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Review Article *Toxicology*

Molecular and cellular basis of micronutrients as antidotes to environmental toxicity related disorders - Nigeria in focus

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ABSTRACT

The environment is the totality of the living and non-living surroundings of an organism needed for sustainability and life. There are several sources by which the air, water, food, and the whole environment gets polluted, becoming unhealthy for living. Human activities result in the generation of harmful molecules that accumulate in the environment predisposing to adverse human health. There are several contaminants present or released to the environment ranging from persistent organic pollutants, toxic metals, hydrocarbons, pesticides and generally induce oxidative stress from the generation of reactive oxygen species, reactive nitrogen species, and free radicals, damaging DNA, protein and lipid structures of the cell, ultimately resulting in various diseases, especially non-communicable diseases such as cancers and development disorders. A favorable antioxidant status is considered protective of human health, enhancing resistance to disease or improving prognosis through redox and molecular mechanisms. Although therapeutic regimens still occupy pride of place in the global health systems, especially in Africa, advances in science provide compelling evidence of the urgent need to have a better understanding of the antioxidant system and its application in reinforcing human defense mechanisms. A pragmatic approach based on sound scientific principles is to adopt the intake of protective factors modulating host defense mechanisms largely antioxidant systems by employing dietary and/or pharmaceutical agents as chemopreventive or biological interventions (bio-actives). Micronutrients are a diverse group of substances including vitamins and micro-minerals which play a significant role as cofactors and enzymes in signal transduction and genetic signaling. These beneficial bio-molecular effects are exerted through the modulation of several important signaling pathways. Micronutrients include potent non-enzymatic antioxidants such as Vitamin C, Vitamin E, carotenoids, retinoids, thiols, natural flavonoids, among others, and trace elements such as copper, manganese, zinc, selenium, and iron which play a significant role as co-factors for the control of the activity of antioxidant enzymes. Recognition of the potential of prime poly-functional micronutrients is pivotal and should be harnessed in Africa, especially Nigeria, at least in part as a proactive and economical approach to disease prevention and management. This article highlights the serious prevalent environmental pollution in resource-limited nations like Nigeria, due to progressive industrialization and attendant sequelae or consequences, and how they can be mitigated by antioxidants based on their molecular cellular and biochemical activities; thus providing a pragmatic economic and sustainable approach to maintaining the health of the population in Nigeria and in the global population optional.

Keywords: Environmental toxicity, Micronutrients, Antidotes, Human health, Antioxidants

INTRODUCTION

There is currently great concern about environmental pollution and its significant contribution to the global burden of disease; environmental pollution is responsible for one in six deaths worldwide as depicted in [Figure 1].[1] Collective environmental pollution accounts for all-cause mortality than infection currently, giving it a greater priority and cause for concern.

The environment is made up of all of an organism's surrounding elements, both living and non-living, that are necessary for its survival,[2] and it includes air, water, land, plants, animal, and humans living on planet earth and the interactions between one another.[2] The characteristic condition of an environment at a given time, therefore, has a significant effect on the living and non-living components of that particular environment.[2] According to recent reports, environmental pollution accounts for approximately one-third of the disease burden in Africa.[1-3]

Environmental pollution arises largely from the mindless introduction of harmful and foreign substances into the environment, potentially damaging either the environment or human health, by interfering with fundamental molecular and cellular processes owing to natural occurrence and/or human anthropogenic activities, as a consequence of industrialization and restructuring activities. Although globally evident, it is at an increasingly alarming rate in low- and medium-income countries (LMICs) currently.[4] The overall effect is the contamination of the pristine nature of the environment, making it unhealthy and toxic for the habitation of living beings [Figure 2a and b].[5,6] All living organisms, especially humans and animals, are at risk of exposure to environmental pollutants most commonly through inhalation.[4]

There are several sources through which the environment including air, water, soil, food, and others gets polluted. These are derived from anthropogenic activities such as agriculture, metallurgy, energy production, and sewage disposal as well as natural disasters.[7] Some of the key pollutants include organic and inorganic molecules, pesticides, and biological agents including toxins, all of which exert harmful effects on living organisms ultimately at the molecular level. Over time, urbanization, industrialization, and technological development have resulted in the increased release of many toxic substances which are released to the environment daily.[8] These largely go unmitigated and exert their destructive effect at the basic and functional levels by interference with biochemical processes in which micronutrients play key roles as cofactors/coenzymes.

Interest in the role of micronutrients in optimizing health, prevention, and/or treatment of health disorders

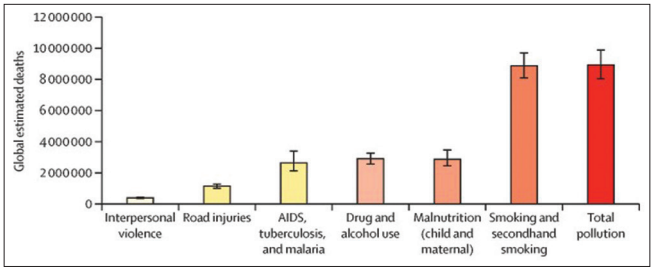

Figure 1: Global estimated deaths by major risk factor or cause, with environmental pollution as the major contributor to number of deaths, even more than major infectious diseases.[1]

Figure 2: (a) Environmental pollution arising from burning of refuse on illegal dumpsite on the road; and smoke emissions from automobiles.[5] (b) Environmental pollution arising from dumping and burning of human waste on the same water used for drinking, fishing, bathing among others.[6]

is fast growing. Micronutrients are a diverse group of nutrients including essential vitamins (organic micronutrients) and trace elements (essential inorganic micronutrients) which are required for intermediary metabolism, regulation of molecular and cellular mechanisms in varying amounts.[9,10] These micronutrients can be obtained from food and food supplements as clearly illustrated in [Figure 3].[11]

They play a significant role in modulating several metabolic and biochemical functions by acting as cofactors/coenzymes, antioxidants, and in genetic control; also in overall human development and well-being, including the regulation of cardiac activity, cellular pH, and bone density among others.[12] This article, therefore, summarizes the extent of environmental toxicity, its related disorders and how micronutrients can serve as antidotes in a developing society such as Nigeria.

