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Review article

Toxicological impact and biotransformation of xenobiotics: Novel biological discoveries to combat toxicity

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ABSTRACT

Environmental pollution has led to significant contamination of air, water, and soil which increases the concentration of xenobiotics in the ecological system. Xenobiotic refers to any strange or foreign compound not in order within the normal metabolic pathways of a biological system. Researchers have shown the effect of xenobiotics toxicity in living organisms but has not recommend natural treatment sources to combat the toxicity. The review assess the toxicological impact and biotransformation of xenobiotics, "Novel Biological discoveries to combat toxicity". Continuous exposure cause significant damage and can display neurological defects, nephrotoxicity, carcinogenicity, hepatotoxicity, immunological toxicity, cardiovascular toxicity, skin toxicity, genotoxicity, reproductive and developmental toxicity. Xenobiotics such as potentially toxic elements, chloro pesticides, polychlorinated biphenyls and polycyclic aromatic hydrocarbons are not easily degradable and are of environmental and human health concern, due to their detrimental effects through toxicological health risks. Antioxidant enzymes such as glutathione reductase, catalase, superoxide dismutase, and glutathione peroxidase are defense mechanism known to reduce (scavenge) reactive oxygen species (ROS) and lipid peroxides are also effected by xenobiotics. Cellular components are affected when xenobiotic-induced ROS production exceeds thresholds, which lead to oxidative stress. The toxicity mechanisms of xenobiotics, treatment options of toxicity, bioremediations, and biodegradations of xenobiotics are highlighted. This literature also discuss the biomonitoring, risk assessment, xenobiotics fate in soil, sediment, air, water, waste sludge, and food. Therefore this review aimed to explore the effect of xenobiotics, antioxidants defense mechanism, bioremediation, biodegradation, toxicity, and novel therapeutics insights from biological sources to combat toxicity.

1. Introduction

The term "xenobiotics" refers to the foreign environmental chemicals (In Greek: xenos, means "stranger" while biotics, means living things or components derived from living organism). Xenobiotics pollution such as potentially toxic elements (PTEs), chloro pesticides (CPs), polychlorinated biphenyls (PCBs) and polycyclic aromatic hydrocarbons (PAHs) in the environment has become a problem, due to their persistence, abundance, toxicity, non-degradability, and ubiquity in the environment [1]. Environment are threaten as a result of their entry through anthropogenic activities (Mining, domestic, and industrial waste) and natural occurrence processes (atmospheric deposition, erosion, storm runoff, leaching from landfills, shipping and harbor operations, and agricultural runoff) [2,3].

Water bodies are also polluted by the release of xenobiotics into water which makes it unsafe for human use and disrupts aquatic biomarkers [4]. Xenobiotics have been shown to disrupt signaling pathways and impact a number of biological functions, including survival metabolism, apoptosis, cell growth, and proliferation. Aquatics can accumulate toxins (toxic metals, CPs, PAHs, and PCBs) from their environment, and continuous exposure through food chain over a period of time can be harmful to human health and pose major risk [5,6]. The metals Arsenic (As), cadmium (Cd), mercury (Hg), and lead (Pb) are hazardous even at lower quantity [7,8].

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Other pollutants include pesticides, petroleum, organochlorines, organophosphates and sewage waste etc.

Xenobiotics have detrimental impacts on human health and are mostly associated with their ability to disrupt antioxidant defense systems, mainly by interacting with intracellular glutathione (GSH) or sulfhydryl groups (R-SH) of antioxidant enzymes like glutathione reductase (GR), catalase (CAT), glutathione peroxidase (GPx), superoxide dismutase (SOD), and other enzyme systems [9,10]. Xenobiotics are not well eliminated from the body, they can build up and accumulate in the body [11] and also alter the functions of enzymatic antioxidant defense system, including catalase (CAT), glutathione reductase (GSPr), glutathione peroxidase (GSPx), and superoxide dismutase (SOD). The enzymatic antioxidant systems protects the biological cells and tissues from reactive oxygen species (ROS) such as the damaging effects of superoxide, hydrogen peroxide, hydroxyl radicals and glutathione free radicals [7,12].

Findings from other researchers shows that continuous exposure to xenobiotics cause significant damage and can display neurological defects, nephrotoxicity, carcinogenicity, hepatotoxicity, immunological toxicity, cardiovascular toxicity, skin toxicity, genotoxicity, reproductive and developmental toxicity [13–16]. This review therefore address several treatment options of xenobiotics toxicity from natural sources which are employed to treat toxicity cause by xenobiotics. Bioremediation is the use of microorganisms (bacteria and fungi) to convert toxic contaminants to friendly substances as a result of the microbial activity from biochemical processes. Bacteria, algae, and fungi are microorganisms that can be used alone or in combination to remediate xenobiotic-contaminated sites. Many microorganisms such as fungi, bacteria, or algae, have be employed to biodegrade xenobiotics. This review aimed to explore the environmental effect of xenobiotics, its defense mechanism, bioremediation, biodegradation, toxicity, and novel therapeutics insights from biological sources to combat toxicity.

2. Xenobiotics

Xenobiotics also include drug metabolites, drugs, and environmental pollutants such as synthetic herbicides, pesticides, and industrial pollutants. Inorganic and organic compounds are the two categories of xenobiotics that have been found to cause various forms of toxicity in biological systems [14,16]. Organic xenobiotics account for 80–90 % of chemically induced toxicity in humans. Hypothesized shows that organic foreign compounds are mostly to cause chemical-induced toxicity effect in the human population, regardless of whether xenobiotics consist of organic or inorganic substances. This may be due to the fact that organic xenobiotics make up the majority of medications and poisons intended for use in living things. Furthermore, according to the IARC [17], over 90 % of Group I agents that cause cancer in humans originate from organic xenobiotics. Xenobiotics have both long and short term effect describe in Fig. 1. Among the different xenobiotics are PTEs, PAHs, PCBs and CPs,

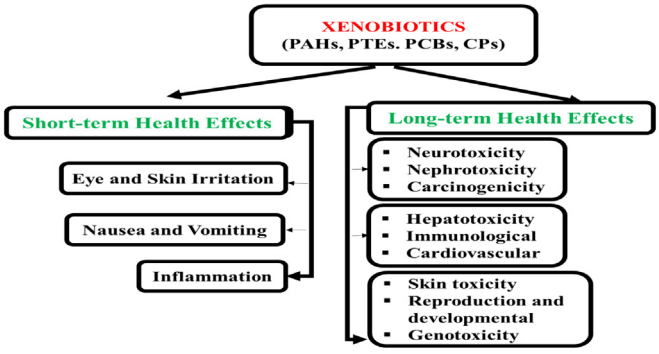

Fig. 1. Short and long term health effects of exposure to xenobiotics.

2.1. Potentially toxic element effect

Potentially toxic elements PTEs (Heavy metal) refers to any metallic chemical with a relatively high density greater than 5 g/cm^3 which are toxic to organism even at low concentrations [18]. Presence of PTEs poses serious risk to fish health and is regarded as a food security concern. Even at low concentrations, metals such as arsenic (As), cadmium (Cd), lead (Pb), and mercury (Hg) exhibit toxicity [19]. The accumulation of PTEs in fish poses a risk to human health.

Metal accumulation in organisms can have long-term consequences, including mutagenic, embryotoxic, gonadotoxic, and carcinogenic [20]. When the excretory, metabolic, storage, and detoxifying systems are unable to prevent uptake, heavy metals can have toxic consequences that lead to alterations in physiological and histopathological changes. Fish and seafood are healthy sources of minerals, protein, polyunsaturated omega-3 fatty acids and vitamins, many populations around the world depend on them for their daily meals [21]. Fish can be a major source of nutrition and significantly increase food security in particular areas.

However, aquatic animals are negatively impacted by their environment and accumulation of heavy metals. Fish has numerous health benefits, but the contaminants in it may seriously endanger the health of the consumer. Metals having extremely hazardous qualities, such as As, Pb, Hg, and Cd, are included in non-essential group. Because of their extremely dangerous qualities, these three are referred to as the toxic trinity among all toxic metals. Therefore, in national and international monitoring programs, this heavy metals are most often determined in the environment [22]. The main heavy metal hazards to human health are lead, cadmium, and mercury exposures. When the body does not metabolize heavy metals and they build up in biological tissues, they become poisonous. The most common accumulating metals in fish can cause problems in the health system if consumed over recommended quantities safe levels of metals and metalloids.

Toxicological effects of heavy metals include harm to the liver, kidneys, lungs, and other critical organs. It also diminished or impaired central nervous system function, and poor energy. Prolonged exposure of PTEs can cause neurological, muscular, physical degenerative processes, Alzheimer's disease, Parkinson's disease, and muscular dystrophy. Rarely, allergies develop, and prolonged, repetitive exposure to particular metals can lead to cancer. Because heavy metals tend to accumulate in aquatic animals, such as the fish *Aplocheilus panchax*, their presence in aquatic habitats is a major cause for concern [23,24]. Concerns on PTEs accumulation and its toxic effects on organisms which can potentially lead to human health problems prompted much study on heavy metals in aquatic [25].

2.1.1. Sources of potentially toxic element

Sources of PTEs includes pesticides, effluents from mining site, vehicle exhaust fumes, household and industrial effluents, urban runoff, disease control agents used on crops, metal inputs from rural areas, leaching of metals from trash and solid waste dumps, batteries, metal pipes for water, paints, fertilizers, textiles, cosmetic products, atmospheric, and petroleum-related industrial activities [26]. Discharging untreated (water, sewage, effluents and sludge) into the waterways can introduce pathogenic microorganism into water body. Consumption of the aquatic organism from heavy metal contaminated water by humans (mostly fish) causes short and long-term health hazards to human. Fishes is the most primary aquatic organisms in the food chain, and fish often accumulate large amounts of Heavy metals from contaminated water, which can be toxic to humans when consumption [27].

Fish metal buildup is influenced by contaminated water and can vary among species living in the same body of water [28]. Metal concentrations in water and fish have been found to be correlated in a number of lab and field investigations; however, it's crucial that the concentration of metal in the fish's body is related to the concentration of metal in the water if the fish is consuming the metal in the water [28,29]. Moreover, heavy metal pollution can come from other variety of sources, including copper

smelting, nuclear fuel preparation, and chromium and cadmium electroplating.

The release of lead and cadmium into dust from rubber tires on road surfaces allows these toxic metals to be inhaled or transferred onto edible plants or top soil. Causes of increased environmental toxicity due to PTEs are both natural and anthropogenic (man-made) [30]. The following are natural sources of toxic metals Wind-blown soil debris, forest fires, volcanic eruptions, biogenic processes, and marine salt while the anthropogenic causes of PTEs contamination include the use of agricultural products such as fertilizer, pesticides, and herbicides, as well as irrigation of crop field with sewage and industrial wastewater.

Trace levels of PTEs in pesticides and fertilizers are a significant source of PTEs contaminants in human food. Man-made practices that contribute to metals contamination include mismanagement of industrial waste, discharge of sewage, aerosol cans, use of Pb as fuel antiknock, traffic pollution, metallurgy and smelting, and construction materials [31–33]. A number of industries, such as the manufacturing of paper, drugs, and pulp preservatives, farming sector, and the chlorine and caustic soda industries, releases Hg into the environment [34]. A certain amount of Cd is present in soils and rocks, including mineral and coal fertilizer.

2.1.2. Arsenic (As)

Arsenic is hazardous substance that is commonly found in aquatic environments. Low levels of inorganic As exposure can have a variety of negative effects on the hematological, hepatic, skin, and cardiovascular systems, among other organs. Due to its acute toxicity, excessive doses of As metal can lead to death, disruptions to central nervous system and cardiovascular system, and unfavorable gastrointestinal tract symptoms [35]. According to the most recent WHO assessment, drinking water contaminated with arsenic increases the risk of developing cancer in the skin, kidneys, lungs, and bladder [36]. Arsenic's most common chronic manifestations affect the blood, liver, lungs, and skin systems.

2.1.3. Mercury (Hg)

Mercury (Hg) is a natural occurring element that is found in the seawater at 0.3 ng/L and in the Earth's crust at about 80 μg/kg [37] and Mercury density is 13.53 g/cm^3. According to Ariya et al. [38], Hg is a liquid element at room temperature and the only heavy metal that primarily pollutes the environment that is gaseous. Mercury is utilized in the manufacturing of gas chloride and caustic soda, as well as in common place items like switches, lightbulbs, thermometers, and batteries. It is also utilized in the dental industry to make fillings. Furthermore, mercury is employed in the chemical sector, gold mining and processing, and the manufacture of fungicides and insecticides [18].

The primary causes of emissions of anthropogenic mercury are considered to be the incineration of sewage sludge, medical and municipal waste, and high-temperature operations like making cement and lime [39]. The United States Environmental Protection Agency (USEPA) reports that, with 37.7 % of emissions worldwide, artisanal and small-scale gold mining (ASGM) is the main cause of man made mercury release. Subsequently, non-ferrous metal production for 15 %, stationary coal combustion accounts for 21 %, and cement production for 11 % [40].

Mercury toxicity include visual field construction, behavioral abnormalities, headaches, memory loss, tremors, spasticity, loss of hair, mental retardation to prenatal malformation, cerebral palsy, blindness, deafness, and muscle rigidity. Blindness, deafness, brain damage, kidney damage, lack of coordination, mental retardation, and digestive problems are all symptoms of mercury poisoning. According to Djingova and Kuleff [41], plants that are able to gather critical metals are also able to acquire other non-essential metals.

