxy-2,2′,5,5′-tetrachlorobiphenyl more persistently to 2,2′,5,5′-tetrachlorobiphenyl. Other investigations have shown that pumpkins (*Cucurbita* sp.) grown in soil polluted with Aroclor had higher PCB concentrations in their stems and leaves.[30] The level of PCBs in the pumpkin roots remained constant, though. These findings confirm that absorption and translocation, as opposed to volatilization and deposition, are the primary mechanisms of PCB transport in plants.

Their dissemination in the environment is influenced by the substantial octanol-water partition coefficients (Kow) of PCBs, which range from 104.10 (20C) for mono-chlorophenyl to 107.93 for deca-chlorobiphenyl.[34] As a consequence, stronger chlorine-based PCB constituents with such an elevated kow (log Kow>6) seem to be more likely to be detected in soils and sediments than reduced chlorinated PCB constituents. Soils frequently have a greater concentration of heavily chlorinated PCB

congeners. Importantly, the majority of study found that plants can only digest tetra chlorinated and lower congeners of PCBs. The capacity of larger Pcbs constituents to be digested by higher plants is constrained by their considerable hydrophobic nature, which renders them less likely to be taken up and transported inside of plants. because of these procedures.[35] High-chlorinated PCB constituents often exhibit greater metabolization resistance than lesser constituents. As a result, when plants decompose after they have died, in biomass, the strong Pcbs alloying elements often accumulate eventually discharge into to the atmosphere. The relatively shallow dispersion of plant roots can limit the efficiency of phytoremediation systems, as does the movement of toxins from florae to other environments. Furthermore, the advent of hazardous or invasive species may negatively impact the ecosystem's plant and animal inhabitants.[36] The Figure (c) showing schematic diagram of dioxin formation and bioremediation pathway.

Conversely, a natural biological process called "bioremediation" or "microbial degradation" employs microorganisms to degrade, convert, and remove pollutants or hazardous substances. Multiple research studies have supplied convincing evidence that microbes can break down PCBs in various environments, including soils, sediments, and water bodies. Two potential mechanisms for microbial PCB degradation are anaerobic dehalogenation and aerobic degradation. In anaerobic conditions, the microbial degradation of heavily chlorinated PCB congeners is often achieved through organohalide respiration.[37]

A biological activity known as organohalide respiration of PCBs may lessen their toxicity by removing chlorines. Hydrogen is used in this procedure to replace the chlorine substituent. The three probable ortho, meta, and para sites for chlorine substituents on the PCB constituents allow them to function as the final electron acceptor. Most typically, a hydrogen atom replaces a chlorine atom at the first two sites. In-situ bioremediation methods have been studied for the past ten years in order to remediate PCB-impacted soils and sediments on-site. Two significant subcategories of bioremediation methods are bio stimulation and bioaugmentation. Based on established studies, halopriming with halogenated aromatic hydrocarbons can increase the dehalogenation bacteriological promoters and activate the genes required for dehydrogenation in the naturally occurring Pcbs dehalogenation microorganisms.[38]

Over the previous ten years, it has been common practice to treat soils and sediments that have been polluted with PCBs via bio stimulation of anaerobic PCB breakdown, however the precise mechanism is yet unclear.[39] However, bio stimulation is also applicable to aerobic bioremediation, in which the microorganisms may break down the PCBs with low chlorine concentration using oxygen. The main substrate that can sustain PCB co-metabolism is biphenyl. The PCB molecule's benzene ring with fewer chlorine

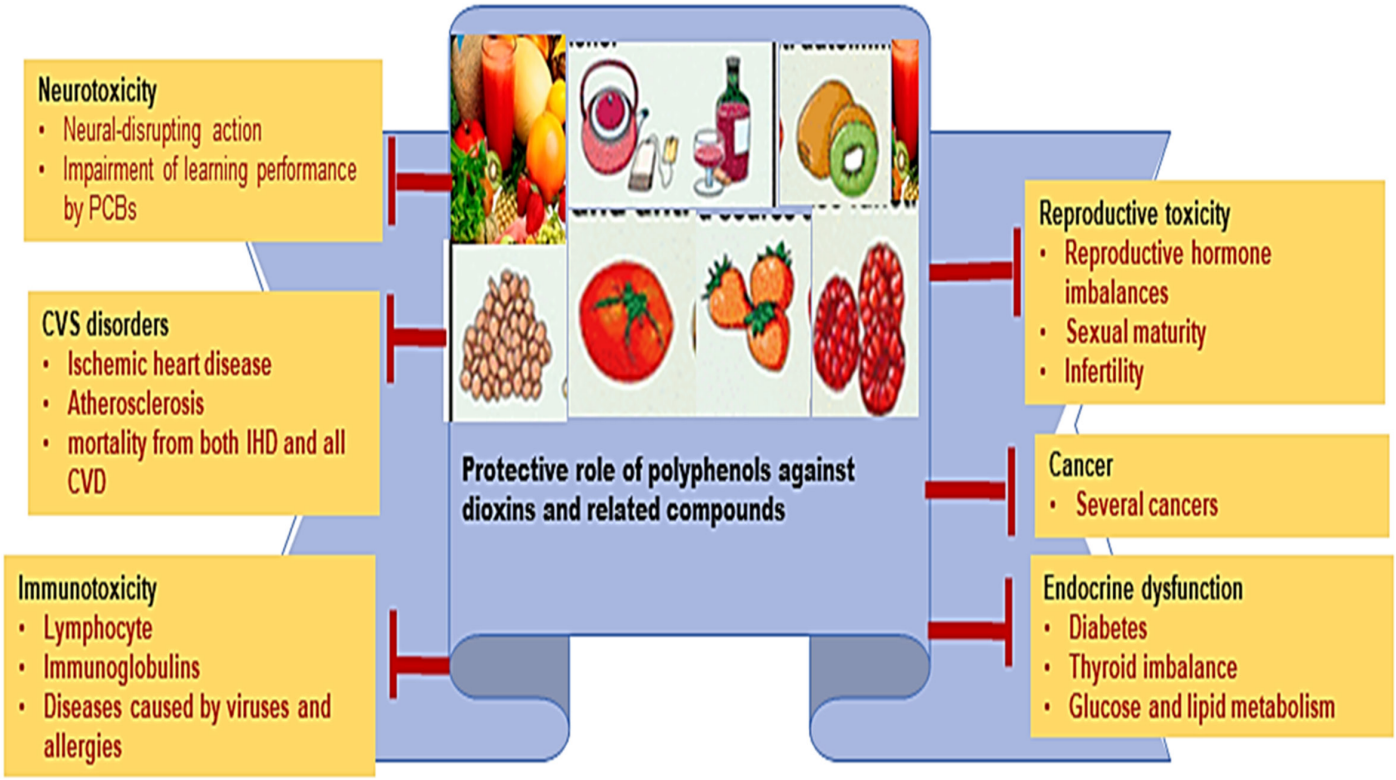


Figure 4a: Effect of dietary polyphenols on health. The primary components of several food substances are polyphenols. The majority of these chemicals have a role in the prevention of the onset of chronic illnesses such cancer, endocrine dysfunction, immunotoxicity, cardiovascular disorders, and reproductive problems.

Table 3: Epidemiological data of dioxins.

Altered functions	Epidemiological Data	Referred studies
Chloracne	Uncommon skin disorder induced by halogenated aromatic hydrocarbon compounds such as dioxins.	54
Gastrointestinal effects and liver enzymes	Dioxin exposure has been linked to gastrointestinal problems, metabolic abnormalities, and liver cirrhosis.	55
Cardiovascular diseases	TCDD contributes to the development of metabolic dysfunction and vascular abnormalities.	56
Changes in lipid levels	Adverse impact of exposure to dioxin at the level of fatty acid metabolism	57
Diabetes	Diabetes risk in epidemiologic research using dioxins as persistent toxicants	58
Reproductive hormones	TCDD (tetrachlorodibenzo-p-dioxin) causes reproductive problems. There is currently no evidence on probable side effects such as endometriosis and fertility in women	59
Neurologic/ psychological effects	Pathophysiology and immunologic problems are caused by dioxin.	60
Respiratory system	Irritative effects and reduced lung function parameters in some studies	61
Urinary system	Pathophysiology and immunologic problems are caused by dioxin.	62
Immunological effects	Dioxin causes a wide range of immunologic consequences, including diminished host resistance to infectious illness and inhibition of the humoral and cell-mediated immune systems in various studies	63
Developmental effects	Studies showed dioxin dose dependent developmental disorders	59
Cancer	considered to be a human carcinogen (based on human, animal and mechanistic data). A threshold approach to risk assessment is most likely appropriate, according to data.	64