Figure 3: Micronutrients food sources. Different food types, fruits, vegetables, seafood, and poultry, among others as rich sources of trace elements and vitamins.[11]

SUMMARY OF ENVIRONMENTAL TOXICITY AND HEALTH-RELATED DISORDERS IN NIGERIA

Nigeria, like most of the LMICs, is rapidly industrializing with increasing use of many types of chemicals and other toxic substances contributing considerably to environmental pollution (air, water, and soil pollution). This is coupled with its share of a high burden of infectious diseases, creating a mixed bag of infectious and non-infectious diseases of equal proportion. Environmental pollution-associated health disorders are also becoming a major concern in Nigeria.[13] Recent reports indicate that the country is ranked as the 10th most polluted country in the world with Kano, a state in the Northern part of the country ranked as the most polluted city in Africa.[13] Sources of environmental pollution in Nigeria include untreated sewage accumulation and open solid waste dumpsites in major cities of the country. Lead poisoning in the Northern part of the country, especially in Zamfara state rated as one of the severe in modern time, large-scale deforestation in South Western states of the country, increased artisanal mining activities, illegal refining, use of leaded petrol, airborne dust, arbitrary discarding and burning of toxic waste, location of production industries in inhabited areas, inadequate environmental legislation, and weak implementation of protective environmental policies, among others. All these have given rise to incomparable contamination and pollution in recent decades.[14] Some of the environmental pollution problems in Nigeria are illustrated in [Figure 4],[2] indicating lead poisoning, water, and air pollution among others in the different regions and states of the country.

Nigeria ranks as the 15th largest producer of crude oil in the world[15] and exploration of the crude oil is associated with well-recognized environmental contamination, especially in the Niger Delta area of the country, and this is a huge source of hydrocarbon pollution in the air [Figure 5a and b].[16] The Nigeria crude oil has been reported to contain relatively high concentrations of toxic metals, including lead (Pb), nickel, chromium, arsenic (As), cadmium (Cd), and vanadium.[17] The toxicity caused by this crude oil pollution has been associated with a wide range of disorders in people, including neurological, renal, and respiratory disease conditions.[18]

In Zamfara State, Nigeria, an epidemic of Pb poisoning from illegal artisanal mining led to the deaths of about 163 persons between March and June 2010, including 111 children <5 years of age.[19] These artisanal mines took very little precautionary measures as depicted in [Figure 6][20] where a young boy sat on a stack of ore sacks in a mining processing site in Bagega village, Zamfara State, Nigeria.

There are also several reports that the level of contamination of farm food crops, agricultural soil, and drinking water by toxic metals, especially in the Northern part of the country and Niger Delta area exceed the World Health Organization/ Food and Agriculture Organization of the United Nations/ European Union permissible limits.[21-23]

Due to the persistent and prevailing epileptic electricity power supply in Nigeria, household generator diesel and petrol emissions are a significant source of air pollution in the country. A recent report estimated that 30% of residences and over 90% of businesses in Africa's most populous country utilize diesel-powered generators, totaling over 15 million units.[24] The increasing incidence of lung cancer in Nigeria among urban non-smoking individuals younger than 60 years of age, the majority of whom use diesel generators regularly appear to provide indirect evidence of the link between diesel emissions and lung cancer.[24] In addition, cases of asthma among adults in Nigeria rose from 5.1% to 7.5% in 2003 to 13.1% to 14.2% in 2006, making Nigeria the country with the second-highest prevalence of asthma in Africa.[25] The possibility of the continued increase in exposure to generator diesel/petrol exhaust cannot be overemphasized.[19] Report from the Health Effects Institute and the Institute for Health Metrics and Evaluation, more than 114,000 people died from air pollution in Nigeria in 2017, the highest figure in Africa.[26]

Recent studies show more evidence of the association between environmental pollution and several severe health conditions, particularly reproductive disorders (e.g., infertility), diabetes mellitus, respiratory disease

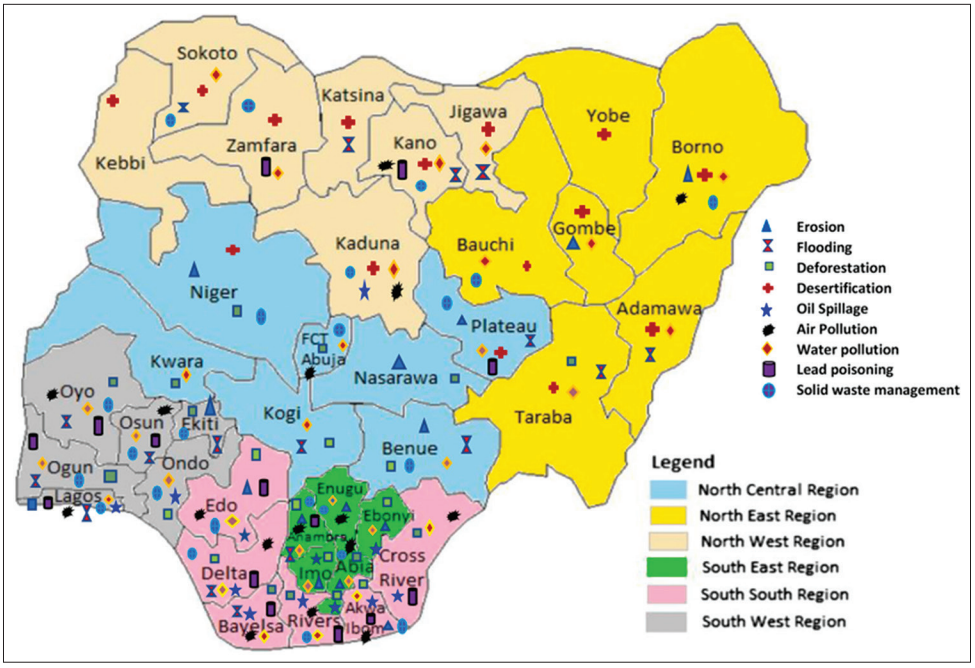

Figure 4: Map of Nigeria showing different locations and environmental problems such as erosions, oil spillage, lead poisoning, water, and air pollution, among others.[2]