2.1.4. Cadmium (Cd)

Cadmium has 48 as its atomic number and a density of 8.69 g/cm^3. Earth's crust has a mean content of 0.1 mg/kg of Cd, with sedimentary rocks and marine phosphates having the highest concentrations of accumulated cadmium (15 mg/kg) [42]. Cadmium (Cd) is a very toxic and hazardous element that can be found in many different areas and is spread through the air and water. An average of 15,000 tons of cadmium are released into the oceans annually due to rock erosion and weathering; 820 tons are released into the atmosphere annually by volcanic [43].

The metal Cd is widely used in electronics industry, ceramics and dyeing industry. In addition, it has been used in the production of batteries, petroleum products, shipbuilding industry for coating the surface of ships, as well as in the production of PVC (polyvinyl chloride), detergents, phosphate fertilizers and petroleum products [14]. Cadmium is an extremely hazardous metal that has been linked to death, severe disease, rheumatoid arthritis (RA), complete skeletal deformities, stunted growth, hypertension, diarrhea, vomiting, stomach issues, bone fractures, DNA damage, infertility, immune system dysfunction, cancer, and fetal deformity [44].

The International Agency for Research on Cancer (IARC) has classified cadmium as a human carcinogen. It was discovered to be associated to renal cell carcinoma and prostate cancer. Livestock may experience gastrointestinal and reproductive effects from significant concentrations of CD. According to [45], Cd can cause acute and chronic poison, with negative effects on the liver, kidney, arteries, and immune system. Cadmium is a highly hazardous heavy metal that can cause a wide range of harmful effects through a number of interrelated processes. The primary molecular processes and mechanisms of cadmium toxicity include interactions with critical metals, oxidative stress, mitochondrial apoptosis, autophagy, and gene regulation [46].

2.1.5. Lead (Pb)

Lead is a silvery-gray, soft metal with a density of 11.34 g/cm^3 and atomic weight of 207.19. According to Jakubowski [47], Pd has a melting point of 327.5 °C and is insoluble in water. Lead is almost approximately found in the crust of the Earth as an ion in the second oxidation state, with an estimated mean amount of 10–14 mg/kg of crust. Lead (Pb) is a ubiquitous contaminant that can find its way into coastal rivers through release of industrial effluents from a different industries, such as textiles, oil refineries, printing, dyeing, and other businesses. Primary sources of Pd emissions into the environment include mining, metallurgy, and fossil fuel combustion. Lead is currently use in the manufacture of lead-acid batteries, metal goods including pipes and ammunition, and X-ray protection systems. Lead functions as a mimetic agent to mimic the effects of vital components involved in metabolism, including zinc, iron, and calcium, both physiologically and biochemically. For example, it directly disrupts the formation of heme by interacting with iron and zinc. Pb binds to a variety of transport proteins, such as calcium-ATPase, metallothionein, transferrin, and calmodulin.

The effect of Pb include heart disease, hypertension, anemia, proximal renal tubular injury, immunological system suppression (antibody inhibition), and neurological harm. Lead causes serious harm to the liver, kidneys, heart, brain, nerves, and other organs. Reproductive problems such as osteoporosis (brittle bone disease) may potentially result from lead exposure. Exposure to lead raises the risk of hypertension, anemia, and heart disease, particularly in men. Smaller amounts of Pb affect early children's brains and nerves, lowering IQ and learning deficiencies, while extensive Pb exposure results in behavioral abnormalities, mental retardation, and memory issues [48].

Lead accumulates in the body organs such as the brain, can lead to injury or even death. Children under the age of six are particularly susceptible to delayed development, reduced IQ, attention deficit disorder, hyperactivity, and mental decline as a result of lead exposure. When adult is exposed to lead, adults typically experience decreased reaction time, diminished fertility, renal system damage, memory loss, nausea, sleeplessness, anorexia, and joint weakness. In plant Pb has an impact on photosynthesis, growth, chlorosis, enzyme activity, and seed germination in plants. In microorganism, lead denatures proteins and nucleic acids and inhibits transcription and enzyme activity [49,50].

2.1.6. Human exposure to PTEs

Human exposure to PTEs is rapidly increasing, and their severity has long been known. Continuous exposure to PTEs through diet and contaminated water sources could cause adverse health effects including cancer [51]. There are several routes humans are expose to toxic metals, including ingestion, inhalation, and dermal absorption. Humans may also be exposed to heavy metals in the environment and at workplace (Table 1). Occupational exposure refers to human exposure to harmful chemicals in the workplace, whereas environmental exposure, also known as nonoccupational exposure, refers to exposure to similar chemicals in the general environment. In mining and industrial operations sites, workers are exposed to heavy metals through the inhalation of dust and particulate matter that contains metal particles [52,53].

Humans are exposed to mercury vapors through mining and extraction of gold. Human exposure to Cd and other harmful heavy metals in tobacco leaves through cigarette smoking. Food and drinking water are two major ways that the general public is exposed to heavy metals. Global urbanization, industrialization, and fast economic growth have all contributed to the intensification of agricultural and industrial processes. Through this activities water, air, and soils may be contaminated with toxic heavy metals. Bioaccumulation of metals in human food chains is as a result of consumption of food crop planted in heavy metal contaminated soil [3,65].

2.2. Polycyclic aromatic hydrocarbons (PAHs)

Polycyclic aromatic hydrocarbons (PAHs) are class of organic contaminants that have two or more benzene rings, and are persistent. The compound contain complex compound like carbon and hydrogen with a fused ring structure, containing at least two benzene rings [66]. Polycyclic aromatic hydrocarbons is found naturally in gasoline, crude oil, and coal. These molecules are widely found in terrestrial and marine settings. Polycyclic aromatic hydrocarbons (PAHs) are produced artificially by burning fossil fuels or naturally by fungi, volcanoes, plants, and bacteria in the environment. They are produced when wood, gas, coal, oil, cigarette, tobacco and garbage are burned [67].

Food like meat produce PAHs when cooked or heated at a high temperature. Because of the possible effect that PAHs may cause to human health and the ecology, they have received much attention. A variety of methods can be used to identify PAHs in edible portions of fish. For instance, fish tissue PAHs are extracted and identified using the GC–MS approach [68].

2.2.1. Sources of PAHs

Source of PAH in humans may be dietary exposure to chemical contaminants, particularly those found in fish. According to Andre et al. [7], exposure frequently happens through breathing air tainted by wood smoke, cigarette smoke, motor vehicle exhaust, or emissions from asphalt roadways. Consuming grilled or charred meats, as well as foods on which airborne PAH particles have settled, exposes people to PAHs [54].

Moreover, spilled oil, shipping activity, fuels, lubricants, human activities, fuels whose effluents are channeled to the water, and untreated or treated wastewater discharge are all potential sources of PAHs [55]. Natural formation of PAHs exhibit hazardous and recalcitrant properties [69]. Natural sources of PAH emissions include forest fires [56], waste burning [57], volcanoes, and hydrothermal activities [58]. The global distribution of PAHs is a result of both natural and anthropogenic sources, as well as global transport processes. They are mostly produce by burning fossil fuels in waste incinerators, during heating operations, and in automotive exhaust. They are pollutants that are poisonous, mutagenic, carcinogenic, and have negative biological impacts.

The products of burning fossil fuels, automobile emissions and refining [70], wood [71], burning biomass [72], charcoals, tobacco [73], wood smoke [74], and garbage [75] all contain high concentrations of PAHs. The movement of PAHs into the environment are primarily caused by transportation activities and petroleum refining [76]. Movement of PAHs can also occur as a result of the industrial effluents discharge.

There are a variety of other sources from which PAHs can be released into the environment, such as gasoline [77] and diesel, tobacco smoke,

Table 1
Summary of different xenobiotic sources, exposure and toxicity.

Various of xenobiotic	Sources	Human exposure	Toxicity
PTEs	Pesticides, effluents from mining site, vehicle exhaust fumes, household and industrial effluents, urban runoff, disease control agents used on crops, metal inputs from rural areas, leaching of metals from trash and solid waste dumps, batteries, metal pipes for water, paints, fertilizers, textiles, cosmetic products, atmospheric, and petroleum-related industrial activities [26].	Continuous exposure to PTEs through diet and contaminated water sources could cause adverse health effects including cancer [51]. There are several routes humans are expose to toxic metals, including ingestion, inhalation, and dermal absorption. Humans may also be exposed to heavy metals in the environment and at workplace.	Toxicological effects of heavy metals include harm to the liver, kidneys, lungs, and other critical organs. It also diminished or impaired central nervous system function, and poor energy. Prolonged exposure of PTEs can cause neurological, muscular, physical degenerative processes, Alzheimer's disease, Parkinson's disease, and muscular dystrophy ([24]; [23]).
PAHs	Wood smoke, cigarette smoke, motor vehicle exhaust, or emissions from asphalt roadways [7]. Consuming grilled or charred meats, as well as foods on which airborne PAH particles have settled, exposes people to PAHs [54]. Spilled oil, fuels, lubricants, human activities [55]. Natural sources include forest fires [56], waste burning [57], volcanoes, and hydrothermal activities [58].	Exposure to PAHs is linked to liver damage in humans and an allergic skin reaction. Prolonged exposure to PAHs increases the risk of cardiac mortality and gene mutation-induced cell damage ([56], [7]).	Carcinogenesis causes bronchitis, respiratory and pulmonary issues, genetic effects on reproduction and development, behavioral, neurological, and other organ system effects are some of these health effects ([59], [60]).
PCB	Incineration, industrial waste, agricultural practices, runoff, and the importation of electrical transformer oils [61].	Acute exposure may cause irritation in the skin, eye, nose, and throat. Chronic exposure may cause Skin pigmentation, porphyria, elevated hepatic transaminases, and thyroid hormone abnormalities may occur. PCB exposure is associated with decreased IQ and other neurobehavioral effects Adeyemi et al. [62] state that the health effects include reduced birth weight, cancer, liver, thyroid, ophthalmic, and dermal.	PCB metabolites may induce DNA strand breaks, resulting in cellular injury. PCBs are irritating to mucous membranes. PCBs, and particularly the PCDD and PCDF contaminants, are mutagenic and teratogenic and are considered human carcinogens [61].
CP	Pesticides, such as DDT and hexachlorocyclohexane (HCH), Industrial Manufacturing, Building Materials & Electrical Equipment, Waste Products, Atmospheric Deposition, Land Runoff [63]	The main method of pesticide transmission from land to aquatic bodies is surface runoff from sporadic rainfall; this causes non-target species like fish to be exposed to pesticides on a pulse basis [64]. Exposure to pesticides can result in acute poisoning or long-term health consequences, such as cancer and unfavorable effects on reproduction	Chloropesticides exhibit high toxicity by affecting the nervous system, potentially causing symptoms from headaches and seizures to long-term neurological damage. Neurotoxicity, immunotoxicity, and potential carcinogenicity, are classified as carcinogenic to humans [63].

and fuel combustion [78]. PAHs can be found in the air [79], sediments and soil [80], groundwater, surface water, and runoff [81]. According to reports [82], it concentrations in sediment and soil at uncontaminated and contaminated sites range from 1 mg/kg to over 300 g/kg.

Both natural processes and human activity (petrogenic and pyrogenic) emit PAHs into the ecosystem. The origin of PAHs in the coastal environment is classified as petrogenic (originating from petroleum, such as natural oil seepage and spills) or pyrogenic (originate from incomplete combustion of fossil fuel and organic waste). Anthropogenic sources of PAHs are from Petroleum products and incomplete combustion of organic matter in power plants, industrial operations, rubbish incinerators, automobile engines, home wood fires, and forest fires are examples [83].

These toxins end up in food because they are present in the environment. In order to measure exposure to PAHs, biomonitoring techniques is use. The results of these assessments have shown that nutrition plays a significant role in nonoccupational exposure to PAHs. Certain PAHs are extremely hazardous, as are their derivatives. Fish's fatty tissues can accumulate PAHs and alkyl PAHs, although the quantities are usually modest since fish can quickly metabolize PAHs and excrete them in their bile.

Fish exposure to PAHs, both recent and continuing, can thus be evaluated using biliary PAH metabolite determination as a biomarker [84]. Among all PAHs, benzo(*a*)pyrene (BaP), chrysene (CHR), benzo(*a*)anthracene (BaA), and benzo (b) fluoranthene (BbF) were classify as carcinogenic to humans, and these four PAH4 are the most hazardous [85].

2.2.2. Human exposure to PAHs

The PAHs are extensively present in the eccosystem, and human exposure cannot be completely avoided. Some of them, like benzo (a) pyrene, are carcinogenic and mutagenic, and it is commonly accepted that they significantly increase the incidence of cancer in human. The main ways which exposes the public to PAHs are through smoking cigarettes, eating food that contains PAHs, breathing smoke from open fireplaces, and using fossil fuels for transportation, cooking, heating, and industry. According to Wang, et al. [56], the presence of PAHs in agricultural leaves crops increases the amount of these compounds that organisms are exposed to via diet.

Occupational exposure to PAHs, such as in the manufacturing of coke, bituminous roofing, oil refining, and coal gasification. Workers in the mining, mechanics, street vendors, and auto mechanics who inhale exhaust fumes at work are exposed to PAHs.

Food contamination can originate from industrial food processing, some home cooking methods, and natural environmental causes, which are primarily human-caused. Airborne deposition and soil and water-borne deposition and transfer are two ways that PAHs might enter the food chain.