atoms is destroyed during aerobic breakdown. Several genes are involved in this process, namely the bph gene clusters bphA (dioxygenation of the biphenyl ring), bphB (dehydrogenase), and bphC. (ring cleavage dioxygenase). The synthesis of dihydrodiol from the deoxygenation of the biphenyl ring is facilitated by the bphA gene. Bio augmentation is the inclusion of bacterial cultures to speed up contaminant degradation, and it is a workable, in-situ PCB transformation method.[40-41] According to Matsuki *et al*. (2008), while acquaint with to polluted soil, the sequestered ultramicrobacterium commencing sediment is adept of dechlorinating Aroclor 1260, that holds double-flanked chlorines.[42] Similar to this, Dehalobium chlorocoercia DF1 was discovered to improve the dehalogenation of weathered Aroclor 1260, which contains double and single flanked chlorines.[41] PCB biodegradation by aerobic and anaerobic bacteria has been extensively researched and applied with success. Compared to the potential PCB cleanup solutions, microbial degradation has comparatively low technological obstacles. As was previously indicated, less hazardous byproducts and cell biomass are often the remains for microbial breakdown of PCBs. Through the process of reductive dehalogenation, highly chlorinated compounds may be broken down, producing two to three chlorine congeners as the main byproducts. Additionally, the microbial degradation of PCBs doesn't quite affect daily life. Because no trash is being transferred off-site, there are fewer potential hazards to both the environment and human health. It is essential to remember that microbial decomposition of PCB-contaminated soils has a lesser environmental impact than incineration.[41] Activated carbon is

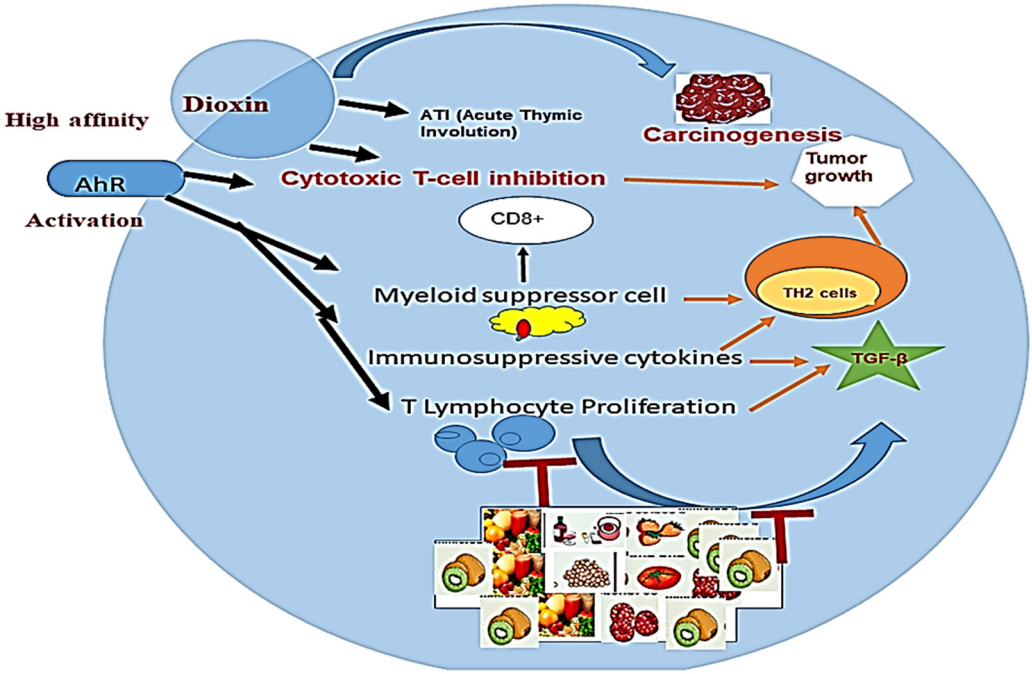


Figure 4b: The carcinogenetic effect conferred on by the activation of TCDD-AhR and preventive ability of polyphenols in mitigating toxicity associated with dioxin.

widely used to eliminate toxic organic and inorganic contaminants because of the extremely porous nature of carbonaceous materials, which increases the surface area (500-2,500 m^2/g) for adsorption or chemical reactions. Adsorbates are physically drawn to the surface structure of substances like activated carbon during the process of adsorption. Due to the environmental and biological stability of dioxin compounds, persistent and widespread human exposure is a consequence. Such chemical exposure can impair the immune system, increase vulnerability, and interfere with the actions of various hormones.[42] Incineration and combustion fonts are the foremost sources of dioxins entering the atmosphere, thus additional effort is needed to improve our indulgent of the pioneer and de novo pathway of dioxin synthesis. It's important to comprehend how chlorine interacts with its precursors. Additionally, it's crucial to determine the circumstances in which carbon, oxygen, and chlorine might turn into limiting reactants in the combustion and incineration chamber.

Phytochemical Compounds for the Prevention and Management of Several Chronic Diseases induced by Dioxin Intoxication

Hazardous chemicals, toxic substances, and their associated materials pose inherent threats to human health. Consequently, two fundamental approaches for mitigating these risks entail the physiological control of persistent organic pollutants and the remediation of contamination.[43,44] Even when the ultimate goal is to achieve comprehensive site cleanup to minimize human exposure, it is crucial to put in place physiologically tailored preventive measures aimed at reducing toxicant exposure before, during, and after remediation activities. In recent times, there has been a notable upsurge in the utilization of phytochemicals as an alternative therapeutic approach to address illnesses induced by oxidative stress. Plant-derived natural compounds have garnered significant attention as potential therapeutic agents in the context of environmental toxicity due to their inherent ability to quench free radicals.[43] Recent research indicates that various phytochemicals play a pivotal role in diminishing the overall harmful impact of environmental contaminants on biological systems. Phytochemicals have demonstrated promising effects in ameliorating a range of disorders associated with dioxins and persistent organic pollutants.[44-45] Large biomolecules such as lipids, DNA, and proteins can endure the effects of oxidative stress caused by an excess of Reactive Oxygen Species (ROS) in the body. This impairment is the fundamental cause of numerous human diseases, including aging, certain types of cancer, and Cardiovascular Diseases (CVD).[46] Antioxidant phytochemicals are thus likely to exert significant influence on both the prevention and management of chronic illnesses. Figure 4(a) illustrates the protective potential of phytochemicals against a range of chronic disorders.

Human studies and *in vitro* research have demonstrated the antioxidant properties of phytochemicals. The consumption of meals rich in antioxidant phytochemicals has been observed to enhance the antioxidant capacity of serum or plasma.[47] The elevated plasma concentration of alpha-tocopherol was unable to explain this augmentation. Considering that 19 out of the 25

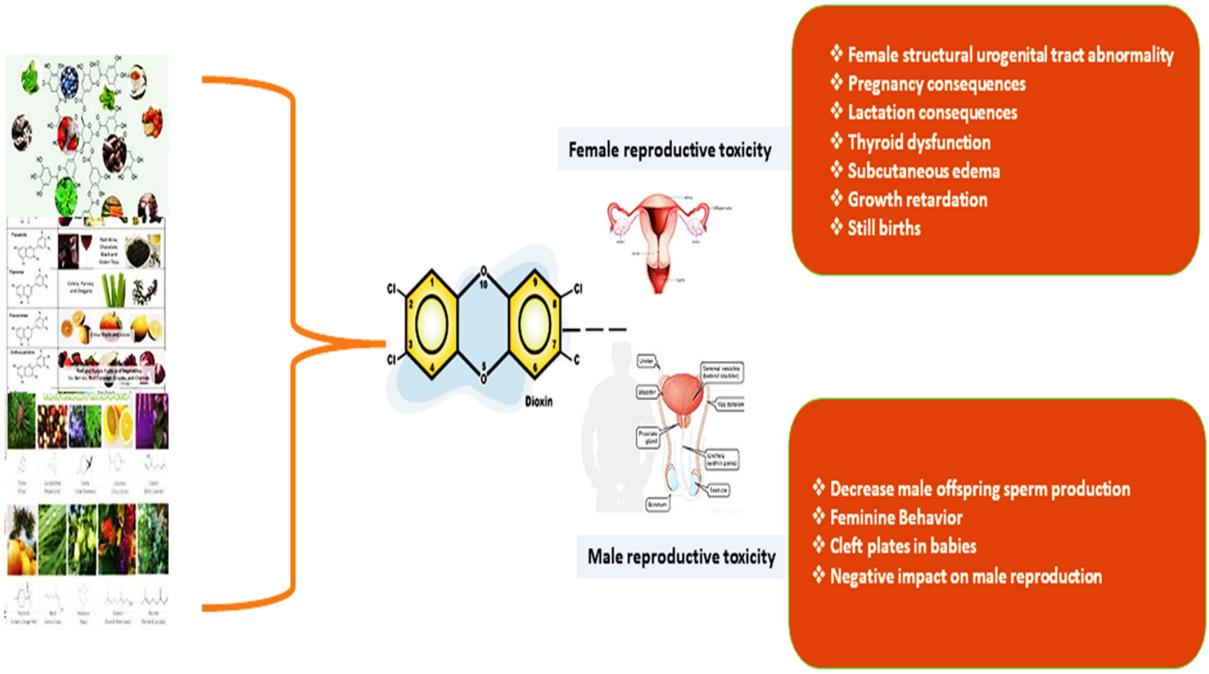


Figure 5a: Phytochemicals and reproductive tract disorders.