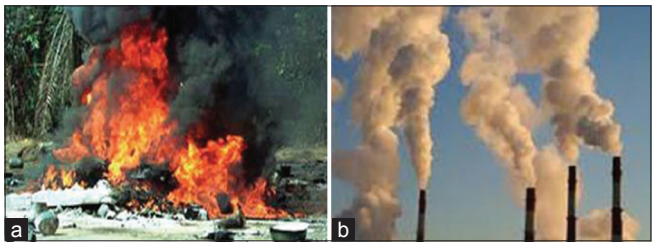

Figure 5: (a) Emissions from fire outbreak following pipeline explosion, commonly due to pipeline vandalization in Nigeria.[16] (b) Cases of gas flare in the Niger delta, resulting in air pollution increases the risk of inhalational toxicity.[16]

Figure 6: A young boy sitting on a stack of ore sacks in mining processing site in Bagega village, Zamfara state, Nigeria.[20]

(emphysema), anemia, bone disease (osteomalacia), impaired cognition, cardiovascular diseases, and breast, testicular, and ovarian cancers among others.[2,27] [Figure 7] shows some of the clinical disorders that could arise from chronic exposure to toxic metal mixtures.[28]

Due to the potential of Cd to bioaccumulate and its half-life of 4–19 years in human bodies, higher levels of Cd in Nigeria's cement dust and clinker constitute a health risk to both factory workers and those in the immediate surroundings.[29] [Figure 8] depicts air pollution from a cement production factory in Nigeria, constituting a health risk (inhalational disorders) to both the factory workers and living beings around the area.[30] Occupational exposure to Cd has been linked with renal tubular dysfunction (hypercalciuria and renal stone production), osteomalacia, and osteoporosis.[31] Despite these weighty reports and evidence, Nigeria has paid little to no attention to the mercury (Hg) content of cement dust among others, which has the tendency to bioaccumulate and exposes workers in cement factories to the development of crippling neurodegenerative diseases such as Alzheimer's disease and Autism.[31]

In 2010, a lingering lead poisoning episode claimed the lives of more than 400 children in Zamfara State, Nigeria.[32] A community survey in Jos, Nigeria, revealed that 70% of toddlers aged 6–35 months had blood lead contents of 10 mg/dL or above, which is more than the safe limits proposed by the Centers for Disease Control and Prevention.[33] Exposure to lead is associated with sterility (through damage to the germinal epithelium and spermatocytes), renal impairment, dental caries,

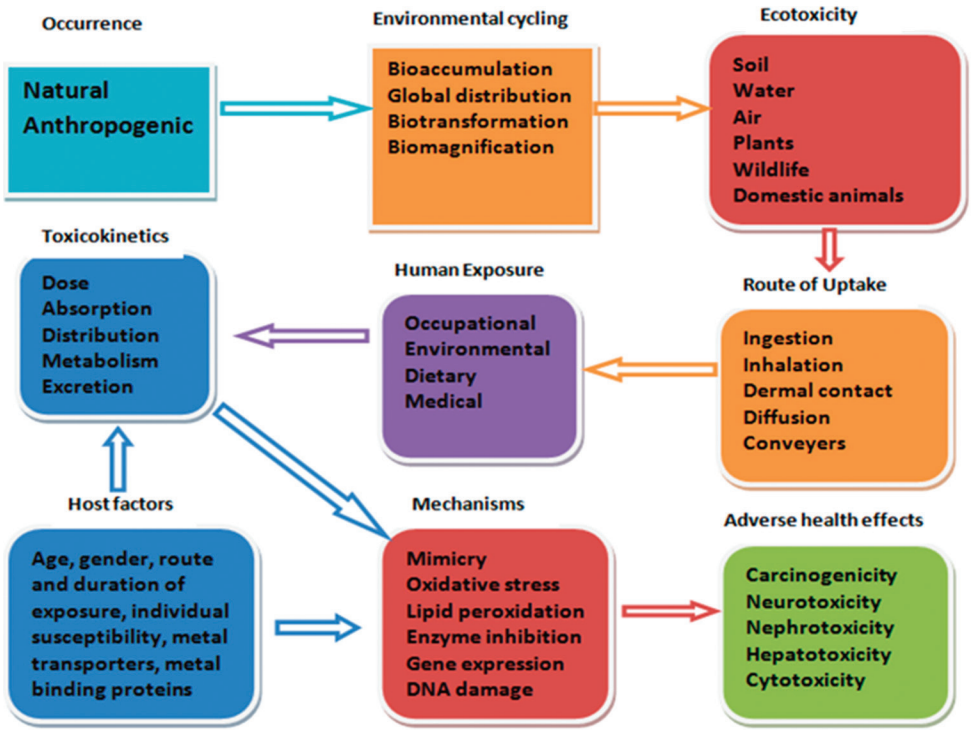

Figure 7: Adverse health effects of human exposure to toxic metal mixture from the environment; molecular and cellular mechanisms of toxicity indicated.[28]

Figure 8: Pollution from cement production factory in Nigeria, this constitutes a health risk (inhalational disorders) to both the factory workers and those in the immediate surroundings.[30]

hypertension, delayed pubertal development, irregular menstruation, preterm births, and stillbirths [Figure 9].[34,35]

Other studies in the Nigerian population have also revealed that women who experience spontaneous miscarriage or other pregnancy difficulties or breast cancer have high blood levels of toxic metals which include Pb, Hg, Cd, and As.[28]

Pesticides are used all over the country, in farms, homes, schools, gardens, and public parks to improve food yield.[36] A food test carried out in Nigeria on 217 different food items revealed that the concentration of pesticides such as dichlorodiphenyltrichloroethane, aldrin, and dieldrin to be higher than the maximum allowable concentration (which ranged from 1.2 to 2160 μg/kg). These chemicals have been linked to the development of cancer, cardiovascular disease, dermatitis, birth defects, morbidity, impaired immune function, neurobehavioral disorder, allergic immune reaction, and some are immunotoxic.[37] [Table 1 and Figure 10] illustrate some of these disorders' evolution.[37,38]

