Tropical Journal of Natural Product Research

Available online at https://www.tjnpr.org

Toxicant-Nutrient Interaction as a Veritable Host Resistance Against Chemical Toxicity in the Rapidly Industrializing Developing Nations

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ARTICLE INFO

Article history:
Received 09 September 2017
Revised 15 October 2017
Accepted 18 October 2017
Published online 05 November

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ABSTRACT

Growing evidence indicates that chemical utilization including toxic waste in the developing countries is on the increase. These nations have limited facilities for sound chemical management involving production, use and disposal of chemicals with minimal adverse effects on human and environmental health. Though concerns are important to all nations, they appear particularly salient to the industrializing countries under pressures to achieve development and eradicate poverty yet with limited capacity for sound chemical management. This increases the risk of chemical toxicity, with consequences such as genotoxicity, cancer and teratogenicity. The growing chemical burden implies the need for an efficient and effective means of xenobiotic metabolism and host resistance. Relevant literature on nutrients and toxicants interaction in various search engines were reviewed. The possible role of host resistance, essentially involving nutritional modulation has been ignored. Nutrient-toxicant response pathways could be affordable strategies against excessive chemical exposure. Zinc, a prime micronutrient is an antioxidant [Cu-Zn superoxide dismutase (SOD)], component of p53, guardian of the genome; active in the repair of DNA damage and apoptosis; protective against carcinogenesis. Zinc also plays an important role in vitamin A metabolism, in turn important in differentiation and central to retinoids involved in gene expression. Zinc is important in all the stages of the cell cycle, derangement of which may be a pathway to carcinogenesis. Use of this and other protective nutrients including folate and selenium, among others, appears a veritable approach to improving host resistance against chemical toxicity and should be considered promising in developing nations.

Keywords: *Chemical toxicity, Genotoxicity, Host resistance, Nutritional modulation, Toxicant-nutrient interaction.*

Introduction

There is more industrialization in developing countries than in developed countries because most of the businesses want to get their products produced from the developing countries, partly because labour and other cost of production are very low in developing countries.[1] While industrialization is an essential feature of economic growth in developing countries, industrial practices may also produce environmental health consequences through the release of air and water pollutants and disposal of hazardous wastes.[1, 2] The key chemicals that are commonly used in the developing countries include persistent or ubiquitous metals such as cadmium (Cd) and lead (Pb) along with polychlorobiphenyls (PCBs). A very recent study by Bakshi *et al.* [3] reported the association between Cd and prostate cancer, which currently is the most common cancer in men.[3] Cadmium is currently classified as a human carcinogen by the International Agency for Research in Cancer (IARC) and the National Toxicology Programme, (NTP).[4,5,6] It is a ubiquitous environmental toxicant because of its widespread use and application in industrial and related activities accompanied by all types of pollution.[1, 4]

In addition to direct industrial pollution such as gas flaring, textile effluents, amongst others, products like waste electronic and electrical equipment (WEEE) or electronic waste (e-waste) exported from developed to developing countries have constituted enormous health risk to a country like Nigeria.[7] In Africa, Nigeria is reported to be the largest e-waste dump yard.[8] This is evident in the number of e-waste imported and received in the major e-waste recycling sites such as Westminster Electronic Market and Alaba International market, Lagos State. There a is disparity in e-waste recycling cost and regulations between developed and developing countries. Considering the risks to human and environmental health, as well as the higher costs of safer recycling processors, developed countries have found it easier to ship their e-waste to developing countries where regulations are poor and labour is cheap. As a result of this disparity in costs and regulations, much of the world's e-waste is currently exported from more developed, affluent countries to less developed countries.[8] Hull [9] reported that the e-waste issue is all about poisoning the poor for profit. E-waste disposal is especially problematic when humans and the environment are exposed to hazardous chemicals during the process of dismantling electronic products. E-waste contains approximately 1,000 chemicals; including mercury, lead oxide, cadmium, and polyvinyl chloride, which are especially hazardous to human health.[10]

Increased reliance on chemicals in industrializing developing countries places new demands on them, as they have limited resources to adequately

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Citation: Igharo OG, Anetor JI, Anetor GO, Nwobi LN, Osagie AO, Osunbor JO. Toxicant-Nutrient Interaction as a Veritable Host Resistance Against Chemical Toxicity in the Rapidly Industrializing Developing Nations Trop J Nat Prod Res. 2017; 1(5):196-198. doi.org/10.26538/tjnpr/v1i5.4

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regulate exposure to these chemicals. Majority of the chemicals cause mutation in DNA, cancer, cardiovascular diseases among others.

The consequences of increased exposure to chemicals on the genome and their mitigation by nutrigenomics; a science concerned with the prevention of genome damage by nutritional factors is poorly recognized in developing nations of the world,[11] possibly due to the paucity of adequate scientifically based nutritional information. Growing evidence indicates that genome instability in the absence of overt exposure to genotoxicants is a sensitive marker of nutritional deficiency. Therefore, the increasing prevalence of chemicals in these countries which contribute to genome disturbances and the widespread nutritional deficiency, at least double the risk of genome instability.[11]

Methodology

In this review, a critical, constructive analysis of relevant literature in the subject areas of toxicant exposure and nutritional modulations was carried out. The literature survey entailed the use of general search engines (Google and Bing); subject specific search engine (GoPubMed) as well as scholarly literature engines (Google Scholar and Base).