anthocyanins present in blueberries were detected in human blood, it is conceivable that the heightened overall antioxidant capacity could be attributed to an increase in polyphenols. The presence of total anthocyanins was associated with the observed elevation in serum antioxidant capacity.[47] The chemical composition of anthocyanins underscores their significant role in disease management. These compounds have demonstrated considerable efficacy across a range of medical conditions, including cardiovascular diseases, neurodegenerative disorders, visual acuity enhancement, cancer, diabetes, and obesity.[48] Furthermore, anthocyanins exhibit anti-inflammatory properties, which are crucial for tissue regeneration and wound healing in response to infections. Inflammatory responses involve various pathways, including the NF-κB mediated cytokine production, the cyclooxygenase-mediated pathway, Mitogen-Activated Protein Kinase (MAPK) activity, inducible Nitric Oxide Synthase (iNOS)-related signaling, Lipopolysaccharide (LPS)-induced macrophage activation, and the expression of endothelial adhesion molecules.[49] Anthocyanins have shown their capacity to inhibit these inflammatory cascades and mitigate inflammation-induced tissue damage. Whether in their natural state or as extracts, anthocyanins have the ability to down-regulate the NF-κB pathway, modulate the MAPK pathways, and reduce pro-inflammatory cytokine expression, as evidenced *in vitro*.[50] Anthocyanins are well-known for their robust antioxidant properties, which make them effective in various models of neurodegenerative diseases. Their high Oxygen Radical Absorbance Capacity (ORAC) value is integral to their neuroprotective function, as they can directly scavenge free radicals, preventing the formation of Reactive Oxygen Species (ROS) in affected cells.[51] Beyond their health benefits, anthocyanins serve as natural protectors for plants exposed to adverse environmental conditions by scavenging stress-induced ROS molecules. This property makes them a viable strategy to enhance stress tolerance in plants.[52] While the nutritional and pharmaceutical aspects of anthocyanins are well-documented, their role in stress response remains an area that requires further exploration. Moreover, anthocyanins exhibit potential as versatile pH colorimetric indicators. When incorporated into polymeric composites, they not only enhance stability but also extend the range of pH-induced color changes. Depending on the application and the choice of polymer matrices, these systems can exhibit improved overall performance, including mechanical and barrier properties. Additionally, the inherent properties of anthocyanins, coupled with their ability to change color in response to varying pH conditions, open up possibilities for additional functionalities such as antioxidant and antimicrobial activity.[53] The Table 3 lists the outcomes of dioxin exposure in human studies.

Protective Action on Carcinogenesis

The most substantial body of evidence regarding the carcinogenicity of 2,3,7,8-TCDD relates to the overall occurrence of all types of cancer, rather than cancers at specific anatomical sites. In subgroups with the highest incidence rates and extended incubation periods, the relative risk for the combined occurrence of all malignancies is 1.4. Although confounding factors do not seem to be the most likely explanation for this relative risk, they cannot be definitively ruled out as contributing factors.[65]

Electromagnetic radiation and smoking, as observed in atomic bomb survivors, serve as illustrative instances of factors that elevate the risk of cancer across multiple anatomical sites. Nevertheless, notably higher risks are discernible for certain specific cancer sites. The classification of TCDD as a Group 1 carcinogen would not have occurred unless there had been modifications in the criteria governing such categorization.[66] Furthermore, the assertion by the International Agency for Research on Cancer (IARC) that a particular chemical functions as a pluri-potential carcinogen, primarily by marginally increasing the risk of all types of cancer in humans while exerting minimal to no impact on the risk of any specific disease, lacks substantiation from previous research. The reclassification of TCDD as a Group 1 carcinogen by the IARC was grounded on comprehensive surveys that specifically centered on the Ah receptor.[67] While the presence of the Ah receptor may be essential for TCDD toxicity, it does not automatically imply that the chemical will also be hazardous or potentially carcinogenic. Caution must be exercised when interpreting epidemiological data, as there has been limited prior research on a multi-site carcinogen without any specific predominant locations. However, the absence of previous data does not rule out the possibility that 2,3,7,8-TCDD may act as a multi-site carcinogen at high doses.[5] It is crucial to emphasize that emissions in industrial centers significantly surpass the levels typically encountered by the general population. The results of this study strongly question the designation of TCDD as a Group 1 carcinogen by the International Agency for Research on Cancer (IARC). Moreover, the data suggests that TCDD may not demonstrate carcinogenic properties even at elevated concentrations, and it may not pose harm to humans at intermediate concentrations.[68-70] Research has indicated that persistent activation of dioxin or aryl hydrocarbon receptors can lead to the formation of stomach tumors. The activation of AhR-mediated transcription factors serves as an initial defense mechanism against potentially harmful environmental pollutants. However, it's essential to recognize that AhR activation and chemical carcinogenesis are intertwined, as AhR's promotion of oxidative metabolic pathways can also result in the creation of highly carcinogenic compounds.[69] The ligand-activated signaling pathway, referred to as the dioxin or Aryl hydrocarbon Receptor (AhR), plays a pivotal role in regulating several genes responsible for encoding key enzymes involved in drug metabolism, thus contributing to the biotransformation process.[70]

The receptor known to engage and promote the harmful effects induced by 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and structurally similar halogenated aromatics is known as the AhR.[71] The stimulation of the AhR receptor is involved in every impact of TCDD and similar dioxin-like compounds. Recognized receptors agonists include environmental toxins the polyaromatic compounds and dibenzo - *p* - dioxins, for example. The lifespan of transgenic mice with constitutively active AhRs was decreased, and the mice developed malignant tumor in the glandular area of the gastrointestinal part confirming the receptor's carcinogenic potential and linking it to the control of cell proliferation. Several studies employing the TRAMP mouse model demonstrate the involvement of AhR ligands on a variety of genitourinary derived malignancies as well as the endogenous relevance of the AhR in prostate cancer. Another study revealed that the AhR was expressed in glioblastoma cell lines and in human tumors, and that the AhR's pro-oncogenic activity was regulated by TGF signaling.[71]

Various chemo protective phytochemicals have been found engage in a variety of cellular interactions, comprising those encompassing the Aryl hydrocarbon (Ah) Receptor (AhR).[72-73] Dietary phytochemicals demonstrate significant agonistic and antagonistic effects on the Aryl hydrocarbon Receptor (AhR), which are greatly dependent on the specific cellular context. Considering the substantial abundance of phytochemicals and other AhR-active substances in the diet, it is indeed vital to take them into account when evaluating the risk associated with dietary toxic equivalents of TCDD and related compounds.[74] The dual agonist and antagonist effects of phytochemicals on the AhR are noteworthy. Various combinations of phytochemicals have been found to exhibit mild AhR agonist and antagonist activity in several cancer cell lines. These observations warrant discussion in the context of their potential implications for the accurate assessment of the hazard of hormonally active drugs (HA drugs) using the Toxicity Equivalency Factor/Toxicity Equivalency Quotient (TEF/TEQ) approach. Such findings can inform the development of dietary TCDD-TEQ recommendations, which would take into account the consumption of HA chemicals alongside significant quantities of "natural/phytochemical" AhR agonists and antagonists.[75] Figure 4 (b) showing the pathway of dioxin toxicity and its amelioration by polyphenols.