Molecular mechanisms of environmental toxicants induced health disorders

The molecular mechanism of toxicity is different for each environmental pollutant. Studies have shown that many of these toxic molecules cause harmful health effects by inducing glutathione (GSH) depletion and disruption of sulfhydryl groups of proteins through binding to them resulting in cellular oxidative stress.[39,40] The effects of environmental toxicants may involve genome instability or non-genomic mechanisms, such as receptor-linked or non-receptor-linked pathway disruptions. Some such as the endocrine disruptors (EDCs) act through estrogenic and androgenic pathways

Table 1: Implications of pesticide usage on humans, Nigerian study.[37]

Pesticides	Application	Health effects
Chlorotoluron	Post-emergence herbicides	Cholinesterase inhibitors
Cyanazine	Pre and post-emergence herbicides	Increase in adenomas and carcinomas of the kidney
1,2-dibromoethane	Fumigant	Increase tumor
Fenoprop	Herbicide	Degeneration and necrosis of hepatocytes and fibroblastic proliferation
Heptachlor and heptachlor epoxide	Broad spectrum insecticide	Kidney tumor
Isoproturon	Systemic herbicide	Marked enzyme induction and liver enlargement
Methyl-parathion	Non-systemic insecticide and acaricide	Decreased cholinesterase activities, sciatic nerve demyelination, anemia
Methoxychlor	Broad insecticide	Carcinogenic potential in the liver and testes
Molinate	Herbicide	Impairment of the reproductive performance
Pyriproxyfen	Broad spectrum insecticide	Increase in liver weight

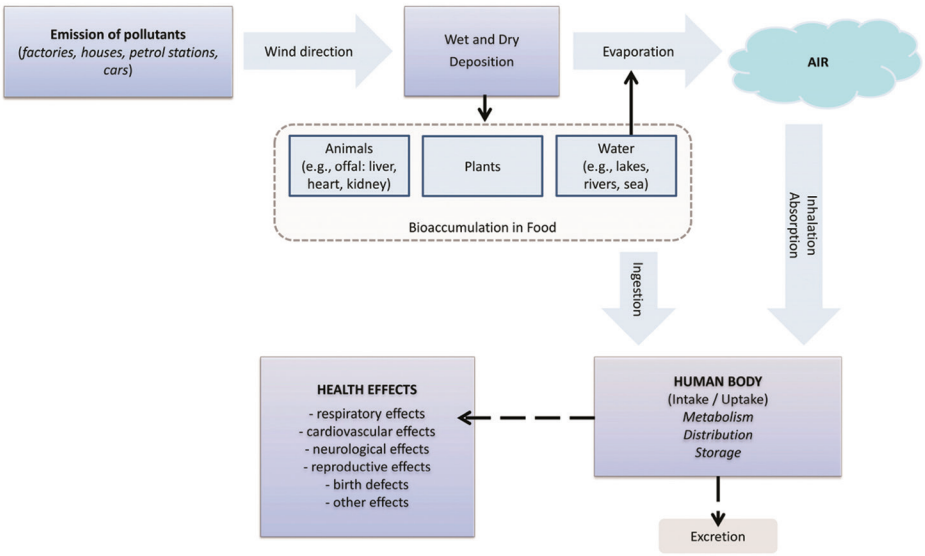

Figure 9: Exposure to lead pollution and possible health effects in humans.[35]

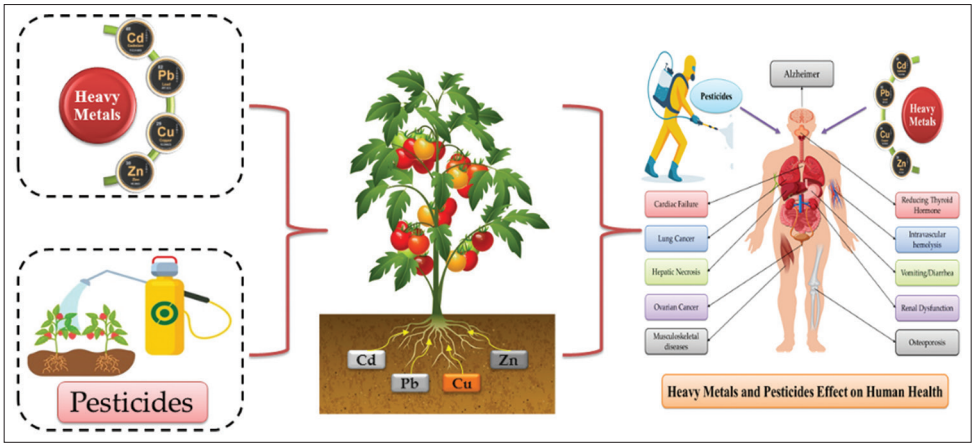

Figure 10: Toxic metals and pesticides; routes of contamination or exposure, and effect on human health.[38]

by either mimicking or opposing actions of the estrogenic/androgenic hormones at their receptor sites.[41]

Available reports indicate that certain EDCs such as organotins, bisphenol A, and phthalates among others, induce obesity and metabolic syndrome by stimulating nuclear hormones and nuclear receptors linked pathways causing adipocyte differentiation.[42,43]

It is also known that some of these environmental contaminants can increase the risk of cancer mainly by the inhibition of histone deacetylases as well as stimulation of the protein kinases resulting in exaggerated hormonal functions and signaling pathways disruptions. An environmental toxicant, methoxyacetic acid administration in rats, has been shown to disrupt estrogen receptor beta and P450 aromatase and thus increase the risk of testicular cancer.[44]

It is well documented that lead competes with essential metals needed by the body, such as calcium (Ca^{2+}), zinc (Zn), and iron (Fe), which drive key molecular processes. The propensity of lead to substitute for Ca^{2+} is a characteristic of many of its deleterious effects. Lead competes with Ca^{2+} for binding sites on cerebella phosphokinase C, altering neuronal signaling. In addition, it builds up in the bone marrow where it disrupts the normal development of erythroid components and interferes with Ca^{2+} metabolism both directly and indirectly (through interfering with Vitamin D metabolism).[45] Lead has a very high affinity for red blood cells where it is substituted for Zn, thereby decreasing the activity of heme-synthesizing enzymes-ferrochelatase and aminolevulinic acid (ALA) dehydratase thus preventing the conversion of ALA to porphobilinogen and the incorporation of Fe into the protoporphyrin ring, respectively, leading to anemia.[46] In summary, Pb has several effects on metabolism and gene expression, including disruption of biological molecules, disruption of various biochemical processes, induction of oxidative stress, rapid depletion of antioxidants in the body, and increased production of reactive oxygen species (ROS) and reactive nitrogen species (RNS).[47] Some of the molecular and cellular mechanism of lead toxicity and associated adverse clinical disorders is shown in [Figure 11].[47]