Through injection and inhalation are the main source of exposure. Inhaling cigarette smoke, being near industrial emissions, driving exhaust, being near hazardous waste sites, jet fuel, fire pits, and eating grilled food are some ways that humans might be exposed to PAHs. Ingesting polluted food, drinking contaminated water, and the air can all expose humans to PAHs. PAHs are regularly tested for a variety of purposes, including air quality evaluation in the atmosphere, health impacts monitoring in biological tissues, and food safety. Vehicle and industrial emissions, waste sites, cigarette, burning biomass, waste burning, municipal incinerators, volcanic eruptions, home heating, and consuming food that has been grilled or smoked over charcoal are some of the sources that can contaminate the environment and expose people to benzo[*a*]pyrene (BaP).

Other exposure is caused by oil spills, land fires [86], charcoals, automobile traffic [87], e-waste and medical waste [88], and smoke from tobacco [73]. Because PAHs are so pervasive, it is hard for anyone to escape being exposed to them. Exposure pathways (inhalation, ingestion, and skin contact in work-related and non-work-related contexts). Certain exposures, such skin and airborne contamination, may occur through many pathways at the same time, impacting the overall absorption dose.

2.2.3. Toxicity of PAHs

The environment is progressively becoming more contaminated as a result of the increasing rate of industrialization, and in the coming years, pollution is probably going to reach disturbing levels. The knowledge of PAHs' toxicity, carcinogenicity, and teratogenicity has led to a rapid increase in their harmful effect. Benzo (a) pyrene (BaP) has the highest propensity for cancer, due to their potential carcinogenicity. PAHs are pollutants of major concern that are found in many different habitats [89].

Generally PAHs are extremely toxic and have the potential to affect living oeganism and the environment. Carcinogenesis causes bronchitis, respiratory and pulmonary issues, genetic effects on reproduction and development, behavioral, neurological, and other organ system effects are some of these health effects. Exposure to PAHs is linked to liver damage in humans and an allergic skin reaction (Table 1). In industrialized nations, PAHs in the air are the main cause of asthma in children. Asthma development and exacerbation have been linked to exposure to traffic-related air contaminants, such as PAH [90].

When PAHs find their way into agricultural soils, they affect soil organisms, agricultural products cultivated in that soil, and also effect human who consume food grown on PAHs contaminated soil. Industries that produce hazardous waste consisting of both organic and inorganic components include fertilizers, pesticides, petrochemicals, and pharmaceuticals. PAHs are one of the most harmful pollutant in the ecosystem and prolong exposure of PAHs causes' lung cancer. Symptoms like diarrhea, nausea, vomiting, and eye irritation have been linked to exposures from a variety of jobs and high concentrations of pollutant mixes containing PAHs.

According to Diggs et al. [59], people that are exposed to PAHs have a higher risk of acquiring malignancies of the skin, lungs, bladder, and gastrointestinal tract. In laboratory animals, PAHs like Pyrene and BaP have been linked to cancer. Many authors have shown that exposure to PAHs can cause skin irritation and redness and also DNA damage [91]. Prolonged exposure to PAHs increases the risk of cardiac mortality and gene mutation-induced cell damage. The consequences of both brief and prolonged exposure to PAHs on humans are depicted in Fig. 8. The Environmental Protection Agencies (EPA) have selected some PAH as pollutants due to their potential negative effects, which include mutagenic, carcinogenic, endocrine disrupting, and reproductive toxicity [92]. A number of PAHs and certain combinations of PAHs are thought to be carcinogens [93]. Through disintegration of fat, PAHs can infiltrate the interior of cells, where they can cause toxicity and mutation in living organisms. When released into the biosphere, due to their toxicity, xenobiotics cause a serious risk to the health of human and animals. The teratogenic, mutagenic, and carcinogenic characteristics of PAHs originating from natural or human sources are noteworthy [60].

2.2.4. Mechanism of PAHs

When PAHs entered the lung, it activate both phase I and phase II metabolic enzymes via the both independent and dependent mechanisms of the aryl hydrocarbon receptor (AhR). Cytochrome P450 (CYP) monooxygenases, such as CYP1A1/2 and 1B1, are examples of phase I enzymes. Epoxide hydrolases (EHs), glutathione S-transferases, UDP glucuronyl transferases, NADPH quinone oxidoreductases (NQOs), and aldo-keto reductases (AKRs) are examples of phase II enzymes.

One of most likely main causes of lung cancer among smokers is probably PAHs. In order for PAHs to cause cancer, they must be metabolically activated. A three-step process that generates diol epoxides and then reacts with DNA to form adducts that can cause mutations and initiate the carcinogenic process is one important pathway (Fig. 9). PAHs enter the human diet through the ingestion of foods that have been grilled over charcoal. When PAHs are broken down by the CYP1A1/1B1/EH, CYP peroxidase, and AKR pathways, the active carcinogens diol-epoxides, radical cations, and o-quinones are created [94]. Benzoapyrene (BaP), one of the carcinogenic PAHs, may contribute to an elevated risk of esophageal cancer [95].

Cytochrome P450 (CYP) enzymes generally metabolize PAHs into oxygenated species. Fish phenanthrene phase I metabolites are primarily dihydrodiols, with a little amount of mono hydroxylated molecules [96]. In contrast to non-alkylated PAHs, alkyl PAHs may experience benzylic oxidations instead of condensed aromatic ring oxidations throughout their metabolic changes [97]. Diol-epoxides, which are produced when PAHs

undergo metabolic activation in mammalian cells, bind covalently to nuclear DNA to form adducts that may result in errors in DNA replication and mutations that could initiate the carcinogenic process.

2.3. Polychlorinated biphenyls (PCBs)

The PCBs are non-polar hazardous organic compounds with a basic chemical structure consisting of one or more benzene (biphenyl) molecules substituted with one to ten chlorine atoms [98]. Aroclors are made of synthetic organic compounds that are utilized as plasticizers, coolants, lubricants, and insulators in a range of materials. They also improve physical and chemical resistance. PCBs are also produced by certain manufacturing processes that include hydrocarbons, chlorine, and heat, such as those that produce paints, printing inks, detergent bars, paints, and agricultural chemicals.

2.3.1. Sources of PCBs and human exposure

The main sources of PCBs in Nigeria are incineration, agricultural practices, industrial waste discharge into waterways, and the importation of electrical transformer oils. Research on laboratory manuals and humans both show a high degree of carcinogenicity associated with PCB exposure [61]. Adeyemi et al. [62] state that the health effects include reduced birth weight, cancer, liver, thyroid, ophthalmic, and dermal. The PCBs were primarily used in plastics, carbonless copy paper, paint additives, transformers and capacitors (dielectric and cooling fluids), lubricants, and flame retardants. Even though PCBs are either prohibited or regulated in many nations, they are nonetheless frequently detected in environmental samples from all around the world. Urban soils contain high concentrations of persistent organic compounds (PCBs), and People are exposed to these compounds via ingestion, skin contact and inhalation (Table 1).

2.4. Chloropesticides

Pollution in the environment is one of the biggest issues facing the globe today. One of the main areas of inquiry is the detrimental consequences of pesticide poisoning on the ecosystem. Pesticides have the potential to contaminate natural water sources either directly, by killing aquatic weeds and insects, or indirectly, by leaking chemicals used in agriculture into the water and then collecting industrial waste and cleaning up various pesticide formulation containers [99]. Significant concentrations of organochlorine pesticides have been found in fish, and reports of these chemicals' presence in fish flesh have been widespread [100].

It has been discovered that fish has a considerable quantity of organochlorine insecticides in its flesh. Organochlorine insecticides have long contaminated fish. Organophosphorus pesticides exhibit lower persistence compared to organochlorine pesticides, and they can considerably diminish fish populations by reducing nutritional value or impacting different developmental stages of fish. In recent times, pesticide residues in food have become a significant concern due to their short persistence and potential to transform into metabolites that are more toxic than their parent compounds. These metabolites can cause acute or chronic hepatic toxicity in humans, as noted by Saad et al. [101]. Pesticide residues have the potential to be a major source of contamination for air, water, and soil. Coexistence of plant and animal populations within the ecosystem may be continuously threatened by this phenomena.

Organochlorine pesticide residues have been found in a variety of foods, including fish. There have been reports of organochlorine chemicals and their metabolites contaminating food that comes from animals in a number of different nations [100]. The main method of pesticide transmission from land to aquatic bodies is surface runoff from sporadic rainfall; this causes non-target species like fish to be exposed to pesticides on a pulse basis [64]. Large exposure to pesticides can result in acute poisoning or long-term health consequences, such as cancer and unfavorable effects on reproduction (Fig. 1) (Table 1) [102,103].

3. General mechanism of xenobiotics

Three stages of Xenobiotic metabolism.

The enzymes in phase 1 initiated the detoxification procedure, which also enables lipophilic xenobiotics to acquire sites for further conjugation reactions and become more polar (Fig. 2). Phase I enzymes include the

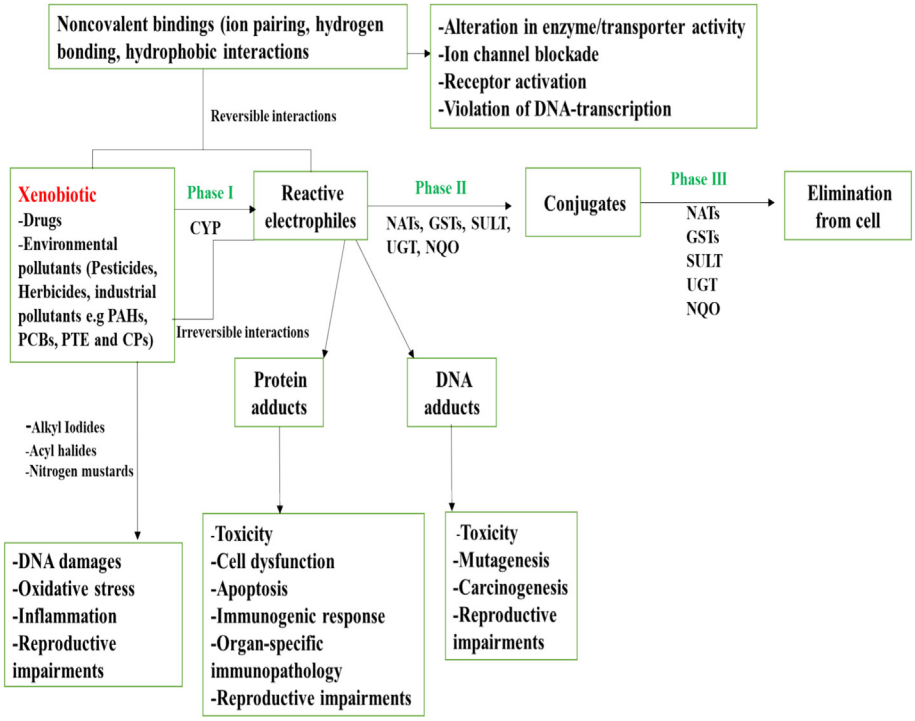

Fig. 2. General mechanism of xenobiotics. Adepted from [105]. Abbrevations: Glutathione S-transferases (GSTs), *N*-acetyltransferases (NATs), cytochrome P450 (CYP), sulfotransferase (SULT), UDP-glucuronosyltransferase (UGT), NQO (NAD(*P*)H quinone oxidoreductase), OATP2 (organic anion transporting polypeptide 2), P-gp (P-glycoprotein), and MRP (multidrug resistance-associated protein).

majority of the 36 gene families that comprise the cytochrome P450 (CYP) superfamily of microsomal enzymes. According to Lewis [104], the CYP1, CYP2, CYP3, CYP4, and CYP7 families are essential for human xenobiotic and drug excretion as well as hepatic and extra-hepatic metabolism.

Phase II enzymes involvs the catalyzation of the conjugation process. The enzymes interact directly with xenobiotics or, more broadly, through their interactions with phase I enzyme-produced metabolites. Sulfotransferases (SULT), UDP-glucuronosyltransferases (UGT), DT-diaphorase or NAD(*P*)H quinone oxidoreductase (NQO) or NAD(*P*)H menadione reductase (NMO), glutathione S-transferases (GST), and *N*-acetyltransferases (NAT) are the superfamilies of phase II enzymes. Families and subfamilies of genes encoding distinct isoforms with distinct substrate and tissue specificities make up each superfamily [105].

Phase III is the elimination through transport. Phase III transporters include organic anion transporting polypeptide 2 (OATP2), P-glycoprotein (P-gp), and multidrug resistance-associated protein (MRP), which are members of the ATP binding cassette (ABC) transporters subfamily.

The three-phase xenobiotic detoxification process. When cytochrome P450 (CYP) the phase I enzyme activates lipophilic molecules metabolically, the substances gain a phase II conjugation reactive center events, which result in the formation of hydrophilic compound. Phase III carriers or passive transport then eliminate hydrophilic compounds. Reactive electrophiles following phase I activation are responsible for the most of the noxious effect, however certain xenobiotics are dangerous even prior to metabolic activity.

4. Xenobiotics toxicity

Xenobiotics can cause acute toxicity, and also cause chronic toxicity after prolonged exposure. Even at low level, xenobiotics such as heavy metal have detrimental effects on human because they can lead to several conditions such as abnormal fetal development, infertility, immunodeficiency, cancer, renal tumor, nephritis, osteoporosis, physical, mental, and neurological diseases, organ dysfunction, congestion of the nasopharynx, elevated blood pressure linked to heart-related condition, shortened lifespan, and extreme cases, death [106,107].