Studies showed various phytochemicals that prevent TCDD from promoting the transformation of rat liver cytoplasm.[76] These findings may subsequently be utilized to generate dietary TCDD-TEQ recommendations that reveal the combined intake of HA chemicals and significant amounts of "natural/phytochemical" AhR antagonists/agonists. Some research links polyphenols' impacts to their roles as Aryl hydrocarbon Receptor (AhR) ligands. The structure-dependent action of flavonoids as AhR agonists and antagonists. In colon melanoma cells, it is shown that only a tiny fraction of 2,2' hydroxychalcones-activated AhR-responsive genes display structure-dependent AhR action.[77] Latest evidence is examining the effects of chalcones, such as ISL, that are both AhR-active and AhR-inactive on the colon in mice models that have both wild-type and inactivated AhR. Additional investigation has revealed the significance of the AhR in inducing the protective immunity to chalcone in the colon.[78]

Further research demonstrates that the cytoplasmic chemosensor AhR serves a crucial role in both healthy and disease as a pleiotropic transcription factor. It is an evolutionarily conserved

protein. Specifically, TCDD along with its derivatives, including other menacing mixtures, have been shown to work through the signaling pathways of AhR signaling pathways which is traditionally known as the "dioxin receptor.[79] Recently, AhR has drawn more interest as a desirable target in the fields of aging, cancer, immunology, and inflammatory bowel illnesses. Plant flavonoids specially are considered the main group of natural dietary ligands of the AhR. Many different flavonoids have been proposed as AhR function modulators.[80] Differences in the molecular effects of flavonoids on the regulation of AhR transcription arise due to the complexity of AhR's role in both physiological and pathological contexts. The ability of flavonoids to reduce receptor transcriptional activity has been linked to their impact on AhR. Another study demonstrated the involvement of Resveratrol and kaempferol as potential natural cancer prevention remedies that function similarly to estrogen receptor agonists and AhR antagonists. Resveratrol and kaempferol were found to inhibit AHR-dependent transcription in MDA-MB-231 and BT-549 breast cancer cells that lacked estrogen receptor expression.[81]

Phytochemicals suppress Dioxin Reproductive Toxicity

Environmental contamination related to dioxin has garnered considerable attention. Health concerns associated with dioxin have risen due to reports of pollution in the proximity of industrial waste sites, municipal incinerators, and workplace exposures among employees in relevant industries. Dioxin is highly detrimental, known for its enduring effects and a unique risk to developing organisms. Consequently, significant research efforts are presently devoted to exploring its implications for reproduction and development.[82]

Dioxins have been found to have a numeral developmental impact on animal reproductive system of both the sexes. The reproductive development of male rats is impacted by a relatively low prenatal dosage of TCDD.[83] Male offspring's sperm production declines as they get older, and their sexual behavior becomes more feminine. Female offspring also have reproductive changes, including structural urogenital tract abnormalities. Although animals are very sensitive to dioxin's effects and since these effects are both irreversible and long-lasting, it is crucial to understand how dioxin continuous improvement.[84] Dioxin exposure during pregnancy and lactation has a wide range of functional consequences on offspring at extremely low concentrations in animal trials. Infants exposed to dioxin through breast milk in humans may experience impacts on thyroid function even if they are not exposed to it after birth.[85]

Animal studies have revealed that embryos are more susceptible to the harmful effects of TCDD (2,3,7,8-tetra chlorodibenzo-p-dioxin) compared to dams (female animals). The impact of TCDD administration is particularly significant in terms of assessing lethality and its outcomes.[86] For example, when pregnant C57BL/6 mice were administered a dose of 24 g/kg of TCDD on day 6 of Gestation (GD6), there was an increase in the occurrence of stillbirths. However, no effects were observed following treatment on GD8, GD10, GD12, or GD14. Additionally, other research has indicated that exposure to TCDD during pregnancy can lead to a variety of species-specific adverse effects, including thymic atrophy, subcutaneous edema, growth retardation, and stillbirths.[87]

Dioxin's teratogenic effects on animals are rare and species specific. Cleft palates are developed in rats exposed to TCDD dosages that are particularly induced on GD11 and GD12, but not on GD14, and that are neither detrimental to the mother nor the baby.[88] A third study found that TCDD exposure during pregnancy may have resulted in a range of deleterious consequences that are species-specific, including as thymic atrophy, subcutaneous edema, growth retardation, and stillbirths. Dioxin seldom causes teratogenic consequences in animals, and these effects vary by species. Mice exposed to TCDD levels that are specifically induced on GD11 and GD12, but not on GD14, and that are neither harmful to the mother nor the infant develop cleft palates. There has been a lot of study on the impact of TCDD on reproduction in perinatally exposed children.[85] A single oral administration of TCDD at a concentration of as little as 0.064 g/kg on GD15 had negative impact on the male reproduction in the progeny of expectant Holtzman rats, according to their findings.

Throughout the world, various cultures have accorded medicinal plants a distinct significance in their cultural traditions, medical approaches, and dietary habits. Natural compounds with intricate chemical structures have garnered considerable attention as modifiers of biological functions. In accordance with a study, the aqueous extract from *Boerhavia diffusa* L. has shown efficacy in mitigating the developmental toxicity induced by the persistent environmental chemical toluene. This extract has been demonstrated as a significant agent that enhances the health and fertility of Drosophila flies affected by toluene poisoning.[88] An additional study investigated the mechanism of action of quercetin and its preventive effects on TCDD-induced cleft palate. *In vivo* experiments revealed that pregnant mice receiving quercetin supplementation could safeguard their unborn offspring from developing cleft palates caused by TCDD exposure.[6] Figure 5 (a) offers a comprehensive insight into the protective effects afforded by various phytochemicals against reproductive disorders induced by dioxin exposure.

Many plants contain Protocatechuic Acid (PCA), a common phenolic compound. Various antioxidant compounds, including PCA derived from plants, are recognized for their protective effects against reproductive toxicity and can be utilized effectively to mitigate the adverse effects of TCDD.[89-90] The combination of PCA with TCDD resulted in the elevation of TBARS levels, reduction in histopathological tissue alterations, and increased

levels of cellular antioxidants (SOD, CAT, GPx), GSH levels, sperm motility, and sperm concentration. These findings validate prior research indicating that PCA can effectively mitigate the toxicity of TCDD. This suggests that PCA's antioxidant properties may offer protection against reproductive damage induced by TCDD.[91] According to research findings, the inclusion of vitamin E in one's diet has demonstrated a beneficial effect in countering the toxicity of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) induced by reactive oxygen species in rat testes. In a previously published study, rats exposed to TCDD experienced testicular damage, but quercetin provided protective effects. Furthermore, a study has suggested that the anti-inflammatory properties of aminoguanidine can safeguard the testicles against the detrimental effects of TCDD.[92]

Dioxins Causing Immunotoxicity and Prevention by Phytochemicals

Although TCDD is undeniably one of the most powerful immunosuppressive compounds in use, its immunotoxic effects have been the subject of research for more than 35 years.[93-94] Many documented studies concerning 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD) involve the following phenomena: Reduced susceptibility to infectious agents and neoplastic conditions, restricted development and growth of fetal cells, and suppression of adaptive immune responses, including antibody synthesis, Cytotoxic T Lymphocyte (CTL) function, and delayed hypersensitivity reactions, all indicative of thymic involution.[95] The persistent, widespread, and highly hazardous environmental compound known as 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) falls within a broad category of planar halogenated aromatic hydrocarbons, including Polychlorinated Biphenyls (PCBs), Polychlorinated Dibenzo-p-Dioxins (PCDDs), and Polychlorinated Dibenzofurans (PCDFs). TCDD induces a wide range of adverse effects, encompassing disturbances in waste management, thymus gland atrophy, disruptions in lipid metabolism, teratogenicity, developmental toxicity, hepatic toxicity, carcinogenicity, and suppression of the immune system. Despite the lack of precise knowledge regarding TCDD's immunotoxic targets and the mechanistic foundations of its immunotoxicity, cellular dysfunction arises from its interaction with an intracellular protein known as the aryl hydrocarbon receptor.[95] The immune system is particularly susceptible to the harmful effects of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD). These effects include thymic atrophy, weakened host defense against pathogenic microorganisms and tumors, halted lymphocyte maturation and differentiation, and suppression of adaptive immune processes, including but not limited to antibody production, cytotoxic T lymphocyte function, and delayed hypersensitivity reactions. These outcomes emphasize the detrimental impact of TCDD exposure on the immune system.[96] Numerous scientific investigations assert that 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD) directly alters the *in vitro* functionality of T and B lymphocytes in a manner analogous to the following pattern.[97]

Many phytochemical compounds have been studied for their potential to alleviate immunotoxic effects. Curcumin, for example, has therapeutic properties that include anti-inflammatory, antioxidant, antiviral, antibacterial, and antifungal effects. Research has shown that curcumin's protective mechanisms may also extend to the regulation of the maturation and activation of T lymphocytes.[98] In a separate study, the findings highlight the potential of curcumin, cineol, and myrcene as immunomodulatory agents. These compounds appear to offer protection against immune damage induced by TCDD exposure. In an intriguing study, Resveratrol is shown to provide protection to both the fetus and the mother during pregnancy against the immunotoxic effects of TCDD.[99] When consumed during pregnancy, the natural plant substance resveratrol may offer maternal and fetal protection from the toxicity brought on by environmental contaminants, which mediate their effects via activating the aryl hydrocarbon receptor. Stilbene in another study has shown beneficial effect against dioxin immutoxicity. The stilbene protected mothers and their fetuses against dioxin immunotoxicity by lowering the expression of CYP1A1 in the thymus of both the mother and the fetus when administered to pregnant and non-pregnant mice.[100] Highly relevant, dietary AhR antagonists may change the propensity for carcinogenesis in children whose mothers were exposed to AhR activators while they were pregnant. Studies on rats revealed that the occurrence of TCDD in the food (2 mg/kg BW) markedly increases the level of TNFα while dramatically reducing the level of interferon γ and interleukins 12 and 13.[101] Additionally, a significant decrease in weight was seen. Treatment with curcumin (100 mg/kg BW), chrysin (50 mg/kg BW), or quercetin (20 mg/kg BW) increased the rodent's humoral immune response and completely reversed the immunosuppressive effects of TCDD.[102]