Arsenic (As) impairs cellular respiration through the inhibition of several mitochondrial enzymes such as nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase) and through uncoupling of oxidative phosphorylation leading to the production of ROS. The majority of As's toxicity is caused by its propensity to bind with sulfhydryl groups on proteins and enzymes as well as to act as a substitute for phosphorus in many metabolic processes [Figure 12].[48,49] By inhibiting pyruvate decarboxylase, As causes thiamine shortage, which can result in encephalopathy.[50] Arsenite also enhances the release of inflammatory mediators such as leukotrienes, prostacyclin, tumor necrosis factor-alpha, neurokinin-1, and substance P[51] and forms covalent links with the disulfide bonds of insulin, insulin receptors, glucose transporters, and enzymes involved in glucose metabolism. As is a suspected carcinogen and has

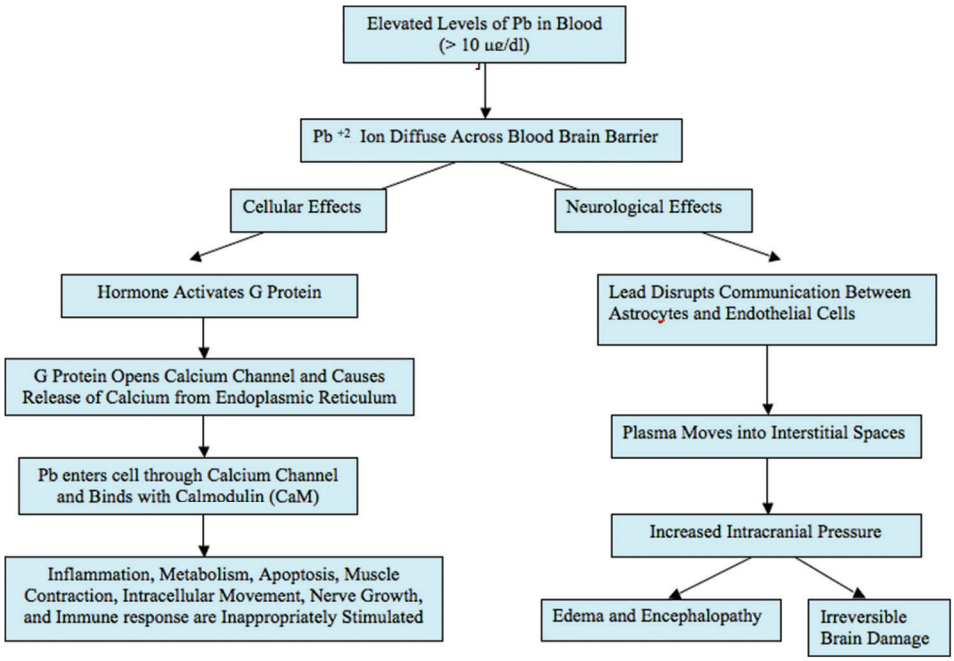

Figure 11: The molecular and cellular mechanism of lead toxicity and associated adverse clinical disorders.[47]

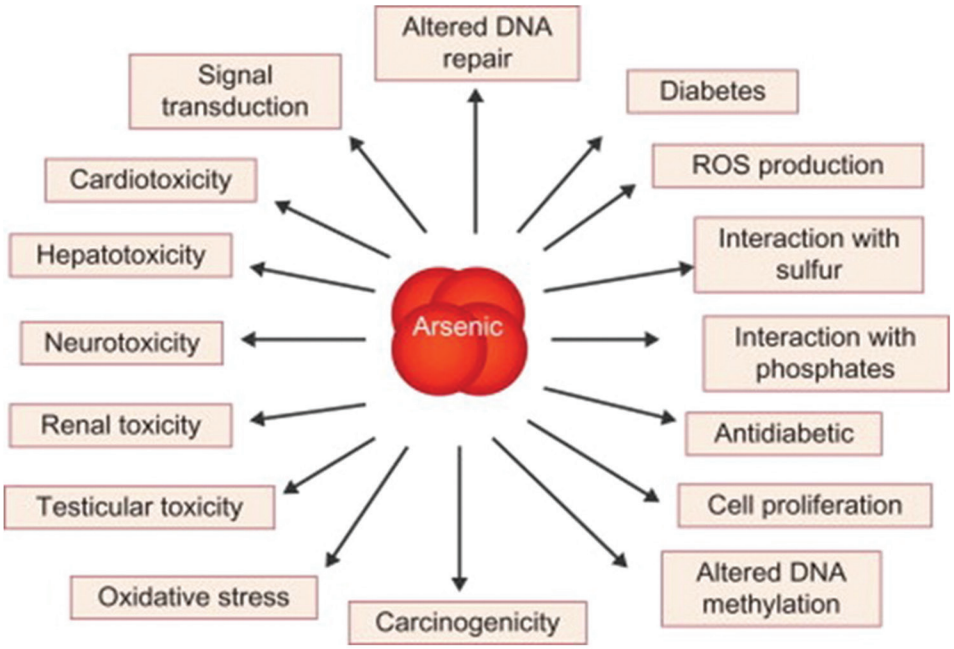

Figure 12: Molecular and cellular mechanisms for arsenic-induced toxicity.[49]

been linked with the disruption of coagulation proteins, the formation of complexes with coenzymes, and the suppression of adenosine triphosphate generation during respiration.[51]

Another important environmental pollutant is mercury (Hg). Hg owes its toxic effects to its ability to damage the mitochondria by GSH depletion and conjugation of thiol groups causing free radical production.[52] Methylmercury induces neurotoxicity by inhibiting serotonin, aspartate, and glutamate uptake by the neuronal cells and also causes a prolonged increase in intracellular cytosolic Ca^{2+} concentrations through disruption of N-type an L-type Ca^{2+} channels leading to necrosis/apoptosis in the central nervous system.[53]