Industrial Pollution in Developing Nations

In Nigeria and most developing countries of Africa, industrialization is a welcome development and of course seen as an essential feature of economic growth. However, worthy of concern as earlier indicated is the fact that industrial practices may also produce adverse environmental health consequences through the release of air and water pollutants and the disposal of hazardous wastes. This is often the case in developing countries, where less attention is paid to environmental protection, environmental standards are often inappropriate or not effectively implemented, and pollution control techniques are not yet fully developed. Also, there is lack of policy documentation of pollutants, government regulatory agencies appear not to be well funded to execute their regulatory and supervisory roles. With rapid economic development, many developing countries, like China and other Asian countries, face some additional environmental problems.[1,2] One is the environmental pollution from hazardous industries or technologies transferred from developed countries, which are no longer acceptable for occupational and environmental health reasons in developed countries, but still allowable in developing countries due to less strict environmental legislation. Another problem is the rapid proliferation of informal small-scale enterprises in townships as well as in rural areas, which often create serious air and water pollution because of lack of sufficient knowledge and funds. [2, 12]

Major industrial activities in developing countries include but are not limited to mining (as seen in the Zamfara Lead Poisoning), asbestos roofing sheet production, textile production, cement production and gas flaring. Others are crude oil refining, WEEE recycling and dismantling, PVC and plastic production, automobile lubricants production, automobile battery production/maintenance as well as paints/pigments production and use. [7, 13, 14]

Nutrition and Environmental Toxicology

A convincing body of research indicates that nutrition is a modulator of vulnerability to environmental insults; thus, it is timely to consider nutrition as a vital component of human risk assessment. Nutrition may serve as either an agonist or an antagonist (e.g., high-fat foods or foods rich in antioxidants, respectively) of the health impacts associated with exposure to environmental pollutants. Dietary practices and food choices may help explain the large variability observed in human risk assessment.[15]

Among the factor that influence cellular response and susceptibility to environmental agents, diet/nutrition has received increasing attention in recent times.[16] While the mechanism of action is complex and multifarious, increased oxidative stress directly is responsible for causing and or aggravating the adverse effects from exposure to a number of environmental or industrial toxic agents.[17, 18] Oxidative damage is a consequence of decreased antioxidant potential and/or oxidative stress. Organs in exposed workers may compensate or adapt to a dietary inadequacy of a given antioxidant by increasing (upregulating) the level of activity of another antioxidant system largely of protect against DNA damage. This is elegantly demonstrated in the relationship between ascorbic acid and uric acid, an endogenous antioxidant reported by Sevania *et al.*[19] and extended recently by Anetor *et al*., [20] in an occupational cohort. Uric acid has been inversely correlated with 8-hydroxy-2-deoxyguanosine.[18]

Micronutrition as Intervention in Host Resistance to Chemical Toxicity

Nutritional state, though of importance in resource-poor countries, has been neglected as an approach to mitigation of chemical toxicity. Nutritional status should be viewed as one of the most important preventive measures available to public health experts in the developing countries where vital micro-nutrients, particularly Zinc (Zn) (a metabolic antagonist of cadmium and competitor with lead) are deficient.[11, 18, 19]

Micronutrient in Host Defense against Haem Biosynthetic Disorder

Zinc is vital for a key enzyme (aminolevulinate dehydratase - ALAD) in the haem biosynthetic pathway. ALAD catalyzes the second step in porphyrin and haem biosynthetic pathway; zinc is essential for enzymatic activity. ALAD enzymatic activity is inhibited by lead and a defect in the ALAD structural gene can cause increased sensitivity to lead poisoning. This is one of the mechanisms by which lead exerts its toxic effects.[20] Thus, optimum zinc level is protective and reduced level increases susceptibility.

Indeed, Zinc is vital for the function of other important micronutrients such as vitamin A (retinoids) and its deficiency has been reported to be one of the top killers in the developing countries. [18, 19] It should be recalled that because of the cereal base of the diet of residents of the northern part of Nigeria, including Zamfara state, zinc deficiency was very likely to be prevalent. The phytate in cereal may complex zinc, hence the high morbidity and mortality of the Zamfara Lead Poisoning episode in Nigeria. Adequate zinc level in the body may reduce the consequences of environmental chemicals.[17, 20, 21]

The concept of nutritional modulation of chemical toxicity is an important one for many developing countries owing to its relative cheapness. As a mitigation strategy, micronutrients (vitamins A, C and E; selenium, zinc, copper amongst others) intake, as well as some phytochemicals (e.g. phenolics and flavonoids), may provide some protection and ameliorate susceptibility to this mixed chemical exposure.[20,21] This should be taken advantage of in industrializing developing countries. In the specific case of lead toxicity, the weight of evidence suggests that much can be achieved in minimizing the health effects of chemical poisoning now widespread in many developing countries by paying attention to the micronutrients.[11, 19]