In other research involving pregnant female mice administered TCDD (10 mg/kg BW), the study confirmed the immunotoxic effects of dioxin on both mothers and their fetuses. This included significant thymus atrophy, increased apoptosis, abnormal expression of TCR (a receptor presents on the surface of T lymphocytes involved in specific antigen recognition), and differentiation of T lymphocytes. The CYP1A1 coding gene was highly expressed in both mothers and fetuses. However, when resveratrol and TCDD (100 mg/kg BW) were administered to pregnant mice and their fetuses, these alterations were not observed. This suggests that certain polyphenols can protect against autoimmune conditions induced by dioxins. In rats, TCDD had adverse effects on their immune systems, body weight, and oxidative stress. However, when Q (possibly quercetin) and CH (possibly chrysin) were combined with TCDD, these negative effects were mitigated. These findings suggest that Q and CH could serve as defenses against TCDD toxicity.[103-104]

Anti-Diabetic Action of Phytochemicals

Type 2 Diabetes (T2D) is one of the most significant public health concerns worldwide, and its prevalence has more than doubled over the past three decades. T2D and prediabetes are increasingly observed in children and teenagers. It is widely believed that lifestyle changes characterized by excessive calorie intake and physical inactivity have contributed to the obesity epidemic and, subsequently, the prevalence of diabetes.[103] Indeed, extensive research suggests that individuals with similar levels of obesity may have significantly different risks of developing Type 2 Diabetes (T2D). Recent evidence has linked environmental toxins to T2D, insulin resistance, and obesity. In January 2011, a conference was convened by the US National Toxicology Program and the National Institute of Environmental Health Sciences program to assess the experimental evidence linking exposure to specific compounds with the development of particular diseases. This highlights the growing interest in understanding the environmental factors contributing to T2D and related health issues.[104] The primary discovery was indeed the strong research linking Persistent Organic Pollutants (POPs) to Type 2 Diabetes (T2D) in humans. POPs are a class of lipid-soluble chemicals that accumulate in the food chain and other living organisms, and they are resistant to environmental degradation. Organochlorine (OC) pesticides that often fall under the category of POPs include lindane, chlordane, hexachlorobenzene, and Dichlorodiphenyltrichloroethane (DDT). Other POPs, such as Polychlorinated Biphenyls (PCBs), Polychlorinated Dibenzo-p-Dioxins (PCDDs), Polychlorinated Dibenzofurans (PCDFs), and polybrominated diphenyl ethers, are created as agrochemicals or byproducts.[104] Dioxin has been recognized as a significant endocrine-disrupting chemical for several years. However, epidemiological studies on its impact on type 2 Diabetes Mellitus (DM) have yielded mixed results. Nevertheless, a German study found that the incidence of DM increased among employees of a phenoxy herbicide manufacturer who were exposed to TCDD following a chemical reactor incident. In contrast, no elevated incidence of DM was observed in a study of TCDD-exposed American employees. This underscores the complexity and variability of the relationship between dioxin exposure and type 2 diabetes in different populations.[105] Research conducted by American veterans who were exposed to Agent Orange and its component TCDD during the Vietnam War, it was discovered that the incidence of DM was higher but this link was not detected in a reanalysis of the data. Women in Seveso, Italy, who were exposed to significant levels of relatively pure TCDD in a broad community, but not males, showed an elevated mortality from DM. In studies on animals, it was shown that TCDD led to hypo-insulinemia in the rabbits and rats. It has been suggested that TCDD can reduce beta cells' ability to produce and secrete insulin via reducing glucose absorption, which is brought on by a decrease in GLUT2 expression.[105] Despite the fact that dioxin exposure and DM have been linked in animal research and that the link is physiologically feasible, epidemiological studies have found contradictory outcomes. Cigarette smoke, which triggers the aryl-hydrocarbon receptor and may be related to quicker PCB excretion, was more prevalent among men.

These are some of the theories on the probable causes of the gender disparity. Women's greater estrogen levels, higher fat percentages, and the ability of certain PCBs and PCDFs to promote the expression of CYP1A1 and CYP1B1 genes all bestow to the prolonged deposit of these lipophilic chemicals and create catechol estrogen 4-hydroxyl estradiol's by catalyzing the hydroxylation of the estradiol A-ring. During metabolic pathways, these 4-hydroxyl estradiol's might generate free radicals via redox-active substances such reactive semiquinone intermediates. It is well recognized that free radicals encourage oxidative stress, which is linked to DM. Exposure to dioxin increases the risk of acquiring diabetes mellitus in both men and women, regardless of age or BMI. In endemic regions of exposure, screening programs to detect DM in its early stages and intervention programs to prevent and control DM should be taken into consideration.[105] A new paradigm suggests that a healthy diet might effectively defend against inflammatory process brought on by environmental toxins and human illness. Numerous studies have looked at how bioactive foods like flavonoids and omega-3 polyunsaturated fatty acids reduce the toxicity of environmental contaminants. However, a large number of these studies rely on *in vitro* assays, which lack the complexity of a comprehensive body organismal approach.[106] Importantly, it should be noted that recently identified groups of bioactive dietary components, such as polyphenols, have been shown to reduce the pro-inflammatory impact of environmental pollutants.[106]

Current evidence suggests that an individual's dietary status can indeed have a significant impact on the severity of diseases induced by environmental toxins, including diabetes and cardiovascular illnesses.[106] People who maintain a balanced diet and emphasize the significance of bioactive-rich foods could be less susceptible to the toxic effects of environmentally obstinate contaminants than those who have poor nutrition. The ability of nutrients like flavonoids to act as a buffer contrary to the toxicity of inflammatory-promoting contaminants may make them less susceptible to environmental harm. In the long run, it is vital to research and develop cutting-edge inventing and remediation technologies that are effective, affordable, and environmentally sustainable. Enhancing the dietary characteristics of people at risk may prove to be a significant moderator of disease induced by toxicants.[107]

It has been demonstrated that the three primary natural anti-inflammatory substances-flavonoids, stilbenes, and alkaloids have the potential to be further developed as cutting-edge therapies for diabetes and its consequences.[108] The pathophysiology of diabetes and its consequences are explained by the dramatic rise in the production of several pro-inflammatory cytokines,

including TNF- and ILs. A study found that berberine inhibits the activity of the enzyme's dipeptidyl peptidase-4 and protein tyrosine phosphatase-1B, preventing the production of reactive oxygen species, the chronic inflammatory biomarker C reactive protein, free fatty acids, cholesterol, and triacylglycerols, as well as other inflammatory substances. In order to lower fasting blood sugar levels, berberine enhanced insulin sensitivity at this time and decreased insulin resistance.[109]

Intriguingly, a diet with olestra supplements totally eradicated high POP concentrations in adipose tissue and corrected POP-mediated clinical disorders including diabetes and hyperlipidemia in a human case study.[44] The physiological system may be primed before a toxic insult by upregulating protective detoxifying enzymes, and it may be protected therapeutically after exposure by increasing the rate of excretion and lowering overall body burden, making dietary-derived bioactive compounds like EGCG attractive modulators of toxic exposure.[44] Intriguing part provided that altering diets to increase fiber and bioactive nutrients from fruits and vegetables would be a beneficial and efficient method to mitigate POP toxicity. New and expanding collective knowledge also suggests the use of bioactive nutrients like quercetin and curcumin as effective components of novel environmentally friendly remediation technologies. Recent and growing research suggests that bioactive nutrients may be included into sensing and remediation components, which may result in workable solutions that avoid many of the drawbacks of the present decontamination platforms.