Cadmium (Cd) yet an important ubiquitous environmental pollutant exerts its toxicity by inhibiting antioxidant enzymes such as superoxide dismutase (SOD) and catalase resulting in excessive ROS generation [Figure 13].[54] It also inhibits nitric oxide synthase (NOS) leading to the depletion of the sulfhydryl group of proteins and a free radical scavenger metallothionein (Zn – concentrating protein containing 33% cysteine).[55] Cd is a metabolic antagonist of Zn which plays a central role in many molecular processes. Smokers had been found to have a high Cd -Zn ratio due to the alteration of Zn status by Cd. This altered ratio had been linked with oxidative stress, DNA damage, mutation, impaired DNA repair, P53 expression, angiogenic effect of copper (Cu), and impaired Vitamin A metabolism. These cellular and molecular abnormalities have been reported to increase the risk of cancers in smokers, especially prostate cancer.[56]

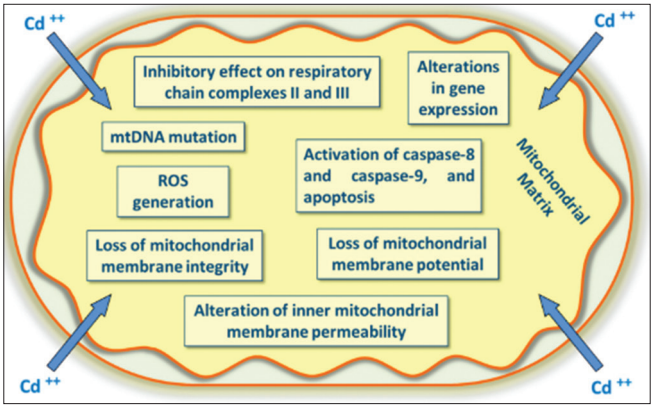

Figure 13: Cellular and molecular mechanism of chronic exposure to cadmium and corresponding adverse health effects.[54]

In addition, it has been observed that Mg and Cd can reduce the activities of the hepatic drug-metabolizing enzymes, cytochrome P450 and P448, as well as microsomal total P450 levels.[57]

MICRONUTRIENTS: TOXICANT INTERACTIONS

The scientific community in the last couple of decades is gradually been persuaded by investigators that rather than focusing on a curative approach, what should be emphasized is strengthening host resistance in disease prevention and management. This is largely driven by micronutrients with a wide range of mechanistic modes of action anchored mostly

on molecular processes. Micronutrients perform crucial functions at the cellular, tissue, and overall metabolism. They play a central role in almost every metabolic, molecular, and cellular process, including signal transduction, primary and secondary metabolism, cell defense, gene expression and regulation, hormone sensing, and reproduction, among others.[58]

A recent groundbreaking development in the era of molecular biology has been the unearthing of signaling pathways that activate many transcription factors that control the expression of many proteins involved in the protection against DNA damage and the development of cancer. Disruption of micronutrient metabolism by environmental toxicants may accelerate the degenerative diseases of aging through the allocation of scarce micronutrients by triage theory. Prasad, in his pioneering studies on the prime micronutrient has extended pre-existing concepts with an overt leaning toward antioxidants and direct inhibition of DNA-damaging reactive carcinogens by vegetable and fruit constituents.[51] This realization prompted numerous nations to create guidelines for including micronutrients in a typical diet.[9] Micronutrients are vitamins and trace elements in which generally fruits and vegetables are common good sources along with animal products. Nutritional interventions to boost the body's level of micronutrients may potentially lower blood concentrations of toxic metals and other hazardous molecules in addition to other health benefits.[9] Micronutrients are known to protect against toxicity of metals by acting at several molecular steps, which include absorption and excretion, transport, binding to target proteins, metabolism, and sequestration. They also protect against resultant oxidative stress from toxic metal exposure by their antioxidant role. Micronutrients include selenium (Se), Zn (inorganic), and Vitamins C and E (organic) among others.

Selenium (Se)

Selenium (Se) is an essential trace element that is an important component of antioxidant enzymes, such as glutathione peroxidase (GPx), thioredoxin reductase (TRR), and iodothyronine deiodinases (IDD). It is vital for the regulation of the synthesis[59] and the proper functioning of several selenoproteins involved in antioxidant defenses within the brain and nervous system in humans.[60] Major sources of Se include meat, cereal grains, Brazilian nuts, and fish.

Se exists in two forms: (a) organic, for example, selenomethionine, selenocysteine, and methylselenocysteine and (b) inorganic, for example, selenite and selenate.[61] The selenoproteins synthesized from Se include GPx, TRR, and IDD which are important intracellular antioxidants in preventing oxidative injury;[62] consequently, the importance of Se supplementation in boosting up the internal antioxidative defense has been emphasized in recent years.[63] Se has antimutagenic properties, thereby preventing the malignant transformation of normal cells.

Se as a component of the antioxidant selenoenzymes and selenoproteins plays its role in protecting against atherosclerosis by reducing oxidative stress, inhibiting low-density lipoprotein oxidation from ROS, and increasing nitric oxide (NO) bioavailability. As part of GPxs and TRR, it is primarily associated with protecting DNA and other cellular components from oxidative damage. It increases the antioxidant capacity of cells by (i) enhancing the activity of SOD associated with the scavenging of free radicals and ROS and (ii) by increasing GSH reductase activity and, consequently GSH content in the cell as part of its protection against toxic metals.[64]

Se forms insoluble complexes with toxic metals, especially Hg, thereby protecting the cells from the damaging effects of these metals. Se therefore exerts its protective function against environmental pollutants through increased production of selenoproteins, competition at key enzyme sites and through the formation of inert Se–metal complexes.[65,66] It has also been reported that Se facilitates the biliary excretion of As.[66]

Zinc (Zn)