According to Ogoko et al. [108], exposure to xenobiotics can lead to a variety of adverse health effects, including impaired or diminished brain and neurological issues, reduced energy, and damage to the lungs, liver, kidneys, other vital organs. Prolonged exposure of toxic metal can lead to degenerative processes that mimic Alzheimer's, multiple sclerosis, Parkinson's, muscular dystrophy, and progressively advance throughout the body, muscles, and nervous system. Repetitive, prolonged exposure with some metals can lead to cancer, although allergies are rare.

Toxic Metals such as As, Cd, Pb, and Hg are non-essential and can effects living things, they have toxic effects on fish, causing damage to their neurological and renal systems with severe pathological changes to their gills. Xenobiotics buildup causes a number of several effects, including inflammation, oxidative stress, genetic abnormalities and histological damage [109]. Fish can accumulate toxic metals through the body surface, gills, and the digestive tract [110].

Toxic metals can enter the fish body via the permeable membranes, such as the gills, and inhibit a variety of activities, including the cell cycle, protein structure disruption, native required metal ion substitution in metabolic enzymes, and DNA crosslink formation [111,112]. Metals in water, sediment, or aquatic life can be seen in particulate, dissolved, or chelated/combined forms [113]. One of the most obvious signs of metal toxicity in fish is growth retardation. Heavy metal reported to be teratogenic, mutagenic, and carcinogenic effects of HMs. Toxic metals result in the generation of ROS, which then induce oxidative stress. Heavy metals toxicity lead to energy loss, damage to kidneys, liver, lungs, brain, blood, and other essential organs. Prolonged exposure result to neurological, tissue, and physical degenerative processes that imitate illnesses such as Parkinson's disease, Alzheimer's disease, muscular dystrophy, and multiple sclerosis (Fig. 3).

Acute lead (Pb) exposure can cause vertigo, lethargy, headaches, hypertension, nausea, arthritis, weariness, insomnia, and hallucinations. Acrodynia, often known as pink sickness, is caused by mercury poisoning. Elevated exposure to mercury may alter the structure of the brain, leading to symptoms such as tremors, shyness, irritability, cognitive decline, visual and auditory impairment [115]. According to Sonone et al. [51] persistent exposure to HMs through food and contaminated water sources may result in a variety of harmful health effects, including cancer. Heavy metals can cause a number of health problems, such as cancer, neurological disorders, and reproductive problems, by disrupting cellular processes, generating reactive oxygen species (ROS), and impairing cellular defenses [116]. Heavy metals can deplete antioxidant molecules like glutathione and prevent antioxidant enzymes activities. This impairment can increase cellular damage and exacerbate oxidative stress [10,114].

The main mechanism of cadmium toxicity may be associated with inhibition of calcium transfer with proteins. These interactions have the potential to interfere with biological functions such as cell signaling, protein synthesis, and DNA replication. Hypocalcemia explain the toxic action of Cd [114,117]. Enzymes involved in iron metabolism and cellular detoxification can be affected by cadmium. This disruption can lead to a cascade of metabolic abnormalities and cellular damage. Toxic metals such as Pb and Ca share similarities in their respective routes of absorption and accumulation within fish. The Ca^{2+} is carried through the basolateral membrane by the Ca^{2+} ATPase after being adsorbed by the gills' apical membrane Ca^{2+}-channel [118]. The metal Pb can enters the body by its remarkable resemblance to Ca, where it participates in various metabolic processes. According to certain research, Pb causes neurotoxic and godanotoxic effects in carp as well as a shift in the nitrogen exchange toward more active catabolism [119,120].

4.1. Nurotoxicity of xenobiotics

When xenobiotics is ingested, the central nervous system experiences cognitive impairment, which lead to neurodegenerative disorders and neurological conditions, such as neurodevelopmental abnormalities. Neurotransmitter balance (serotonin) and synaptic transmission are also altered by xenobiotics poisoning [121]. Several apoptotic processes are induced by arsenic's neurotoxic effects and intracellular calcium upturn. Arsenic and its methylated metabolites promote caspase-induced apoptosis in neural cells through the intrinsic mitochondrial-apoptotic mechanisms and the Mitogen-activated protein kinase (MAPK) signaling pathways, which include the Extracellular signal-Regulated Kinase 2 (ERK2), c-jun N-terminal kinase (JNK) [114].

Xenobiotics has a significant impact on peripheral nervous system (PNS) and central nervous system (CNS) functions [122]. It can cause a variety of clinical symptoms, including peripheral neuropathy, olfactory dysfunction, neurological disorders, learning disabilities, and mental retardation. It can also impair motor function and cause behavioral abnormalities in both adults and children. Xenobiotics such as Cadmium's neurotoxicity results from apoptosis, which causes brain cell death. It has a number of apoptosis-inducing components, such as endocrine disruption, neurogenesis impairment, neuron gene expression suppression, and epigenetic effects [123].

4.2. Nephrotoxicity of xenobiotics

All organs are negatively affected when expose to xenobiotics such as toxic metals, PAHs, CPs, and PCBs, but the kidneys are most affected. Xenobiotics such as Heavy metals induced nephrotoxicity which causes severe phosphaturia, aminoaciduria, Fanconi-like syndrome, and glucosuria [124]. When Cd is exposure to the kidneys, it affects the proximal tubular epithelium, leading to decreased renal tubular phosphate reabsorption, aminoaciduria, 32-microglobulinuria, glucosuria, and a high amount of Cd in urine [125]. Excessive exposure can cause hypercalciuria, renal failure, and renal tubular acidosis [126]. Chronic Pb nephropathy is

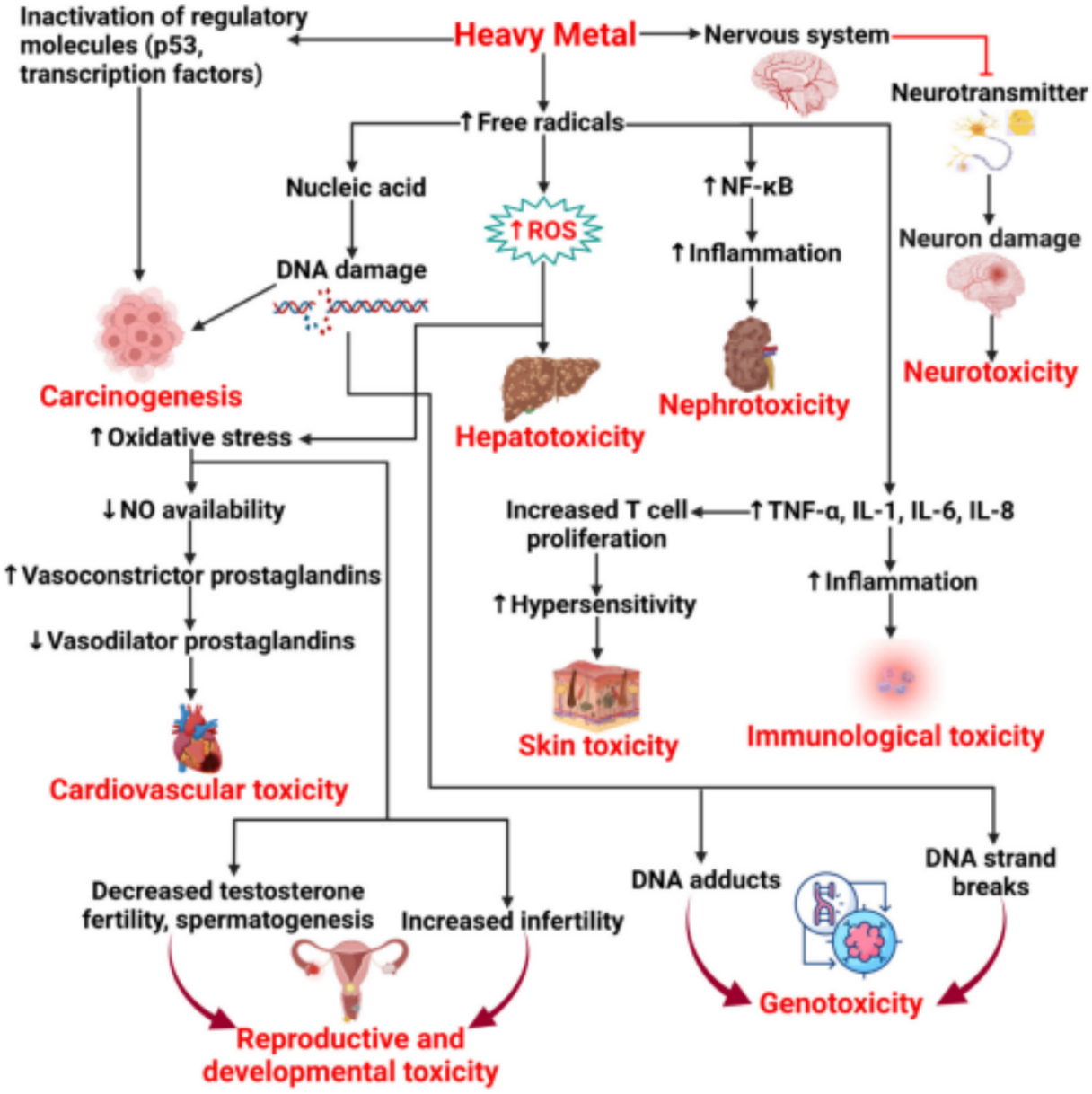

Fig. 3. Mechanism of xenobiotic toxicity in human. Adopted from [114].

characterized by hyperplasia, interstitial fibrosis, tubular atrophy, renal failure, and glomerulonephritis.

Acute Pb nephropathy results in proximal tubular dysfunction and Fanconi-like syndrome. Acute exposure xenobiotics such as Hg in the kidneys, results in acute tubular necrosis and many clinical symptoms, including acute dyspnea, altered mental status, stomach discomfort, excessive salivation, tremors, vomiting, chills, and hypotension. Chronic exposure to Hg damages the necrosis in the proximal tubule's pars recta and the epithelium. Mercury-induced chronic kidney damage manifests as tubular failure, increased excretion of albumin and retinol-binding protein in the urine, and a nephritic state characterized by membranous nephropathy [127].

4.3. Carcinogenicity of xenobiotics

Xenobiotics such as Arsenic causes DNA damage, epigenetic changes, histone modifications, DNA methylation, altered expression of the p53 protein, and decreased expression of p21 [128]. According to Garcia-Esquinas et al. [129], arsenic poisoning slows down the DNA repair process and binds to proteins that bind DNA, increasing the risk of cancer. Lead is a carcinogen that releases reactive oxygen species (ROS) that harm the DNA repair system, cellular tumor-regulating genes, and chromosome structure and sequencing. Reactive oxygen species (ROS), which are produced in large quantities by mercury's peroxidative activity, can promote the formation of malignant cells and protumorigenic signaling. By causing damage to cellular proteins, lipids, and DNA, ROS can aid in the development of cancer [130] (Fig. 7).

4.4. Hepatotoxicity of xenobiotics

Exposure to xenobiotics increases oxidative stress which result in liver damage (Fig. 7). Organic solvents, combined with lead, can cause injury to the liver because some solvent have same characteristics as lead [131]. Long-term exposure to xenobiotics such as heavy metal Pb may be harmful to liver cells, which causes cellular infiltration and glycogen depletion, both of which can contribute to chronic cirrhosis [132]. Cadmium target the renal cortex and the liver [133]. During the acute exposure of Pb, it accumulates in the hepatic tissue that linked to a variety of liver dysfunctions.

Cadmium changes the cellular redox balance which can result in oxidative stress and hepatocellular damage [134]. Both acute and chronic cadmium-induced hepatotoxicity results in liver failure, which raises the risk of cancer [135].

4.5. Immunological toxicity of xenobiotics

Pesticides, aromatic hydrocarbons and heavy metals exposure, both acute and chronic, produces a number of immunological responses, including increased susceptibility to allergies, infectious illnesses, and autoimmunity, as well as cancer [136]. A high risk of lung, stomach, and bladder cancer in several demographic groups has been linked to lead exposure [137]. Lead exposure has been associated with an increased incidence of bladder, stomach, and lung cancer in a number of demographic groups [138]. Lead exposure generate B and T lymphocytes [139].

Xenobiotics like pesticide and toxic metals altered the function of T-cells and raising vulnerability to the emergence of autoimmunity and hypersensitivity, it can affect humoral and cellular responses [140]. The exposure of cadmium at work or in the environment may have immunosuppressive consequences [114]. Numerous immunological abnormalities, such as immunosuppression and immunostimulation, were observed in laboratory experiments with mice and rodents exposed to heavy metals. Laboratory animals injected with mercury chloride that were mercury-insensitive exhibited immunosuppression, or decreased cellular activity in the immune system. The human immune system, however, does not seem to be impacted by mercury, despite Swedish authors' conclusion that amalgam, a mercury alloy, has an effect on the immune system [114].

4.6. Cardiovascular toxicity of xenobiotics

Acute or chronic exposure to xenobiotics causes a number of problems in the human body. Long-term exposure to xenobiotics such as Pb can result in arteriosclerosis and hypertension, thrombosis, atherosclerosis, and heart disease by increasing the oxidative stress (OS), decreasing Nitric oxide (NO) availability, raising vasoconstrictor prostaglandins, changing the renin-angiotensin system, decreasing vasodilator prostaglandins, interfering with vascular smooth muscle Ca^{2+} signaling, making inflammation and endothelium-dependent vasorelaxation worse, and modifying the vascular response to vasoactive agonists, increases arterial pressure [141].