Protective Action of Phytochemicals against Dioxin Induced Cardiovascular Disorders

Over through the last ten years, persistent organic pollutants in living organisms, such as pesticides, dioxins, and polychlorinated biphenyls, have been connected to overt Cardiovascular Disease (CVD) and cardiovascular risk factors.[109-110] Furthermore, a connection between CVD and Plastic-Associated Chemicals (PACs), such as bisphenol A and phthalates, has also instigated to appear.[111] Numerous strategies have been used to assess these commonalities, such as case-control or cohort studies that use measured data of the levels of different environmental pollutants that are swirling in the general population, industrial exposure studies, geographic studies of subjects living close to contaminated areas, and accidents with high levels of exposure.[111,112] The most significant source of POPs nowadays is consuming contaminated food, despite the fact that exposure to POPs in the past was either occupational or inadvertent. Additionally, POPs are slowly excreted after ingestion, which causes an age-dependent body load in people. POPs exposure is still a problem for the worldwide community since it continues to build in the food chain, exposing humans to low but ongoing levels of POPs.[113] According to growing studies, environmental contaminants may be latent, inevitable CVS risk factors in the general population. In particular, Myocardial Infarction (MI), stroke, and more generally, hypertension have all been linked to PCBs. Parallel to this, compelling investigational evidence seems to point to mechanisms involving irritation, ROS production, endocrine disruptor, immunotoxicity, and altered gene manifestation forms in vascular cells as the means by which manifestation to PCBs and dioxins seriously blights endothelial function and promotes the development of atherosclerosis.[114] Cardiovascular Disease (CVD) results from atherosclerosis, a complex condition in which fatty deposits, cellular inflammation, and scar tissue accumulate within the arterial walls. Both observational population evidence and the aforementioned experimental data indicate a direct role for PCBs and dioxins in the development of atherosclerosis.[112] PCBs are also associated with an increased risk of atherosclerosis. Studies in animals and *in vitro* have shown that exposure to environmental xenobiotic chemicals that signal through the Aryl hydrocarbon Receptor (AHR) can lead to alterations in endogenous AHR function and have adverse cardiovascular effects, potentially contributing to the etiology of coronary heart disease. In both preclinical and clinical studies, TCDD, one of the most potent AHR agonists, has been linked to cardiovascular diseases and age-related damage.[114] According to prior research in fish, birds, and mammals, the young are more susceptible to TCDD than the adults, and developmental exposure has deleterious effects in adulthood. An upsurge in the creation of Reactive Oxygen Species (ROS), biologically active prostaglandins, pro-inflammatory cytokines, and a wide range of oxidative metabolic enzymes are the most well physiochemical predictors of the toxic effects of dioxin and cause a number of comorbidities, especially cardiovascular disorders.[115]

Given the perceived harmful effects of dioxins on human health, there is an urgent need to develop effective defenses against or remedies for their toxicity. Some of the tested phytochemicals appear promising in this regard. Phytochemicals found in edible plants are particularly sought after due to their potential. Recent epidemiological studies have linked the consumption of dietary antioxidant phytochemicals such as carotenoids, phenolic compounds, and flavonoids to a reduced risk of cancer and cardiovascular diseases.[108] The potent pharmacological advantages of medicinal herbs used for the treatment of illnesses have drawn a great deal of attention considering that they are native medicines, possess harmless phytochemicals, and therefore are healthier than manufactured pharmaceuticals.[116] Zerumbone and 13-HOA have shown a significant reduction in the expression of MMP-3 mRNA induction when compared to other phytochemicals. Their effect is particularly noticeable when MMP-3 mRNA is induced by 1 M DDT over a 24 hr period.[117,118] MMP-3 was chosen because of its well-known effects on tissue inflammation and damage caused by macrophages, particularly through its contribution to the etiology of various CVS disorders through the destruction of extracellular matrix. In another study, the preventive effects of an ethanolic extract of Eruca sativa leaves on male rats' abnormal lipid metabolic processes induced

by dioxin were investigated. When the ethanolic extract of Eruca sativa leaves was progressively administered to TCDD-exposed rats, there was a significant increase in the levels of serum and testis Cholesterol (CHOL), Triglycerides (TG), Phospholipids (PLs), Total Lipids (TL), Low-Density Lipoprotein Cholesterol (LDL-c), and Very-Low-Density Lipoprotein Cholesterol (VLDL-c). However, the level of High-Density Lipoprotein cholesterol (HDL-c) decreased. These outcomes may be attributed to the elevated levels of polyphenols, flavonoids, and polyunsaturated fatty acids in the extract. It's worth noting that omega-3 fatty acids are known to increase HDL cholesterol levels, and lower HDL cholesterol levels are associated with an increased risk of stroke and heart disease.[119]

For many years, synthetic compounds have been widely used as medications to treat a variety of ailments. Additionally, traditional plant-based medicines have a long history in healthcare, dating back to ancient times. Vegetables, fruits, medicinal and aromatic plants, as well as their leaves, petals, and roots, all contain phytochemicals. These phytochemicals serve as the body's natural defense mechanisms against diseases.[120] Phytochemicals found in natural products encompass a diverse range of chemical compounds, including vitamins, steroidal saponins, flavonoids, polyphenols, and flavonoids. Many bioactive compounds, often derived from terrestrial plants, have been demonstrated to reduce the risk of cardiovascular diseases and promote cardio protection, which primarily focuses on the prevention of heart disease.[120] These substances include isoflavones, diosgenin, resveratrol, quercetin, catechin, sulforaphane, and tocotrienols. The antioxidative, antihypercholesteremic, antiangiogenic, anti-ischemic, suppression of platelet aggregation, and anti-inflammatory properties of the different phytochemicals may contribute to their cardio protective benefits by lowering the risk of cardiovascular diseases. The structure-function link of phytochemicals, which mediates their multifaceted activity, can be used to develop cardiovascular drugs in the future.[121]

Environmental toxins, including pesticides, heavy metals, petroleum byproducts, and other harmful compounds, can have detrimental effects on the cardiovascular system. While there is limited research on preventive strategies specifically for dioxin-induced cardiotoxicity, it's important to note that these environmental toxins are challenging to break down and persist in the environment for a long time. Furthermore, they can become enriched in the human body through processes like bio-concentration and bioaccumulation in the food chain, leading to adverse health impacts.[122] A research conducted by abarikwu in 2014 surveyed the impact of quercetin on membrane-bound ATPases, MDA profiles, cardiac marker enzymes, and antioxidant profile in Cd-intoxicated rats. They found that pretreatment with quercetin may protect the rat hearts from oxidative damage when Cd is added.[123] In different research, it was shown that grape seed proanthocyanidins, an *in vivo* antioxidant, had cardioprotective benefits by preventing inflammation, apoptosis, and membrane disruptions in cardiomyocytes in male Wistar rats given Cd.1[124]

Cardiotoxicity is a critical consideration when evaluating the toxicity of environmental contaminants, as cardiac damage can have devastating and often irreversible consequences. Addressing this issue is challenging because the mechanisms by which environmental contaminants induce cardiotoxicity are complex and involve multiple targets within the cardiovascular system.[122] Patients who have been exposed to environmental toxins may find potential benefits in the development of medications that effectively counteract cardiotoxicity by harnessing the therapeutic properties of medicinal plants as a source of new and beneficial chemical compounds. This approach could provide novel treatments for individuals affected by environmental contaminants' adverse effects on the cardiovascular system.[125]

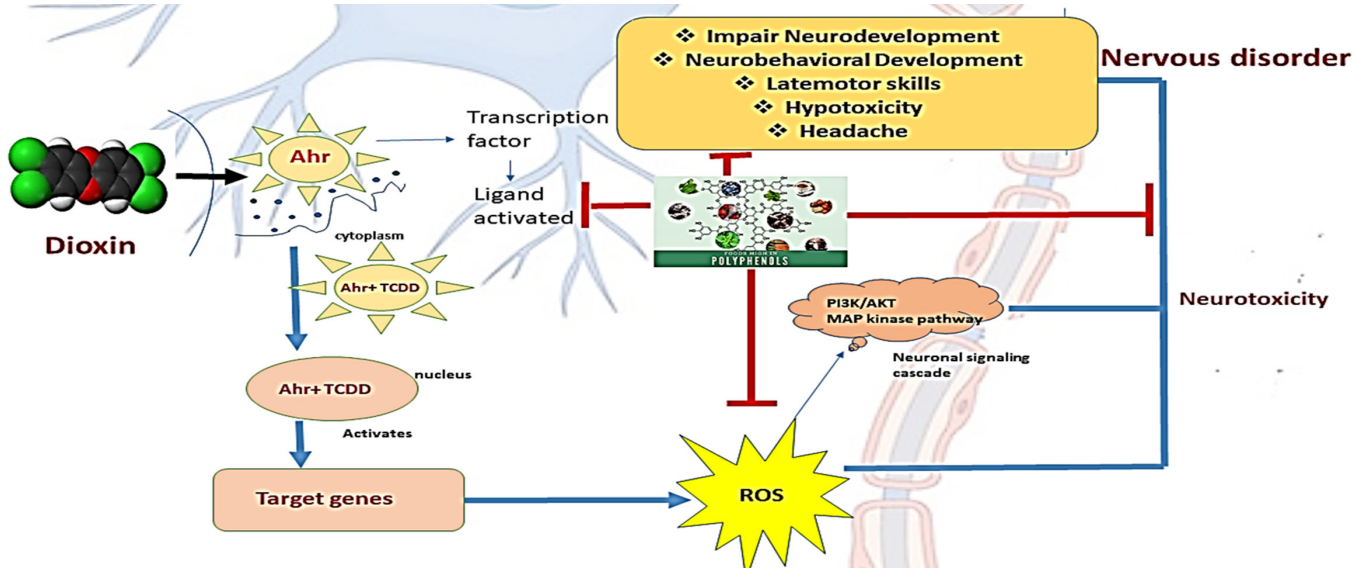


Figure 5b: Pictorial representation of various Polyphenolic constituents against dioxin induced various neurological disorders.