Zinc (Zn) works as an antioxidant in a variety of ways. First, Zn displaces Fe and Cu redox-active metals that catalyze the formation of hydroxyl radicals (OH.) from hydrogen peroxides (H_2O_2) by competing with them for binding to cell membranes and proteins. Second, Zn attaches to biomolecules' (SH) sulfhydryl groups, shielding them from oxidation. Third, Zn decreases the activities of oxidant-promoting enzymes such as inducible NOS and NADPH oxidase and increases the activation of antioxidant proteins, molecules, and enzymes such as GSH, catalase, and SOD. It also inhibits the production of lipid peroxidation products. Fourth, Zn stimulates the production of metallothionein, a metal-binding protein that is very cysteine-rich and a good scavenger of hydroxide ions (OH^-).[67]

By interacting with an antioxidant-responsive element in the target gene's promoter region, nuclear factor erythroid 2-related factor 2 (Nrf2), Zn controls the expression of antioxidant proteins and enzymes such as GSH and SOD as well as detoxifying enzymes such as glutathione-S-transferase-1 and heme oxygenase and by increasing the activity of Nrf2, thereby lowering oxidative stress.[68] It is well known that Zn is an important regulator of immune response to microbial infections. Zn inhibits nuclear factor kappa B (NF-κB) activation by inducing a Zn finger protein A20, resulting in a decrease in the gene expression and protein generation of various inflammatory cytokines. Decreased activation of NF-κB by Zn also results in decreased gene

expression and generation of intercellular adhesion molecule 1 as shown in [Figure 14].[69] Zn forms soluble complexes with toxic metals thereby increasing urinary excretion of these metals.

Vitamins

Vitamins include Vitamin A (retinoids), Vitamin E (primarily α-tocopheryl succinate), Vitamin C (primarily sodium ascorbate), and carotenoids (primarily polar carotenoids). Experimental evidence has shown that Vitamins C and E act by direct removal of ROS from the intracellular compartment by hydrophilic Vitamin C; and within the cell membrane by lipid-soluble Vitamin E, while the polyphenols and phytosterols neutralize ROS directly by donating electrons or hydrogen atoms from their hydroxyl (or carboxyl) groups.[70]

Vitamin C is a water-soluble vitamin that exists in the body primarily in its reduced form, ascorbic acid and it works as an antioxidant to prevent oxidative stress-related cellular damage. The oxidized form of the vitamin, dehydroascorbic acid, also has antiscorbutic activity because it is easily reduced intracellularly to ascorbic acid. The ability of the vitamin to provide electrons and readily be converted back to its reduced form by GSH accounts for its particular effectiveness as an *in vivo* antioxidant.[71] It is an essential cofactor for α-ketoglutarate-dependent dioxygenases such as prolyl hydroxylases, which play a role in the biosynthesis of collagen and in the downregulation of hypoxia-inducible factor (HIF)-1, a transcription factor that regulates many genes responsible for tumor growth, energy metabolism, and neutrophil function and apoptosis. Vitamin C-dependent inhibition of the HIF pathway may provide alternative or additional approaches for controlling tumor progression, infections, and inflammation.[9,72] Vitamin C also contributes to the activity of endothelial NOS a key enzyme in the production of the vasodilator, NO which is an important homeostatic regulator of numerous essential cardiovascular functions.

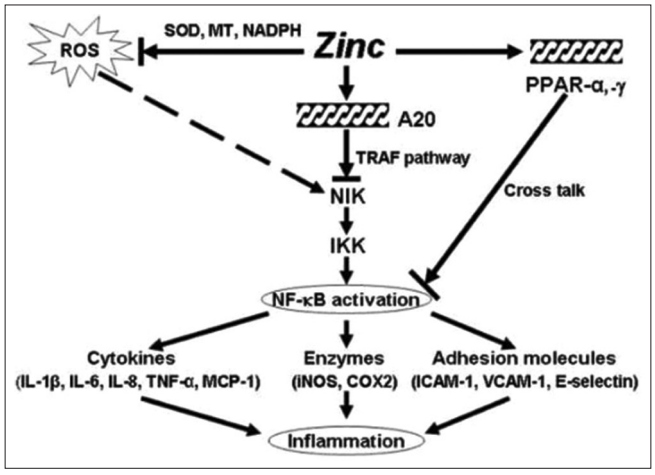

Figure 14: Cellular and molecular antioxidant mechanisms of zinc.[69]

Vitamin E is the term for a group of tocopherols and tocotrienols, of which α-tocopherol is the form of Vitamin E with the highest biological activity.[73] It is predominantly found in the membranes of cells and organelles where it serves as the first line of defense against lipid peroxidation and oxidative damage. As a vital lipid soluble antioxidant, Vitamin E (-tocopherol) scavenges hydroperoxyl radicals in the lipid environment. Vitamin E is a potent antioxidant that prevents the formation of ROS molecules during fatty acid oxidation and free radical reactions. It also can shield proteins from alkylation by electrophilic lipid peroxidation products. In addition to oxidizing other lipids, tocopheroxyl radicals can also undergo further oxidation to produce tocopheryl quinones, interact with one another to form non-reactive tocopherol dimers or be reduced by other antioxidants to tocopherol.[74] It has been discovered that although gamma-tocopherol captures and neutralizes the existing free radicals, alpha-tocopherol mainly inhibits the creation of new free radicals; as a result, Vitamin E may aid in preventing or delaying the development of chronic diseases linked to ROS molecules.[75]

Other micronutrients as molecular antidote to environmental toxicants

Iron (Fe) has been shown to protect against the toxic effects of lead by competing inhibition for uptake in the intestine. It also acts by competing with the binding of toxic metals to active sites of enzymes.[76,77]

Copper (Cu), like Fe, is generally thought of as a pro-oxidant that causes free radical damage and lipid peroxidation. However, Cu is an essential nutrient and an integral part of the antioxidant enzymes Cu, Zn-SOD and ceruloplasmin. It has been proposed that nutritional Cu deficiency impairs antioxidant status by decreasing the activity of these enzymes. Cu deficiency also alters other cell components such as Fe, catalase, Se, and GSH that influence antioxidant status. Cu, Zn-SOD is located in the cytosol and dismutates the superoxide radical to H_2O_2, which is eventually converted to water.[78]

Manganese (Mn) belongs to the class of transition elements of which +2 oxidative state is the most stable. It is an essential element that is a cofactor for a variety of enzymes, among which are oxidoreductases, demitasses, transferases, hydrolases, layers, isomerases, and ligases through which it exerts its molecular and cellular effects. Mn also modulates the binding activities of lectins, especially those involving carbohydrates, transmembrane receptors, the integrins, and in the regulation of the metabolism of glucose and lipids in

humans. In addition, Mn is one of the required components for MnSOD, which is mainly responsible for scavenging ROS in mitochondrial oxidative stress.[79] Mn has been reported to be an inhibitor of lipid peroxidation (a-lo), particularly in microsomes challenged by NADPH/Fe(II)/ADP or cumene hydroperoxide.[80]

MICRONUTRIENTS AS ANTIDOTES TO ENVIRONMENTAL TOXICITY

The global burden of environmental pollution continues to be a major public health concern with developing countries like Nigeria particularly being vulnerable and bearing the brunt of the negative effects.