The metal PAHs and Cd are carcinogenic, it induces kidney disease, bone disease, and cardiovascular disease [142]. Chronic kidney disease, myocardial infarction [143], diabetic atherosclerosis, peripheral arterial disease, hypertension [144], stroke, and heart failure [145] are all consequences of xenobiotics exposure. According to prospective research, Cd was associated with a higher risk of cardiovascular death in the US general population [146]. In humans, mercury has been shown to be the cause of neurotoxic, cardiovascular, nephrotoxic, and hepatotoxic [146].

4.7. Skin toxicity of xenobiotics

Prolonged exposure to foreign compound such as arsenic (As) can cause a number of potential skin disorders, such as hyperkeratosis, hyperpigmentation, and various forms of skin cancer. Hyperpigmentation is the most prevalent skin alteration caused by extended As exposure. Arsenic exposure potentially induce Bowen's disease, a type of early skin cancer. The soles and palms are typically affected by As hyperkeratosis, although it can also affect the legs, toes, fingers, arms, and dorsum of the hands. The skin, which is the body's outermost organ, acts as a barrier against many pollutants, and some hyperkeratotic and Bowen's disease lesions can progress to invasive cancers [147]. Mercury and compounds containing mercury are responsible for a number of skin diseases, such as acrodynia (pink disease), a frequent dermatological condition in which exposure to heavy metals, especially mercury, causes the skin to turn pink [148].

Individuals who have tattoos that contain the red pigments mercury sulfide and cadmium sulfide may experience inflammation restricted to specific areas six months following the tattoo. Mercury-containing compounds can induce acute contact dermatitis, which manifests as moderate swelling, scaling, vesiculation, and irritation. Mercury toxicity is the most common cause of dermatological issues, according multiple research [149].

4.8. Reproductive and developmental toxicity of xenobiotics

In experimental animals, xenobiotics like arsenic (As) produces abnormalities, including neural tube malformations, which is a known reproductive toxin in humans [150]. Arsenic decreasing the weight of the testes, accessory sex organs, and sperm in the epididymis, inorganic arsenic hinders male fertility. In addition to influencing sperm production, exposure to inorganic arsenic alters gonadotropin and testosterone levels and disrupts the steroidogenesis process [151]. Consumption of As is linked to a higher risk of endometrial cancer in female. Exposure to As during pregnancy impairs endometrial angiogenesis, which is essential for embryo growth. These problems result in endometriosis symptoms, subfertility, prematurity, sterility, and spontaneous abortions [152].

More than 10 % of women are at risk of infertility due to exposure to heavy metals like Pb, Cd, Hg, and other pollutants, which are the most common environmental contaminants that can cause reproductive disorders, according to several World Health Organization (WHO) studies [153]. Infertility is a problem that mostly affects women more often than males, according to a WHO study. Women's subfertility is often caused by ovulation problems [154]. Reproductive hormones can be used to treat ovulation problems, which are typified by irregular or nonexistent menstrual periods. Increasing amounts of xenobiotics exposure led to chromosomal abnormalities in oocytes, delayed ovulation, and hormone disruption, all of which increased the chance of infertility in women. The most common cause of female infertility at the moment is heavy metal poisoning, which disrupts the endocrine system and exacerbates hormonal imbalances in women [155].

4.9. Genotoxicity of xenobiotics

The genotoxicity of xenobiotics like toxic metal arsenic causes deoxyribonucleic acid (DNA) alteration, including chromosomal abnormalities, mutation, micronuclei production, deletion, and sister chromatid exchange shown in Fig. 3. Genetic factors have been identified as the fundamental source of the significant interindividual variability in receptiveness to arsenic poisoning that has been found in several investigations [156].

The mechanism of arsenic's genotoxic effects, which include the disruption of DNA repair and the production of oxidative stress [157]. Despite its low mutagenicity, arsenic affects the mutagenicity of other carcinogens that is why it is considered a weak mutagen. For instance, exposure to UV radiation has been shown to increase the mutagenicity of arsenic in human cells [158]. Teratogenesis and carcinogenesis are the two main pathways by which the genotoxic effects of chemical compounds on humans alter genetic material. Teratogenesis is when a chemical compound alters genetic material. While the second one shows up as the development of cancers in those who have been directly exposed, the first one may show up in the progeny as congenital malformations (Fig. 3). However, the relationship between mercury exposure and carcinogenesis (one of the most serious outcomes of DNA-induced damage) is still up for debate, as some experiments seem to show that mercury has genotoxic activity, while others have not proven such DNA-damaging effects [159]. Certain mercury compounds, known as teratogenic agents, are particularly harmful to the developing neurological system and have an impact on the development of the central nervous system [160].

5. Treatment options of xenobiotics toxicity from natural sources

5.1. Neurotoxicity treatment

According to an analysis using the polyphenolic extract Euphorbia suppina (PPEES) from a Korean prostrate spurge can effectively reduce

Mn-induced neurotoxicity by antioxidants by modulating endoplasmic reticule (ER) stress and ER stress-mediated apoptosis. Research has indicated that curcumin and arsenic may significantly mitigate the oxidative stress and dopaminergic alterations caused by arsenic in the brain of rats. Curcumin has also been shown in another study by Yousef et al. [161] to protect rats' brains and livers against metabolic alterations caused by carcinogens [162]. Another study examines the neuro-protective effect of curcumin against arsenic-induced changes in biogenic amines, their metabolites, and NO levels in rats, given the importance of the behavioral and neurochemical functions of brain biogenic amines and NOs [163] (Fig. 4).

Long-term supplementation with almond and walnut supplies essential nutrients that can overcome dietary deficiencies and reduce heavy-metal intoxication, according to current study [164]. Curcumin has antidepressant, anti-inflammatory, and antioxidant properties [162]. Furthermore, curcumin has improved the fly's nitric oxide level accumulation and restored outbreak rates and cellular antioxidant state. According to survival rates, durability testing, and antioxidant status restoration, curcumin has improved the flies' oxidative damage [165]. Additionally, copper-induced neurotoxicity can be treated with apigenin [166].

5.2. Nephrotoxicity treatment

Chronic cadmium toxicity (Cd) is acquired by oral Cd administration and causes serious kidney damage. Curcumin pretreatment has improved the histologic modifications caused by Cd, and curcumin has a significant protective effect against nephrotoxicity caused by Cd. [167]. Protocatechuic acid treatment improved overall protein levels in cadmium-induced toxicity [168] as shown in Fig. 4. A study shows that silymarin and dimercaptosuccinic acid lower blood lead levels and offer protection against genotoxic effects [169]. Spirulina platensis, eugenol, extra virgin olive oil, and simvastatin are commonly used to eliminate chromium-induced nephrotoxicity; it also significantly reduces pathological changes in the kidneys both before and after mercury treatment. In addition, diallyl sulfide, curcumin, zinc sulfate, and silymarin can eliminate thallium-induced nephrotoxicity [170].

5.3. Carcinogenicity treatment

Treatment with *Rosmarinus officinalis* extract, shows that the levels of lipid peroxidation and lead-mediated hepatic and renal damage products were significantly reduced. Blood cells from *Rosmarinus officinalis* still contain renal and hepatic cells [171]. According to Liu et al. [172], quercetin prevents nickel-induced hepatic dysfunction, increases the histology changes in the liver of nickel, lowers the expression of inflammatory markers in the livers of mice exposed to nickel, lowers the DNA methylation in the livers of rats exposed to nickel, and lessens carcinogenicity. Another option for treating nickel-induced carcinogenicity is metformin [173].

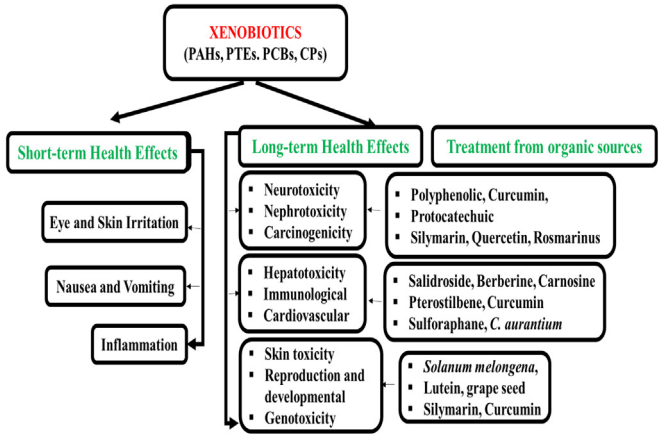

Fig. 4. Long term health effect xenobiotic treatment.

5.4. Hepatotoxicity treatment

Salidroside (SDS) exhibits pronounced antioxidant activity and can improve liver tissue structure by lowering oxidative stress and increasing antioxidant stress activity, hence treating lead acetate-induced liver damage. Lead-induced hepatotoxicity can be eradicated using this method [174]. Additionally, it was found that berberine increases serum albumin, which lessens the hepatotoxicity caused by lead [175]. Additionally, carnosine, curcumin, and thymoquinone drastically decreased the histological and hepatological problems associated with lead. Selenium (Se) was discovered to be an effective chemoprotectant of Cd in a study. Selenium treatment has been demonstrated to lower hepatocyte death and morphological alterations brought on by Cd. Concurrently, Se enhanced reduced glutathione (GSH) levels, boosted selenoenzyme (glutathione peroxidase, GPX) activity, and lowered ROS formation, all of which contributed to the reduction of Cd-induced oxidative stress. It was found that Se may prevent hepatotoxicity caused by Cd by blocking the ER stress response [176].

Rats were divided into six groups and given 20 mg/kg body weight of nickel sulfate in normal saline before being fed with *M. oleifera* for 21 days in order to examine the effect of *M. oleifera*-based diets on nickel (Ni)-induced hepatotoxicity. Within twenty-four hours of the last treatment, all of the animals were sacrificed. After being exposed to nickel, rat plasma's levels of alkaline phosphatase, aspartate transaminase, and alanine transaminase increased significantly. Ni decreased levels of high-density lipoprotein cholesterol while raising levels of triglycerides, total cholesterol, and low-density lipoprotein cholesterol. Ni exposure decreased glutathione levels while raising malondialdehyde in rat plasma.

According to the histopathology results, exposure to Ni caused cellular damage and inflammation. Diets based on *M. oleifera* have been demonstrated to shield rats from Ni-induced hepatotoxicity by improving lipid profiles, liver function markers, and cellular integrity and architecture [114].

5.5. Immunological toxicity treatment

The naturally occurring substance pterostilbene (PT) is primarily present in blueberries. Studies have demonstrated that PT is a potent antioxidant and anti-inflammatory. The administration of PT to the mouse significantly decreased the intensity of the skin reactions in the epicutaneous elicitation test. Furthermore, PT therapy decreased apoptosis and inflammation in HaCaT cells in vitro. Myo-inositol shields mice from Cd-induced thyroid damage when combined with Se [177].

Another study assessed the anti-asthmatic effects of curcumin (diferuloylmethane), a naturally occurring compound obtained from the rhizomes of *Curcuma longa*, using a guinea pig model of airway hyperresponsiveness. In order to determine whether curcumin could prevent airway blockage, it was administered to guinea pigs either during sensitization or after they experienced signs of airway obstruction. The results showed that curcumin (20 mg/kg body weight) significantly reduces OVA-induced airway constriction ($p = 0.0399$) and airway hyper reactivity ($p = 0.0043$). Specific airway conductance (SGaw) was measured using a non-invasive technique called constant-volume body plethysmog raphy to detect the status of airway constriction and hyper reactivity. Curcumin is helpful in correcting defective airway characteristics in OVA-sensitized guinea pigs [178].

5.6. Cardiovascular toxicity treatment

Cadmium and mercury are extremely dangerous substances that can cause major cardiac issues in both humans and animals. Positive results for heart damage were found in a study that examined the therapeutic effect of vitamin C against metals in rabbits [179]. In a different study, rats fed with *C. aurantium* peel extract (300 mg/kg) significantly decreased the histological and biochemical changes found in their hearts following exposure to $K_2Cr_2O_7$. They found that *C. aurantium* peel extract prevented cardiac damage caused by $K_2Cr_2O_7$ due to its antioxidant activity [180].

According to a recent study, sulforaphane (SFN) decreased the effects of $K_2Cr_2O_7$ on oxidative stress, hematological alterations, structural disorders, cardiomyocyte apoptosis, and heart dysfunction.

5.7. Skin toxicity treatment

A study examined the potential benefits of *Solanum melongena* peel extract for treating arsenic-induced Bowen's disease. Eight patients with arsenic-induced Bowen's disease were selected from the two arsenic-endemic sites, and each patient received an ointment containing peel extract, which they were instructed to apply twice daily on the lesion site for a duration of 12 weeks. Notable progress was noted in reducing the Bowen's disease lesion [181].

In a different study, two male patients with chronic chromium contact sensitivity were treated with photodynamic tultraviolet A (PUVA) therapy. One patient who was simultaneously photosensitive responded quite well; his light tolerance increased and his skin problems cleared entirely. This was followed by a decrease in photopatch test reactivity and the extinction of patch-test reactivity on PUVA-exposed (pigmented) skin. PUVA therapy increased lymphocyte activation and decreased rosette-forming T cells in both cases [182].