According to a study by Turkmen in 2022, rat cardiac tissue suffers oxidative and histological changes after exposure to TCDD at a level of 2 g/kg/week. Additionally, beta-glucan (50 mg/kg/day) displayed substantial antioxidative properties and helped mitigate some of the harmful effects of TCDD on histopathological alterations.[126] Studies indicate the protective effects of beta-glucan against TCDD-induced toxicity and the viability of beta-glucan treatment in the development of possible defenses against TCDD-induced cardiotoxicity and oxidative stress.[126]

Human exposure to TCDD has been associated with cardiovascular issues. One-way TCDD induces cardiovascular events is by increasing the production of Reactive Oxygen Species (ROS), leading to elevated TBARS levels and reduced levels of antioxidant enzymes such as SOD, GSH, and CAT in the heart. Melatonin acts as an antioxidant and can mitigate lipid peroxidation while also reducing ROS formation by activating several antioxidant enzymes.[127]

In a study conducted by Sarihan and colleagues, rats were orally administered TCDD for 45 days at a dosage of 2 mg/kg. This exposure resulted in a loss of body weight and a decrease in heart weight in the rats.[128] Following exposure to TCDD, there was a decrease in various hemodynamic measures, including Mean Arterial Pressure (MAP) and Blood Pressure (BP). It was demonstrated that a 45-day treatment with melatonin at a dose of 5 mg/kg/day (administered intraperitoneally) reversed the hemodynamic abnormalities and body weight loss. Additionally, rats exposed to TCDD experienced a significant decline in oxygen (PO2) saturation.[129] Melatonin treatment markedly raised oxygen saturation in comparison to the rats that had been exposed to TCDD. Rats exposed to TCDD also had aberrant cardiac rhythms, as well as an increase in block and duration of their PR, QRS, and QT intervals.[129] According to a study, exposure to TCDD led to oxidative stress in cardiac tissue, and yogurt with added roselle extract was found to significantly reduce the levels of Malondialdehyde (MDA) in the blood. Based on the findings of this study, it can be concluded that feeding the hearts of rats (Rattus norvegicus) exposed to TCDD with yogurt supplemented with purple roselle extract at doses of 0.5% and 1.5% has the potential to prevent the increase in MDA levels and histological damage. Therefore, a feasible strategy to mitigate TCDD toxicity may involve consuming yogurt enriched with purple roselle extract, which can help reduce oxidative stress.[129] Another study shown that rat cardiac tissue suffers oxidative and histological impairments as a consequence of TCDD administration with a dosage of 2 g/kg/week.[130] Furthermore, beta-glucan (50 mg/kg/day) had strong antioxidant activities and assisted in reducing a number of the detrimental consequences of TCDD on pathological changes. The prevention of TCDD-induced toxicity by beta-glucan therapy points to a possible source for the creation of potential inhibitors.[130]

Neuroprotective action of phytochemicals against dioxin causing neurotoxicity

The accrual of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD), a prominent environmental toxicant, has been documented to manifest in both ecological settings and biological organisms. The detrimental influence of TCDD on the nervous system represents a significant public health concern associated with its presence.[131] Recent research has shown that TCDD significantly impairs mice' neurodevelopment and neurobehavioral development. According to epidemiological studies, high doses of PCB/TCDD mixes accidentally exposed cause children to develop their motor skills later and have a greater prevalence of hypotonicity.[132] Professionals who were inadvertently exposed to 2,3,7,8-Tetr achlorodibenzo-p-Dioxin (TCDD) exhibited a notably elevated incidence of neurological issues, including headaches. These observations suggest that TCDD could potentially exert a substantial influence on neurotoxicity in both rodent models and human populations.[132] The Aryl hydrocarbon Receptor (AhR) represents a ligand-activated transcription factor that typically remains sequestered in the cytoplasm in an inert state. Upon interaction with 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD), the AhR rapidly relocates to the nucleus and initiates the activation of a multitude of target genes. The activation of these genes, in turn, instigates downstream processes that promote the deleterious effects associated with TCDD exposure. A principal facet of TCDD-induced AhR activation is believed to involve the generation of Reactive Oxygen Species (ROS), which is also considered a pivotal element in the neurotoxic effects induced by TCDD. Thus, a more comprehensive understanding of ROS's role in eliciting neurotoxicity may aid in elucidating the mechanisms underpinning TCDD's detrimental impacts on the nervous system. Numerous stressors, including ROS, DNA damage, cytokines, and oncogenic activities, have been demonstrated in research to significantly accelerate the phenomenon of cellular senescence, commonly referred to as stress-induced premature senescence. This accelerated senescence brought about by adverse stress-related agents may constitute a pivotal factor in the development of various human maladies, including cancer and neurological disorders.

Although TCDD is clearly hazardous to the nervous system, it is still entirely unclear how it affects neuronal cells. According to several recent studies, exposure to relatively large concentrations (200-1000 nM) of TCDD caused fast death in cultured neuronal cells. It is believed that this consequence, rather than being a normal outcome of TCDD-mediated neurotoxicity, is an acute toxic response.[133,134] Additionally, although the specific physiological consequences are still completely unclear, exposure to a considerably lower dosage of TCDD was shown to generate substantial ROS buildup in cultured primary neurons (0.1-10 nM) and brain tissues (46 ng/kg/day).[135] Since ROS are potent inducers of premature senescence, TCDD-induced ROS production may

accelerate senescence in neural cells. The acceleration of neuronal aging through ROS production may be a component of TCDD's neurotoxic mode of action. It is critical to thoroughly evaluate the long-term effects of TCDD ingestion since TCDD exposure can cause a considerable buildup of ROS in brain tissues.[135] Figure 5 (b) illustrates how polyphenols protect against the neurotoxicity caused by dioxin.

Chemoreceptors, frequently situated in cytoplasmic or transmembrane locations, serve as cell mechanisms for detecting chemical cues originating from external or internal origins. The pleiotropic transcription factor and evolutionarily conserved cytosolic chemosensor, Aryl hydrocarbon Receptor (AhR), assumes a pivotal role in maintaining homeostasis as well as contributing to pathological conditions. Notably, 2,3,7,8-Tetr achlorodibenzo-p-dioxin (TCDD) and its derivatives, alongside other highly hazardous compounds, have been demonstrated to modulate signaling pathways associated with what was historically recognized as the "dioxin receptor.[136] AhR has gained considerable interest lately as a prospective target in cancer, immunology, inflammatory bowel diseases, and aging. A better examination of the molecular processes and the patterns of AhR activation and inactivation in response to ligand binding is still necessary. Additionally, proven to have antioxidant action against TCDD-induced nephrotoxicity were Qct and Chrysin (CH). According to this study's findings, Qct and CH effectively protected the kidney from the damage brought on by TCDD by increasing levels of SDO, CAT, GSH, and GPx enzyme activity and dramatically attenuating lipid peroxidation (TBARS) levels.[137]

Dietary flavonoids' have ability to protect neurons from damage brought on by neurotoxins. They are neuroprotective because, among other things, they can improve memory, learning, and cognitive function.[138] This variety of impacts seems to be supported by two similar mechanisms. They first engage with crucial neuronal signaling cascades in the brain, which inhibits apoptosis caused by neurotoxic species and promotes neuronal survival and differentiation. Numerous protein kinase and lipid kinase signaling cascades are involved in the regulation of pro-survival transcription factors and gene expression, most prominently the PI3 K/Akt and MAP kinase pathways.[139] The amounts of flavonoids found in the brain seem to be high enough to have this kind of pharmacological impact on receptors, kinases, and transcription factors. Second, they have been shown to alter cerebrovascular blood flow by inducing favorable alterations in the peripheral and cerebral vascular systems. These modifications are expected to cause angiogenesis, the creation of new nerve cells in the hippocampus, and changes in the shape of neurons, all of which are known to be crucial for maintaining the best possible neuronal function and neurocognitive performance.[76]

Flavonoids, flavones, and flavanols in aglycones have been shown in certain investigations to block the AhR transformation antagonistically, indicating that they protect against dioxin toxicity. Several outstanding investigations have demonstrated the physiological amounts of dietary flavonoids.[137] Dietary aglycones and glycosides are eliminated in urine as free aglycones and conjugates. Because the conjugations take place in the intestines and liver, the dietary flavonoids persist as free aglycones at least momentarily in these organs, which are important dietary dioxin transporters.[137-139] Dietary flavones and flavanols defend against the toxicity of dioxin because the alteration of AhR has been recognized as a key and crucial stage in the development of dioxin toxicity.[137]

The amelioration of neurotoxicity caused by persistent environmental chemicals by herbal principles is significant since they are inexpensive, extremely active, and have no side effects. In addition, several vitamins and a variety of chelating organic compounds are being tested in the hope that they may form coordination complexes with environmental contaminants and help remove them, freeing the damaged organs or tissues from metal load and toxicity.[137]