Free radicals have been extensively researched in experimental and clinical medicine over the past few years. The actions of both the enzymatic and non-enzymatic antioxidant systems counteract the effects of ROS and RNS. There are several proposed techniques to protect, correct, and remedy the deleterious effects of environmental pollutants, ranging from physical methods of soil reclamation to chemical methods of degradation of accumulated pollutants to biological methods based on the activity of micronutrients.

Conventionally, exposure to environmental pollutants, especially toxic metals, can be treated by chelation therapy where the chelating agent binds metal ions forming complex ring–like structures enhancing their elimination from the body. Chelation therapy has some shortcomings which include failure to remove these toxic metals from the intracellular sites rather they promote the redistribution to other body tissues. Chelation therapy does not provide protection in terms of clinical or biochemical recovery; it also chelate essential metals inducing their loss from the body; some of the therapies may be hepatotoxic and they are expensive and not readily available.[66,81] This knowledge about the shortfalls of chelation therapy has increased the scientific search for better antidotes for environmental toxicity-related health disorders which are easily available, affordable, and with little or no side effects.

Micronutrients have been proposed as a worthy alternative to the toxic metal chelators. These micronutrients target various steps in the pathophysiology of the toxicity of these pollutants including interaction during uptake, binding or excretion, alteration of metabolism and transport, while others are antioxidants or anti-inflammatory. Vitamin C, Vitamin E, carotenoids, thiols, natural flavonoids, etc., are the most potent non-enzymatic antioxidants, while GPx, catalase, and SOD are examples of enzymatic antioxidants. Nutritional variables, such as some trace nutrients, may influence the endogenous activity of antioxidant enzymes. Trace elements including Cu, Mn, Zn, Se, and Fe have proven to be significant cofactors for the control of the activity of antioxidant enzymes. [Figure 15] shows the summary of role of both endogenous and exogenous antioxidants in protecting against environmental pollution and oxidative stress.[82]

It was reported in a recent study that dietary supplements, a healthy diet, and lifestyle improvement can go a long way in militating against the effects of oxidative stress, inflammation, and abnormal mitochondrial dynamics among others, which may be induced by chronic exposure to environmental contaminants. This study even proposed that the above approach could be an alternative management in patients with neurodegenerative diseases, which has been suspected

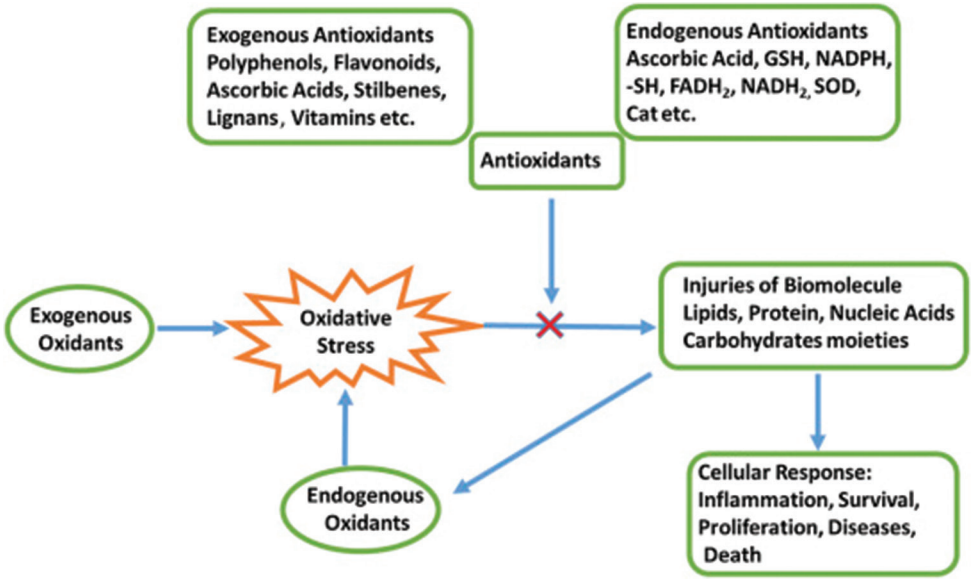

Figure 15: Antioxidants and vitamins; roles in cellular function and metabolism.[82]

and may also result from chronic exposure to environmental toxicants.[83]

Another study on Wistar rats exposed to common household insecticide demonstrated an inverse relationship between As and Zn concentrations. It was then suggested that Zn supplementation can also protect against damaging molecular and cellular effects of As, especially among users of insecticides which is known to have high concentrations of As.[84]

CONCLUSION AND RECOMMENDATION

Chronic exposure to environmental toxicants elicits insidious effects including reproductive, cardiovascular, metabolic, and neurologic diseases. Developing nations including Nigeria are recognized to be more seriously at risk of these deleterious effects due to inadequate policies and data to mitigate the negative effects. Micronutrients which are obtained from natural food sources and food supplements have the potential to serve as antidotes and counteract the deleterious effects of these pollutants. They regulate key molecular activities such as, signaling, DNA repair, inhibition of reactive oxygen species damaging activities, and are needed for cell cycle regulation and functional p53 expression and retinoid gene activation. They are also a readily available and affordable means with little or no side effects. Hence, micronutrients through their molecular and cellular activities serve as pragmatic antidotes to protect the population.

Ethical approval

Not applicable.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

Dr. Okezie I. Aruoma is on the editorial board of the Journal.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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