5.8. Reproductive and developmental toxicity treatment

A recent study showed the value of grape seed *proanthocyanidin* extract, which activated Nrf2 signaling to reverse arsenic-induced reproductive toxicity and decreased oxidative stress damage in mice testis [183]. Another investigation examined the effect of lutein on reproductive damage caused by arsenic. In male mice, the results showed that lutein decreases reproductive toxicity caused by arsenic through Nrf2 signaling. This suggests a potential mechanism for lutein to prevent reproductive harm and clarifies that consuming plant sources high in lutein can lessen reproductive toxicity caused by chemicals [184].

Anthocyanin Purple sweet potato (APSP) also aids in the reduction of enzymatic and non-enzymatic antioxidants caused by lead. The effects of APSP could be reversed by Pb. Finally, APSP may be a useful therapeutic treatment for preventing Pb-induced reproductive harm due to its anti-apoptotic and antioxidant properties as well as its control of the JNK signaling system [185].

5.9. Genotoxicity treatment

Arsenic is a well-known genotoxicant that damages cells by activating oxidatively sensitive signaling pathways, producing an excess of reactive oxygen species (ROS), and inhibiting antioxidant enzyme systems. Epigallocatechin gallate (EGCG), the main polyphenolic catechin in green tea, has demonstrated strong genoprotective, free radical scavenging, and antioxidant properties in vivo. Researchers investigated whether curcumin nanoformulations, as opposed to free curcumin, might offer superior protection against arsenic-induced genotoxicity. The data imply that nanoformulations had a better protective benefit than free curcumin [186].

Silymarin and dimercapto succinic acid (DMSA), a chelating agent, were tested for their ability to prevent lead (Pb) poisoning in rats, either separately or in combination. The blood lead levels (BLLs) significantly increased after being exposed to lead acetate. Following the administration of DMSA and silymarin, BLLs decreased. It was discovered that silymarin and DMSA provided a respectable level of protection against the genotoxic effects of lead [169].

6. Bioavailability and bioaccumulation of xenobiotic in food

Many aquatic fish species are endanger by heavy metal pollution, and fish that are continuously exposed to these harmful metals, directly takeup this metals from there environment. The intake or consuption of polluted fish increases risk to human health concurrently. Accumulation of heavy metals from foods like fish can occur when they are consumed over an extended period of time, which can harm human health [93] (Fig. 5).

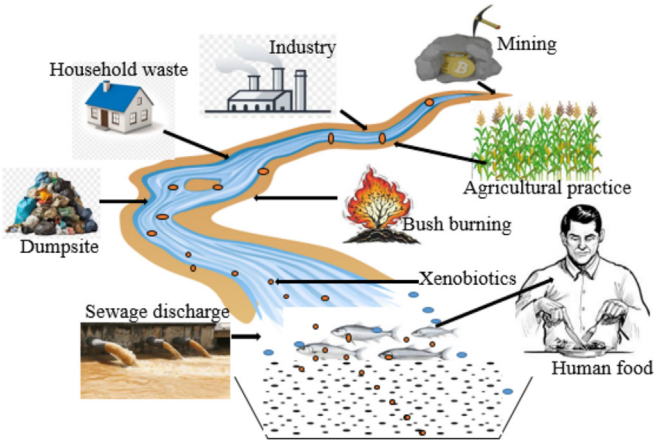

Fig. 5. Bioavailability of xenobiotics in food webs.

According to Liu et al. [187], fish accumulate toxic metals through food intakes and the incorporation of sediment particles. The Bioaccumulation shows the rate of element concentration between fish and its environment (water and sediment). In the environment, important components and trace elements are move from abiotic to organism, which is then accumulate in the biota. (Fig. 5). Organisms with high trophic levels are susceptible to biomagnification in the food chain. High concentrations of toxic elements in organism with high trophic levels can put organisms in danger due to bioamplification.

Salinity, temperature, redox conditions, bacteria, phytoplankton, and other factors that can influence the form of chemical compounds [188]. The bioaccumulation of heavy metals by freshwater fish is a serious ecological, environmental, and social problem. Species that are exposed to toxic metals build up higher levels of these metals, which in turn causes bioaccumulation. The bioaccumulation of HMs is influenced by fish characteristics such as sex, feeding habits, size, reproductive cycle, and swimming patterns. Environmental factors also influences the accumulation of toxic metals like the bioavailability and concentration in water columns, physicochemical properties of water [20].

6.1. Biomonitoring and risk assessment of xenobiotics

Accumulation of xenobiotics in animals and plants are mostly utilized for xenobiotic biomonitoring. Biomonitoring captured the results of all exposures, no matter the route [189]. Due to the lipophilic properties, xenobiotics can accumulate in the food chain. Frequent ingestion of fish that have accumulated pollutants, such as xenobiotics, can be harmful to human health. Fish oxidize and further convert xenobiotics like PAHs to water-soluble compounds that are excreted by the living organism, the average concentration of xenobiotics in fish muscles is lower. The risk assessment method is used to analyze the potential impacts of pollutants on biological systems.

Health risk assessments are frequently carried out to evaluate humans total exposure to these pollutants in a specific area [190]. Risk assessments usually considered the possible consequences of pollutants on humans, whether they are carcinogenic or not. The four steps involved in the assessment of risk are exposure measurement, toxicity (dose–response) computation, hazard identification, and risk description. Different researcher have assessed the dangers of eating infected fish using different methodologies [191–193].

7. Bioremediation of xenobiotics

Bioremediation is an effective method for the removal of organic pollutants, such as volatile organic compounds (VOCs), PCBs, PAHs, and CPs.

Bioremediation consists the use of microorganisms (bacteria and fungi) to convert toxic contaminants to friendly substances as a result of the microbial activity from biochemical processes. Bacteria, algae, and fungi are microorganisms that can be used alone or in combination to remediate xenobiotic-contaminated sites. Nevertheless, careful thought and research must be put into the process of making decisions regarding the effective cleanup of specific contaminated site, as developed technology offers benefits and drawbacks when it comes to treating various pollutants. Two novel technologies that have the potential to address many environmental pollution issues are bioremediation and phytore mediation in conjunction with microbes.

7.1. Fungal bioremediation

The potential uses of fungi's non-specific oxidative enzymes have drawn scientific attention to them as bioremediation agents. However, some non-white-rot fungi, mostly belonging to the phylums Ascomycota and Zygomycota, have demonstrated potential in the enzymatic breakdown of pollutants found in the environment. As a result, they have been able to overcome certain of the restrictions associated with white-rot fungus, including their inability to grow in pH level that is neutral, their opposition to unfavorable environments, their inability to outcompete naturally occurring microbes. Though these fungi are found in a wide variety of soil and water environment, their enzymatic processess is not fully known and degradation routes that these microorganisms use to change hydrocarbons. In their evaluation of the bioremediation process of non-ligninolytic fungus potential for xenobiotics such as PAHs, PTEs and chlorinated hydrocarbons, Marco-Urrea et al. [194].

7.2. Microbial bioremediation

The bacterial laccase from *Escherichia coli* and *Bacillus subtilis* can oxidize xenobiotics; however, the process are limited due to low oxidation rate and copper dependence. Sediment samples shows that 53 strains of bacteria that break down PAHs were found. A common technique in bioremediation is microbial degradation; Materials that are inexpensive and natural can serve as supporting matrices to increase the process' effectiveness. PAH adsorbents are clay and clay-modified minerals, which are also easily accessible natural soil and sediment provide microorganisms with a substrate and habitat.

Critical research is necessary because the process underlying Clay's ability to biodegrade organic compounds is sometimes unclear. Numerous biodegradation studies have focused on the survival of isolated bacteria in an attempt to increase the bacterial population and, consequently, the biodegradation effectiveness of PAHs. Study has also been done on reinoculating isolated bacteria to improve their performance [195].

7.3. Phytoremediation of xenobiotics

Green technologies that use biological energy and involve plants (phytoremediation) and microorganisms (bioremediation) have become more prevalent in recent years. Phytoremediation has been the subject of much research, with many presenting this technology as the ideal procedure combining environmental acceptability, low cost, and efficiency [196]. The application of soil microbes and plants to mitigate the harmful effects of persistent agricultural pollutants (PAHs) on the environment is known as phytoremediation. A new technique for removing locations contaminated with dangerous chemicals is called phytoremediation. Phytoremediation is a type of method that uses rhizosphere biodegradation, phytoextraction, and phytodegradation to completely eradicate organic polluting elements from contaminated environments. The benefits of phytoremediation include resource reuse, reduced environmental disturbance, and comparatively cheaper costs.

PAHs from soils are dissipated in soils where grasses and legumes are present, despite the lack of data supporting the idea that PAHs from soils are significantly accumulated in plant. Specifically, Microbial degradation in the rhizosphere in which microbes in the soil communities consume organic materials as carbon-based growth substrates is the main mechanism controlling this process. Usually, the exudates from the roots induce this. The breakdown and complete mineralization of the pollutants is the process's ultimate outcome. Carbon dioxide and sunshine are the carbon and energy sources that plants use. Plants have developed some amazing detoxifying processes in response to the harmful substances that they acquire from the environment and from us.

Thus, the idea of phytoremediation was furthered by the employment of plants to clean up contaminated soils. The kind of plant was thought to have a major impact on how effective phytoremediation was. It has been shown that phytoremediation is an effective remediation method for soils contaminated with petroleum pollutants. The challenge of managing soil that has been contaminated by persistent organic pollutants (POP) is becoming more pressing due to legal limitations and the significant influence of human activity on soil resources. Treatments that completely eliminate the harmful chemicals being targeted are the most often utilized management strategies. Environmentally friendly procedures should be employed wherever possible. In recent years, green technologies utilizing biological energy involving the emerged of phytoremediation and bioremediation (Plant and microorganism).

Phytoremediation has been the subject of much research, with many presenting this approach as the ideal combination of cheap cost, environmental acceptability, and efficiency. Nevertheless, the effectiveness of phytoremediation has not yet shown itself to be as great when applied to soils contaminated by organic chemicals that are bio recalcitrant, like PAH. Microbial activity is assumed to be the process causing the phytoremediation of polluted soil. The potential of soil to digest toxins and the population levels of bacteria that break down contaminants usually increase during phytoremediation, so lending support to this theory [197].

7.4. Biosufactant bioremediation

Bacteria that grow on alkane generate biosurfactants. Molecules resembling detergents, biosurfactants have a lipophilic tail and a hydrophilic head. They aid in the breakdown of PAHs. For instance, it has been demonstrated that the biosurfactant generated by *Pseudomonas aeruginosa* that grows on naphthalene or phenanthrene increases the solubility of these PAHs in their apparent form. It has been demonstrated that naturally occurring surfactants improve PAH solubilization, which in turn increases PAH-microbe interactions and facilitates the soil removal of PAHs. Decontaminating soil with PAHs has become commonplace with the use of surfactant-enhanced remediation (SER). For cleaning up soil, surfactant aided remediation is a potent technique. Nevertheless, this technology has been hindered by some issues, including cost and the secondary contamination [198].

7.5. Rhizoremediation

The bioavailability of PAHs has increase due to a wide range of recent advances, including enhanced surfactant utilization, rhizoremediation, and electrobioremediation. Breakdown and removal of xenobiotics are greatly aided by the makeup of the fungi and bacterial communities in rhizosphere. Rhizozoidal microorganisms have been shown to preferentially boost the population of bacteria in the rhizosphere that degrades PAHs, hence offering intriguing prospects for bioremediation of soils contaminated with PAHs and high levels of root mucilage when combined with other strategies [199]. The bioremediation industry and the environment would both benefit from the incorporation of different methods (such rhizomisation) into workable remediation processes.

7.6. Electroremediation

This method uses an electric current to encourage the migration of pollutants and is mostly utilized for heavy metal extraction. These days, using this method by itself or in conjunction with other methods like Fenton or

bioremediation is producing excellent results for the removal of PAHs [200]. Though research on using an electric field to decontaminate soil with PAHs is still in its early stages, numerous studies have shown how effective the treatment is. They discussed the fundamentals of conducting electroremediation on soils contaminated with PAHs, and various options to enhance PAH electroremediation and novel approaches to PAH removal through the use of hybrid technologies.

8. Biodegradations of xenobiotics

Many microorganisms such as fungi, bacteria, or algae, can biodegrade xenobiotics. Both immobilized (IC) and free (FC) cells have the ability to biodegrade PAHs and other xenobiotics. The biodegradation of xenobiotics by microorganisms has been extensively reviewed, and there is evidence supporting the biodegradation of xenobiotics such as PAHs. In comparison to large molecular weight molecules, low molecular weight PAHs degrade more readily. According to Thomas et al., [201], microbial degradation is a viable technique for soil remediation when it comes to PAHs, which regularly pollute certain post-industrial sites. Biodegradation is a methods for cleaning and removing toxins from the environment.

8.1. Bacteria biodegradation

Numerous strains of bacterial from various classess breakdown xenobiotics such as PAHs. Bacteria species from soil or sediments are use to to breakdown contaminants. A starins of bacterial such as burkholderia, sphingomonas, pseudomonas, mycobacterium, sphingomonads, sphingobium, *burkholderia fungorum* [202], novosphingobium, and sphingopyxis have been found to be the main players in PAHs and xenobiotics breakdown in soil.