Polyphenols' neuroprotective impact is linked to their capacity to stimulate suitable signaling pathways and so cause alterations in synaptic plasticity and neurogenesis. They can improve memory and cognitive abilities in this way.[140] Additionally, various polyphenolic constituents' thwart neurodegeneration by minimizing various inflammatory processes happening in brain tissue and enhancing neuronal survival (e.g. by inhibiting the activity of microglia, nitric oxide synthesis, and apoptosis). Polyphenols can help alleviate the neurotoxic effects of amyloid accumulation. Further research is required to understand the function of polyphenols in reducing the effects of dioxin toxins because of their biological and chemical properties, abundance in the plant component of diets, and protective action against many xenobiotics.[141]

DISCUSSION

Dioxins can arise as a result of natural occurrences, such as volcanic eruptions and forest fires, although industrial activities represent the primary source of their generation. Dioxins are inadvertent byproducts that emerge from diverse industrial processes, including, but not limited to, metal smelting, chlorine-based paper pulp bleaching, and the production of various pesticides and herbicides.[141] Uncontrolled waste incineration facilities, which encompass both solid waste and medical waste incinerators, tend to exhibit the highest levels of dioxin emissions into the environment due to the phenomenon of incomplete combustion.[3] Regulated waste incineration technologies are available and have the capacity to markedly reduce dioxin emissions. Despite the primary generation of dioxins at localized sources, their dispersion spans across global ecosystems. Dioxins constitute a widespread environmental issue of global significance, with elevated concentrations detected in a range of food products, including dairy, meat, fish, and shellfish, as well as in sediment

and soil. The extended half-lives of dioxins, ranging from decades to centuries, have historically presented significant challenges in the natural environment, exerting notable effects on both human health and the well-being of ecosystems.[5] Significant financial resources are dedicated to extracting such contaminants from crude oil, primarily aimed at preventing catalytic poisoning during the oil refining process and subsequently eliminating them from the natural environment. These efforts, on the whole, carry adverse economic implications. Progress in the development of cutting-edge elimination methods that utilize mitigating agents like sulfur, microbiological strategies, and photo-dissociation can greatly benefit from a deeper understanding of the mechanisms underlying the formation of these toxins in industrial procedures and combustion occurrences.[7] It is of paramount importance to foster awareness among environmental regulatory authorities and healthcare professionals concerning the pressing need for an environment free from toxicants, especially in developing nations. This urgency is rooted in the acute toxicity of dioxins, which poses significant and dual threats to public health and the environment. Over the past two decades, the widespread presence of Polychlorinated Dibenzo-p-Dioxins (PCDDs) and Polychlorinated Dibenzofurans (PCDFs) in environmental ecosystems and human biological tissues has emerged as a substantial and growing health concern. Substantial progress has been made in elucidating the mechanisms by which this chemical family elicits unique enzyme responses.[18] Pollution resulting from a wide array of Persistent Organic Pollutants (POPs) is escalating on a global scale. The multifaceted and adverse effects of toxic compounds generated by dioxins and similar substances are significant contributors to the worldwide increase in the prevalence of various diseases. POPs have been linked to a spectrum of health ailments, encompassing neurodevelopmental disorders, inflammatory conditions, cardiovascular diseases, hepatotoxicity, insulin resistance, allergies, metabolic disorders, and cancer. While recent international initiatives have aimed to reduce hazardous pollutant emissions, it remains equally imperative to advocate for protective measures at the individual level.[142]

The onset of diseases or the management of those associated with environmental exposure are significantly influenced by nutrition. A rich nutrition especially one high in polyphenols may minimize the toxicity associated with the harmful effects of POPs such acrylonitrile, polychlorinated biphenyls, dioxins, phthalates, and bisphenol A.[143,144]

Dietary polyphenols are receiving a lot of interest because of their favorable impact on human health. The current experimental findings clearly imply that polyphenols can mitigate the negative health effects of significant persistent organic pollutants.[5] Conventional polyphenols, like resveratrol, are under scrutiny for their protective attributes, and less explored alternatives may exhibit comparable or heightened efficacies in specific contexts. The protective properties of polyphenols primarily stem from their impact on components of the antioxidant system, enzymes responsible for xenobiotic metabolism, and consequently, the levels of Reactive Oxygen Species (ROS).[117] Experimental findings indicate that polyphenols have anti-inflammatory, anticarcinogenic, hepatoprotective, and nephroprotective effects.[143,144] An accumulating body of evidence indicates that polyphenols can profoundly modulate chronic or delayed effects stemming from prolonged (sub-clinical) exposures. Numerous studies illustrate that polyphenols can mitigate acute consequences arising from short-term hazardous exposures. In specific scenarios such as certain cancers, exacerbations of preexisting conditions, and neurodegenerative complications where environmental chemicals pose a risk factor, epidemiological investigations suggest an enhanced capacity to ameliorate the chronic effects of toxic exposures with increased polyphenol consumption. Additionally, polyphenols counteract immunosuppressive effects and provide protection against gonadotoxicity. Currently, substantial clinical research on the safety and effectiveness of polyphenols in safeguarding against dioxin and related chemicals is lacking. Importantly, polyphenols are generally well-tolerated in human subjects, warranting the development of specific studies to translate preclinical findings related to environmental toxins into novel nutritional and therapeutic approaches.

CONCLUSION AND PROSPECTS

In conclusion, the therapeutic promise of polyphenols in managing conditions related to Persistent Organic Pollutants (POPs) warrants further exploration. Increased clinical trials are necessary for a comprehensive evaluation. It's crucial to acknowledge the complex metabolic changes polyphenols undergo, leading to metabolites with potentially varying bioactive properties, urging detailed investigations. Development of innovative delivery methods is essential to ensure minimal compound degradation and maximal bioavailability. Additionally, understanding the potential of specific polyphenols like resveratrol, Epigallocatechin Gallate (EGCG), quercetin, apigenin, and curcumin sourced from diverse diets is imperative. These compounds offer cost-effective nutritional components that may address environmental contaminant risks while promoting overall health.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ROS: Reactive Oxygen Species; **AHR:** Aryl Hydrocarbon Receptor; **PCDDs:** Polychlorinated Dibenzo-*p*-Dioxins; **PCDFs:** Polychlorinated dibenzofurans; **PCBs:** Polychlorinated Biphenyls; **WHO:** World Health Organization; **ROS:** Reactive Oxygen Species; **TNF-α:** Tumor Necrosis Factor-alpha;

LOX: Lipoxygenase; **iNOS:** Inducible Nitric Oxide Synthase; **NF-kB:** Nuclear Factor-Kappa B; **POPs:** Persistent Organic Pollutants; **MAPK:** Mitogen-Activated Protein Kinase; **ORAC:** Oxygen Radical Absorbance Capacity; **TCDD:** 2,3,7,8-Tetrachlorodibenzo-p-dioxin; **IARC:** International Agency for Research on Cancer; **AhR:** Aryl hydrocarbon Receptor; **TEF/TEQ:** Toxicity Equivalency Factor/Toxicity Equivalency Quotient: **CTL:** Cytotoxic T Lymphocyte; **DDT:** Dichlorodiphenyltrichloroethane; **PACs:** Plastic-Associated Chemicals; **TG:** Triglycerides; **PLs:** Phospholipids; **TL:** Total Lipids; **LDL-c:** Low-Density Lipoprotein Cholesterol; **VLDL-c:** Very-Low-Density Lipoprotein Cholesterol; **HDL-c:** High-Density Lipoprotein cholesterol.

SUMMARY

This research article delves into the impact of dioxins, persistent environmental pollutants notorious for causing various health issues. These compounds trigger cellular toxicity through Reactive Oxygen Species production, affecting the body's Aryl Hydrocarbon Receptor system and leading to ailments like cancers and immune system deficiencies. The study focuses on exploring how polyphenolic compounds, found in certain plants, can mitigate dioxin-induced toxicities. By analyzing both lab experiments (*in vitro*) and studies on live subjects (*in vivo*), the researchers found that polyphenols show promise in reducing dioxin toxicity. While preclinical studies demonstrated significant effectiveness, clinical trials provided mixed results. However, they suggest that these plant-based compounds could complement conventional therapies for dioxin-related health issues by influencing processes like oxidative stress, inflammation, and gene regulation. This investigation serves as a comprehensive review, shedding light on how polyphenols interact with environmental contaminants at a molecular level. The findings underscore the need for further clinical research, emphasizing the importance of targeting specific patient groups, identifying relevant toxicity markers, and understanding how polyphenols impact these markers. Overall, this research highlights the potential of polyphenols as a supplementary approach in managing dioxin-induced health problems, while calling for more focused clinical investigations for a better understanding of their therapeutic role.

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