Modification of environmental toxicity by nutrients: implications in atherosclerosis

It has been hypothesized that nutrition can modulate the toxicity of environmental pollutants and thus modulate health and disease outcome associated with chemical insult.[15,21,20] There is now increasing evidence that exposure to persistent organic pollutants, such as polyhalogenated aromatic hydrocarbons, for example, polychlorinated biphenyls (PCBs) can contribute to the development of inflammatory diseases such as atherosclerosis. Activation, chronic inflammation, and dysfunction of the vascular endothelium are critical events in the initiation and acceleration of atherosclerotic lesion formation.[14, 21] The studies by Hennig *et al.*[16] indicated that an increase in cellular oxidative stress and an imbalance in antioxidant status are critical events in the PCB-mediated induction of inflammatory genes and endothelial cell dysfunction. Furthermore, it was found that specific dietary fats can further compromise endothelial dysfunction induced by selected PCBs and that antioxidant nutrients (such as vitamin E and dietary flavonoids) can protect against endothelial cell damage mediated by these persistent organic pollutants. In addition, PCB- and lipid-induced inflammation can be down-regulated by ligands of anti-atherogenic peroxisome proliferator-activated receptors (PPARs).[15] It was further suggested that antioxidant nutrients and related bioactive compounds common in fruits and vegetables protect against environmental toxic insult to the vascular endothelium by down-regulation of signalling pathways involved in inflammatory responses and atherosclerosis.[14, 15, 21]

Nutrigenomics: Promising Antidote to Genotoxic Environmental Insults

The consequences of increased exposure to chemicals on the genome and their mitigation by nutrigenomics appear to be poorly recognized in the developing countries. Growing evidence indicates that genome instability in the absence of overt exposure to genotoxicants is a sensitive marker of nutritional deficiency.[11] Therefore, the increasing prevalence of chemicals in these countries which contribute to genome disturbances and the widespread nutritional deficiency, at least double the risk of genome instability. Environmental pollutant such as polychlobiphenyls, metal fumes, and fly ash, common in these countries are known to increase the urinary level of 8-hydroxy deoxyguanosine (8-OhdG), a maker of oxidative DNA damage, precursor of genome instability.[11] Increasing evidence emphasizes the importance of Zinc in both genetic stability and

function. Zinc deficiency has been linked with oxidative stress, DNA damage and impairment of repair mechanisms as well as the risk of cancer. Zinc plays an important role in vitamin A metabolism from which the retinoids are derived. Zinc is also an important component of p53 company protein, a DNA damage sensor which prevents genetic lesions contributing to genome instability. Zinc deficiency ranks among the top 10 leading causes of death in developing countries.[11, 21, 22] A large proportion of the population in these countries ingests less than 50% of the recommended daily allowance for Zn. These make the genome protective nutrient among others grossly inadequate. Folate now also recognized for its role in genome stability, is the nutrient frequently cited as critical to genome stability. Folate deficiency of sub-clinical degree is common. Reduced folate intake causes as much genome damage as that reduced by exposure to a high dose of ionizing radiation.[11] Even moderate folate deficiency causes very severe damage to the genome in the general population. All these accentuate the susceptibility of the population in the nation to an environmental toxic assault requiring preventive measures employing the science nutrigenomics, probably augmented with adaptive response pathways such as the Nrf2 signally pathway. Human populations in developing countries are increasing exposure to diverse array of industrial chemicals which adversely modify the genome, the precursor of many diseases especially cancer. Nutrigenomics encompasses nutritional factor that protects the genome from damage and is a promising new field that can be exploited perhaps augmented with the Nrf2 signaling pathway with international collaboration in these nations as an antidote to chemical-induced genome instability.[11,22] This and other studies on the modulatory effects of nutritionally essential factors on toxicants should attract attention for deeper future research particularly in developing countries with rising chemical utilization and increased pollution levels.

Conclusion

Based on recent evidence, this review concludes that nutrient-toxicant interaction can serve as a veritable host resistance against chemical toxicity and insults in the rapidly industrializing developing nations like Nigeria. Indeed, nutrition can modulate the toxicity of environmental pollutants and thus modulate health and disease outcome associated with chemical insults. Nutritional awareness in environmental toxicology is critical, because of opportunities to develop dietary guidelines which specifically target exposed populations. Nutrition may provide the most sensible means to develop primary prevention strategies of diseases associated with environmental toxicology.

Recommendation

We recommend that nutritional awareness in environmental toxicology should be on the increase in industrializing developing nations. Additionally, that future direction in environmental health research explores these nutrient-toxicant interactions to develop and utilize nutritional interventions, which may provide the most sensible means to developing primary prevention strategies of diseases associated with many environmental toxic insults.

Conflict of interest

The authors declare no conflict of interest.

Authors' declaration

The authors hereby declare that the work presented in this article are original and that any liability for claims relating to the content of this article will be borne by them.

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