8.2. Fungi biodegradation

Studies on fungi's breakdown of xenobiotics such as PAHs are not mostly use than bacteria's breakdown. The benefit of fungal exoenzymes is that they can spread to the extremely mobile HMW-PAHs. Xenobiotics are oxidized by a wide variety of nonligninolytic and ligninolytic fungus. Laccases, Mn-dependent peroxidase, and lignin peroxidases are the mechanisms by which lignin is extracellularly oxidized by ligninolytic fungus. These enzymes oxidize a broad range of organic molecules because they are non-specific.

8.3. Algae biodegradation

In the last few years, there has been a vigorous push toward the intensive study of lignolytic fungi's role in microbiological degradation. A fresh water microalge called *Selenastrum capricornutum* [203] is utilized to break down xenobiotics like PAHs. Naphthalene is breaken down by prokaryotic and eukaryotic marine algae (cyanobacteria, green algae, and diatoms), into smaller metabolites. The BaP was nearly entirely broken down into dihydrodiols by green algae. Higher level of xenobiotics such as PAHs are also phytotoxic to algae, as *S. costatum* and Nitzschia sp. accumulate and break both fluoranthene and phenanthrene at the same time.

8.4. Enzyme biodegradation

Dehydrogenase, lignolytic enzymes, and oxygenase are the enzymes that break down xenobiotics. Manganese peroxidase, laccase, and lignin peroxidase are examples of fungal lignolytic enzymes. They are extracellular and catalyze the oxidation process that generates radicals, which destabilizes bonds within molecules. Both aerobic and anaerobic environments have been shown to support the biodegradation of xenobiotics, and preparation of soil that is contaminated with chemicals or physical means can accelerate this process. The bioavailability of xenobiotic such as PAHs and the metabolic of the bacterial can both be increased by the addition of light oils and biosurfactant-producing bacteria.

8.5. Photodegradation

Photodegradation of low molecular weight xenobiotics such as PAHs is known to occur when they absorb photons. At wavelengths that are relevant to the atmosphere, Grossman et al. [204] measured the photolysis kinetics of the PAHs pyrene and anthracene in water, a variety of organic solvents, and miscible and phase-separated aqueous-organic mixtures. Their findings imply that even in the absence of photon absorption, organic matter may have a significant impact on the photochemical property of xenobiotics in aerosols.

9. Fate of xenobiotics

9.1. Xenobiotics in aquatic ecosystems

When xenobiotic (heavy metals, PAHs, PCB, and CP) entered the aquatic environment, they are distributed between the water phase and bottom sediments. Several processes like sorption, dissolution, or precipitation as well as variables like temperature, pH, mixing of water masses, and the concentration of dissolved oxygen in water all affect their fate [205]. Higher pH results in the precipitation of metals and their adsorption on the surface of sediments, whereas lower pH and greater temperature promote the release of xenobiotics into the aquatic environment.

When it comes to the type of xenobiotics present in the environment, the physiocochemical factor are highly significant. For instance, most heavy metal hydroxide precipitates are hardly soluble at normal water pH levels; yet, these complexes dissolve at lower pH values. Furthermore, the pace at which pollutants are released into the surrounding waters is influenced by the amount of dissolved oxygen, which in turn influences the rate at which organic matter oxidizes [206].

The amounts of dissolved oxygen and sulfide have a major impact on the formation of precipitates. Only a small portion of free metal ions are dissolved in water due to the processes of adsorption, hydrolysis, and coprecipitation that occur in aquatic environments; the remainder is deposited in sediments. The multiple component interactions that occur between the organic ligand, the metal, and the other components of the system at the absorbing surface have a significant impact on adsorption.

9.2. Xenobiotics in air

Xenobiotics are dangerous organic molecules that enter the environment as byproducts of incomplete combustion. Airborne PAH emissions can come from burning refuse, industrial processes (like the production of coke), vehicle emissions, and heat and power generation (like the use of coal, gas, wood, oil, and charcoal) [207].

Emissions from cooking, smoking, incense, mosquito coils, and materials containing pesticides and PAHs (petroleum products and synthetic fuels), can expose humans to airborne levels of PAHs, PCBs, and CP [208,209]. Road dusts are regarded as a significant source of polycyclic aromatic compounds (PACs) pollution for urban populations and in other environmental compartments. Street dust serves as a gauge for the level of PAH pollution in urban areas. For most people worldwide, burning solid fuels exposes people to PAHs, which is a serious public health concern. However, knowledge about exposures at the individual level is still lacking. One significant cause of indoors ambient PAH exposure is air pollution from using indoor stoves [70,209–211].

In metropolitan areas, traffic from vehicles is a major source of air pollution, like PAHs, PCBs, CP, and PTEs. In contrast to non-commuters, it is unclear how much different commuting behaviors contribute to air pollution and whether there are real differences in air pollution exposure depending on the method of transportation [212]. Another source of PAH emissions in urban areas is parking garages. Major sources of PAHs include road/street dust, carpet dust, and kitchen smoke [77]. According to Parnis et al. [213], atmospheric organic pollutants, or PAHs, are found in the air and are usually monitored using active or passive air samplers.

9.3. Xenobiotics in water

Xenobiotic which are main categories of man-made environmental contaminants, were found in the waters. The prevailing presence of congeners in PAHs indicates fuel oil and its combustion byproducts, in addition to other pyrogenic sources, were the major sources of xenobiotics. Diesel engines accounted for the majority of the vehicle emissions.

9.4. Xenobiotics in soil and sediment

The environment in both established and emerging nations are always under pressure to reduce pollution due to the increased levels of pollutants released from different sources, including garbage, human and industryactivity. Human activities have been closely associated with xenobiotics in the environment, which have been extensively researched for their geochemical significance as markers.

In the coastal sediments, riverine inputs are the main sources of xenobiotics, and soil has been found to be the main source of xenobiotics in the United Kingdom. Waste from industries, and household finds its way to the water bodies and the contaminants end up in soil sediment beds, suspended in water, or dissolved [214].

9.5. Xenobiotics in sewage sludge

Due to overpopulation and increasing industrialization, waste sewage sludge from homes and industries sources have recently increase. Farmland are also frequently irrigated with the waste water, and applying sewage sludge is a popular technique to enhance the qualities of the soil. However, waste water and sewage sludge may contain contaminants, such as PTEs, PCBs, CPs, and PAHs. The use of sew age sludge for soil restoration and fertilization is significantly limited by the presence of pollutants. The presence of petroleum-associated hydrocarbons (PAHs) in sewage sludge varies greatly according on the amount of industrial effluent that is added. Wastewater sewage sludge may contain pollutants, including PAHs. It was enacted to discourage its application in agriculture and to control its usage in order to prevent negative impacts on the land, plants, animals, and people [215].

9.6. Xenobiotics in food

Consumption of food is a major pathway that environmental pollutants like PCBs, CP, PTEs, and PAHs can enter the human body. Dietary consumption is one of the main ways that xenobiotics are exposed to humans, and it occurs often. When fish or marine life inhabit contaminated water, or when crops or plants are cultivated in contaminated soil, xenobiotics can enter the food chain through food preparation or processing methods. The main way that humans are exposed to xenobiotics is through their diet [5]. Toxicants in the air, soil, or water, as well as those used in food preparation and cooking, can contaminate food.

Xenobiotics in food, may cause serious health risk especially to humans. Many different kinds of raw food contain them at measurable quantities, which is a reflection of their existence in the environment. Furthermore, cooking can release PAHs into food. In addition, raw food processing and curing can produce PAHs before it is cooked. Dietary exposure to xenobiotics is the primary cause of human exposure.

Meat are the main dietary sources of PTEs, with the exception of areas where meat cooked over an open flame is highly consumed. Due to their widespread use, cereals and cereal products have been found to be a significant source of PCB, CP, and PAH ingestion. Toxic elements concentrations are typically higher on the outside of the plant (outside leaves, peel) than they are inside the plant. Fish and seafood may be subjected to xenobiotics found in water and sediments as a result of oil spills or air pollution.

These compounds are produced by fat dripping onto hot coals or flames, even if they are not in direct contact. These compounds are then transported back onto the food's surface. It has been demonstrated that the amount of meat fat, the cooking time, and temperature employed all affect generation of PAHs when charcoal grilling.

There is a noticeable decrease in the amount of PAHs that contaminate food when cooking at low temperatures for long periods of time, choosing lean meat and fish wherever possible, and avoid food with smoke while grilling or barbecuing. Most of the time, it is determined that the main way that humans are exposed to toxicants is through their diet. Diet is a significant source of exposure to xenobiotics, according to more current biomonitoring techniques designed to evaluate human exposure to toxicants.

9.7. Xenobiotics in coal and petroleum products

Assessment of coal and its combustion leftovers is required due to the continuously increasing energy demand for environmentally sustainable industrial development [7]. When coal is processed, incomplete combustion of organic materials releases a significant amount of PAHs and hazardous metals into the atmosphere [216]. Based on the various levels of decomposition of compounds found in various oil pollutants, petroleum product contamination has negatively impacted the ecosystem.

Antioxidant enzymes act as a defense mechanism against oxidative stress and cells that produce ROS may also produce elevated levels of peroxidases (GPx) shown in Fig. 6. Antioxidant enzymes like glutathione reductase (GPr), catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx) are known to reduce (scavenge) both ROS and lipid peroxides. Cellular components are affected when xenobiotic-induced ROS production exceeds thresholds, which is refer to as oxidative stress. Oxidative stress (OS) occur, when the activities of the antioxidant defense systems decrease, or high production of ROS [217]. Disorders, such as rheumatoid arthritis, motor neuron diseases, diabetes-induced pathologies, Alzheimer's disease, Parkinson's disease, and neuro degeneration, are known to be influenced by oxidative stress (OS) [218].

Antioxidant enzymes activity, such as GPx, GPr, SOD, and CAT, prevents cells from the damaging effects of oxidative stress. The DNA is protected against OS by a variety of antioxidant enzymes, including SOD, CAT, GPx, GPr, and Glutathione S-transferases GST. Organisms can use CAT and SOD to scavenge reactive oxygen species (ROS) in response to oxidative stress, protecting cellular equilibrium.

10. Xenobiotics initiate reactive oxygen species intracellular targets

10.1. Oxidative damage to proteins

Protein oxidation can lead to increased electrical charges, peptide chain fragmentation, aggregation of cross-linked reaction products, and amino acid change. Increases in oxidized proteins may cause loss of several physiological and biochemical because they are more prone to proteolysis. Aging and cataracts are caused by free radical damage to proteins [220].

10.2. Oxidative damage to lipids

In the cell membranes, lipids have a crucial structural and functional role. Membrane lipids can undergo peroxidation after cell death, and certain lipid peroxidation assays may be misinterpreted as a result of this process. Polyunsaturated fatty acids are vulnerable for the ROS attack. The OH• is a significant reactive moiety and initiator for the ROS chain reaction and polyunsaturated lipoperoxidation process. Lipid peroxidation results in the production of a number of chemicals, including isoprostanes, malondialdehyde, and alkanes. These substances have been linked to diseases such as diabetes, heart disease, and neurodegenerative disorders. They are used as markers in the lipid peroxidation test [220].

10.3. Oxidative damage to DNA

Activated oxygen and substances that generate oxygen-free radicals, such as ionizing radiation, encourage DNA damage that results in mutations, deletions, and other lethal genetic effects. Both the base moieties

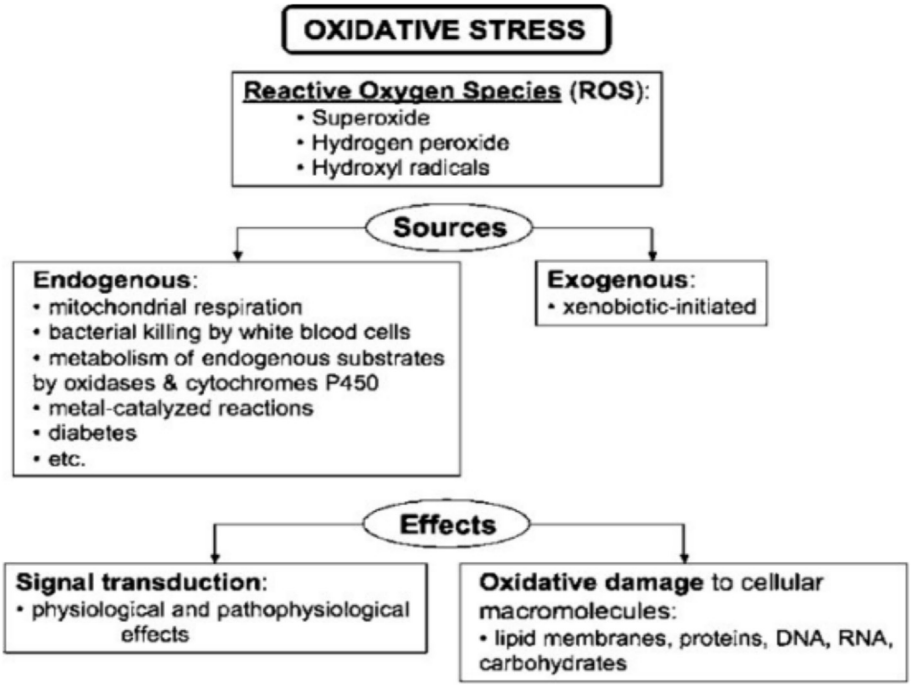

Fig. 6. Sources and effect of ROS [219].

and sugar are vulnerable to oxidation as a result of this DNA damage, which can result in base degradation, single-strand breakage, and cross linkages to proteins. According to Azat Aziz et al. [220], free radical damage to DNA is linked to both accelerated aging and cancer.

10.4. Oxidative damage to carbohydrates

Glycoxidative damage may be caused by the generation of oxygen-free radicals during early glycation of carbohydrates (Fig. 7). The fragmentation of sugar during the initial stages of nonenzymatic glycosylation results in short-chain species such as glycoaldehyde. These species are susceptible to autoxidation due to their short chains, which allows them to generate superoxide radicals. These radicals can then form β-dicarbonyls, which are well-known mutagens. The free radical oxidation processes of carbohydrates and lipids are similar. Low molecular carbohydrates, such glucose, mannitol, and deoxyribose, react with HO• to generate oxidized intermediates, which has no effect on the quality of food [220].

11. Xenobiotics defense mechanism

11.1. Enzymatic antioxidant

Enzymatic antioxidants such as SOD, CAT, GPx, and GSPr can prevent lipid hydroperoxides from damaging tissue and protect erythrocytes from H_2O_2-induced oxidative damage shown in Fig. 8. In addition to their ability to scavenge ROS, these enzymes serve as effective oxidative stress indicators and can be employed as diagnostic and prognostic tools to evaluate the impact of a large number of individual and interactive processes in aquatic organism [221].

Cells contain a large number of antioxidant enzymes which prevent or repair the damage caused by reactive oxygen species (ROS) and to regulate redox-sensitive signaling pathways. The enzymes, such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), are essential to life in all oxygen metabolizing cells [219]. The antioxidant enzyme SODs convert superoxide radical into hydrogen peroxide (H_2O_2) and molecular oxygen, while catalase and peroxidases convert hydrogen peroxide into water. In this process, the hazardous compound hydrogen peroxide and superoxide radical are converted into water which is safe. The enzymatic antioxidants SOD and CAT can operate without co-factors, while GPx needs five isoenzymes in addition to a number of proteins and co-factors to work. Glutathione reductase (GPr) and glucose-6-phosphate dehydrogenase (G-6-PD) in the glutathione system facilitate the GPx's activity but do not directly act on ROS.

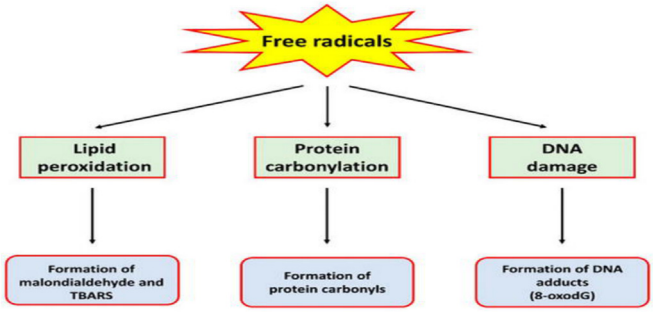

Fig. 7. Detrimental effects of free radicals on biomolecules [220].

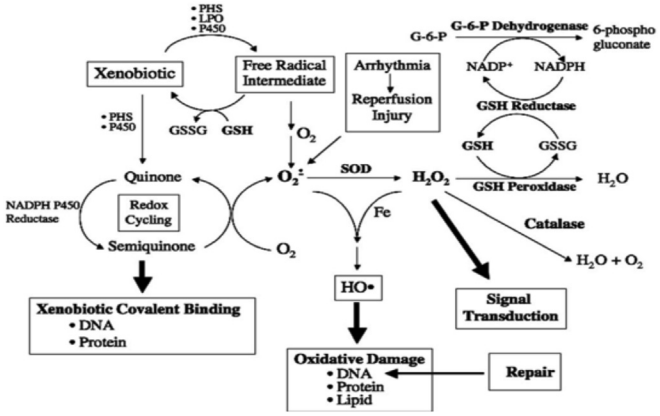

Fig. 8. Biochemical pathways of xenobiotic free radical intermediates [222].

11.1.1. Superoxide dismutase

Superoxide radical is converted by SODs into molecular oxygen and hydrogen peroxide. Activity gels and activity assays are two methods for measuring SOD activity. Nitroblue tetrazolium (NBT) reduction is employed as an indication of O_2 production in the biochemical approach, which uses xanthine-xanthine oxidase to produce O_2. The SOD and NBT will compete for O_2, and the amount of SOD present is indicated by the percent inhibition of NBT reduction. To get rid of the H_2O_2 that SOD produces, catalase is added.

The three highly compartmentalized SOD enzymes are Superoxide dismutase that contains manganese (MnSOD) is found in the mitochondria; superoxide dismutase that contains copper and zinc (CuZnSOD) is found in the cytoplasm and nucleus; and extracellular SOD (ECSOD) is expressed extracellularly in certain tissues. Other compartmentalized antioxidant enzymes include catalase, which is found in cytoplasm and peroxisomes, and GPx, which can be found in many sub-cellular compartments including the nucleus and mitochondria depending on the family member. Thus, the many forms of each of these enzymes reduces oxidative stress in the different parts of the cell.

The CuZnSOD comprises 90 % of total SOD activity in a eukaryotic cell. Besides its primary distribution in the cytosol, a small fraction of this enzyme has been found in cellular organelles such as peroxisomes, nucleus, and the lysosomes. The CuZnSOD (about 2 %) has recently been found to be present in the intermembrane space of mitochondria, and it has been proposed that this localization is crucial for enhancing ROS defense and preventing superoxide radicals from escaping the mitochondria.

Although CuZnSOD and ECSOD both use copper and zinc as catalytic cofactors, ECSOD is the only isoform of SOD that is expressed extracellularly and found in the extracellular matrix of many organs. Cell types and tissues, including the lung, kidney, plasma, lymph, ascites, heart, and cerebrospinal fluid, are highly restricting the ECSOD. Because of its heparin-binding domain, ECSOD, in contrast to other SODs, has affinity for heparin sulfate proteoglycans found in extracellular matrix and on cell surfaces. The binding of ECSOD to cells is mediated by the heparin-binding domain, which makes it significant.

Moreover, CuZnSOD is an unglycosylated homodimer (32 kDa) while ECSOD is a glycosylated high molecular weight homotetramer (155 kDa). The 88 kDa protein MnSOD is present in the mitochondrial matrix and may be induced in eukaryotes by paraquat, radiation, and hyperoxia, indicating that MnSOD induction is crucial for defense against oxidative stress. Furthermore, it has been discovered that many cancer cell types have low MnSOD levels, and that many malignancies' malignant phenotype can be reversed in vitro and in vivo by raising MnSOD levels.

11.1.2. Catalase

Hydrogen peroxide is converted by catalase into oxygen and water. Catalase activity is mainly located in subcellular organelles known as peroxisomes. Targeted delivery of catalase to the liver by galactosylation suppresses hepatic metastasis and decreases matrix metalloproteinase (MMP) activity, while reduces in catalase correlates with carcinogen-initiated emergence of the malignant phenotype in mouse keratinocytes. Catalase also attenuates both the basal and MnSOD-dependent expression of MMPs and collagen deposition [223].

11.1.3. Glutathione peroxidase

Hydrogen peroxide (H_2O_2) is coverted to water (as well as lipids or hydroperoxides to alcohols) by the GPx while Glutathione (GSH) is simultaneously being oxidized to Glutathione disulfide (GSSG) [224]. The liver is a major site of detoxification and also the first target of ingested oxidants and a very crucial organ in the study of the role of GPx in protection from lipid peroxidation. The selenoprotein (cytosolic glutathione peroxidase) was initially identified as an enzyme that protects hemoglobin in red blood cells from oxidative damage. As seen in Fig. 7, in order for GPx to function at high efficiency, it requires several secondary enzymes (glutathione reductase and glucose-6-phosphate dehydrogenase) and cofactors (reduced glutathione, NADPH, and glucose 6-phosphate). As was previously mentioned, there are five GPx isoenzymes, with GPx1 being regarded as a key enzyme in the removal of H_2O_2. This enzyme's overexpression prevents oxidative damage to cells, inhibits H_2O_2-induced apoptosis, and changes the aggressive phenotype of pancreatic cancer.

11.2. Mechanism of enzymatic antioxidant

In mammalian cells, the three main type of intracellular antioxidant enzymes includes catalase (CAT), glutathione peroxidase (GPx), and superoxide dismutase (SOD). The SODs convert superoxide radical ($O_2^{\bullet}$) into hydroperoxides (H_2O_2), while the GPx and CAT convert hydroperoxides H_2O_2 into water (Fig. 9). In this way, the two toxic species $O_2\bullet$ and H_2O_2 are converted into safe product water. When the H_2O_2-removal process is inhibited, then there is direct toxicity resulting from H_2O_2-mediated damage. For the GPx to operate efficiently, it needs a number of secondary enzymes, such as glutathione reductase (GPr) and glucose-6-phosphate dehydrogenase (G-6-PD), as well as cofactors, such as glutathione (GSH), nicotinamide adenine dinucleotide phosphate (NADPH), and glucose-6-phosphate [220].

If GPr is inhibited, cells cannot remove H_2O_2 through the glutathione peroxidase system and which increases the concentrations of glutathione disulfide (GSSG). If glutathione synthesis is inhibited, either by inhibiting γ-glutamyl cysteine synthetase (γ-GCS), or gluthatione synthetase (GS), glutathione will be depleted and GPx will not be able to remove H_2O_2. If CAT is inhibited, cells cannot remove H_2O_2. Finally, if glucose uptake is inhibited creating a chemically induced state of glucose deprivation, hydroperoxide detoxification will also be inhibited (Fig. 9).

The GPx neutralized H_2O_2 through taking hydrogen from two glutathione (GSH) molecules forming two molecules of GSSG and water. The GPr then regenerates GSH from GSSG and CAT which is the essential part of enzymatic defense, neutralizes H_2O_2 into water. By Fenton reaction, H_2O_2 is converted to the extremely reactive $OH^{\bullet}$ and then to water via oxidation of Fe^{2+} to Fe^{3+}. Peroxides are produced during metabolism and then eliminated by GPx and GST. The ratio of GSH/GSSG to oxidized glutathione (GSSG), which is a recognized indicator of oxidative stress, is regulated by GPr. The oxido-redox state of the organism is maintained by the action of GRd, which is crucial in increasing the level of GSH.

The precursor for the generation of ROS is oxygen (O_2). The first electron reduction of O_2 produces the superoxide radical (O_2-). The produced O_2^- is converted into H_2O_2 by the enzyme superoxide dismutase (SOD), and the H_2O_2 are neutralized by the enzyme glutathione peroxidase (GPx) or catalase (CAT). One molecule of reduced glutathione (GSH) is used by the GPx to create oxidized glutathione (GSSH), which is then converted back to GSH by the enzyme glutathione reductase (GR). The GPr uses one molecule of NADPH and NADP + is produced and reduced back to NADPH by the enzyme Glucose-6-phosphate dehydrogenase (G6PD). Glutathione S-transferase (GST) enzyme neutralizes xenobiotics with the help of GSH.

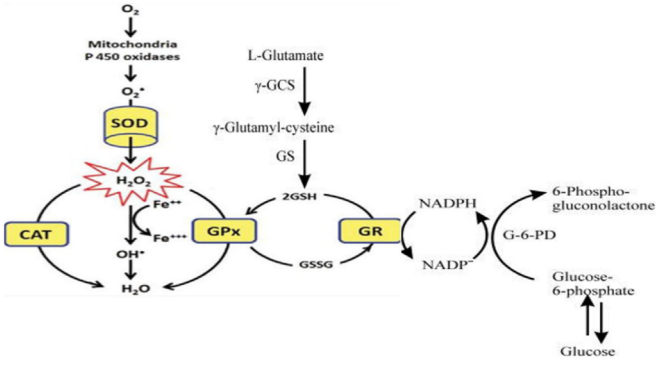

Fig. 9. Mechanism of enzymatic antioxidant. Adopted from [220].

12. Conclusion

The literature indicates the different treatment option from natural sources that can be used to combat the various toxicity cause by xenobiotics and also to breakdown xenobiotics to non-hazardous compound. These processes also remove or reduce pollutant in an eco-friendly manner. They also reduce the carcinogenicity, mutagenicity and teratogenicity of xenobiotics in contaminated soil, water, sludge and food. Bioremediation such as fungal, Microbial, phytoremediation, biosufactant, Rhizoremediation, and electroremediation are effective method for the removal of organic pollutants, such PTEs, PCBs, PAHs, and CPs in the environment. The use of microorganisms (bacteria and fungi) can be used to convert xenobiotic to friendly substances as a result of the microbial activity from biochemical processes. The various biodegradation methods like Bacteria, fungal, algae, enzyme, and photodegradation can be apply in the removal of xenobiotics from the environment. The various biological techniques for the treatment of xenobiotics develop sustainable solutions for pollution, improve drug discovery, and mitigate health risks from environmental contamination.

CRediT authorship contribution statement

Oguh Collins Egwu: Writing – review & editing, Writing – original draft. **John Yisa Adama:** Supervision, Methodology. **Hadiza Lami Muhammad:** Supervision. **Ajai Alexander Ikechukwu:** Supervision. **Famous Ifeanyi Ossamulu:** Writing – review & editing, Supervision. **Makun Hussaini Anthony:** Validation.

Consent for publication

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Ethics approval and consent to participate

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Funder not applicable.

Data availability

We confirm the availability of all the data included in this study.

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