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Review Article

Role of Toxicants in Oxidative Stress Mediated DNA Damage and Protection by Phytochemicals

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Abstract

DNA of all the living organisms is normally stable. The genomic DNA gets damaged due to its continuous exposure to numerous environmental factors including toxicants resulting into development of diverse heritable syndromes which are transferred from one generation to the next. A biological cell always stays under a threat of DNA damage by both the endogenous and exogenous factors. Both natural and anthropogenic toxins enter into the body of an organism through several routes of exposure such as dermal contact, inhalation, ingestion, injection and accidental. The environmental factors inducing DNA damage are termed as genotoxic agents. Production of free radicals in excessive amount decreases the level of cellular antioxidants and further induces an imbalance between antioxidant defense system and free radicals that finally results into a condition called as oxidative stress. They induce their effects by distorting the structure of DNA by breaking of hydrogen bonds involved in DNA strands stabilization. The present review article illustrates the natural and synthetic toxicants mediated DNA damage in different organisms. It has been attempted to include the possible mechanisms involved in these important cascades of events. Simultaneously, an updated account of plant-based principles exhibiting protection potential has also been presented.

Keywords: *Environmental Factors; Oxidative Stress; DNA Damage; Phytochemicals; Antioxidants*

Introduction

Environmental factors involving both the abiotic and biotic factors have been reported to possess genotoxic properties. The abiotic factors comprise physical agents such as radiation (UV and IR or medical X-rays) and heat, chemical agents such as heavy metals, pesticides, some food additives, solvents, cigarette smoke, air born pollutants, chemotherapeutic drugs and industrial chemicals [1,2]. The biological factors constitute toxins derived from plant and animal sources including their metabolites including phytochemicals [3,4]. In addition, some bacterial and viral infections such as *Helicobacter pylori*, human immunodeficiency virus (HIV) and human papilloma virus have been shown to possess DNA damage potential [5].

The exposome research involves the totality of human environmental exposures from conception onwards, complementing the genome which only deals with non-genetic exposures. A biological cell always stays under a threat of DNA damage by both the endogenous and external factors [6]. Usually, the DNA of all the living organisms is stable. The genome gets damaged due to its continuous exposure to numerous environmental factors, thereby resulting in diverse heritable syndromes that are transferred from one generation to the next. Both natural and anthropogenic toxins enter into the body of an organism through several routes of exposure such as dermal contact, inhalation, ingestion, injection and accidental. These chemicals are reported to cause membrane damage, protein dysfunction, DNA impairment,

metabolic disorders, mutagenicity, cancer and cell death [7]. The environmental factors inducing DNA damage are termed as genotoxic agents. They induce their effects by distorting the structure of DNA by breaking of hydrogen bonds involved in DNA strands stabilization. The types of DNA damage include oxidative damage, hydrolytic damage, and DNA strand breaks [8]. The degree of toxicity of any toxicants depends on its dose, duration and rout of exposure. In general, a given amount of a toxic agent will elicit a given type and intensity of response. The dose-response relationship is a fundamental concept in toxicology and the basis for measurement of the relative harmfulness of a chemical. There are four routes by which a substance can enter the body: inhalation, skin (or eye) absorption, ingestion, and injection [2]. This review highlights the updated information available as on date about the preventive effects of herbal medicinal plants against DNA damages by toxicants via oxidative stress and also provides leads to engage them in animal studies and future clinical investigations.

Mechanism of oxidative stress mediated DNA damage

The oxidative DNA damage mechanisms have not been clarified properly. However, Fenton reaction of oxidative damage to DNA has been observed as the most acceptable hypothesis in this context. Commonly, free radicals are called as reactive oxygen species (ROS)/ reactive nitrogen species (RNS) that contain one unpaired electron in its outer-most orbit [9,10]. Production of free radicals in excessive amount decreases the level of cellular antioxidants and further induces an imbalance between antioxidant defense system and free radicals that finally results into oxidative stress mediated damage (Figure 1). The existing reports suggest that the production of hydroxylated deoxyguanosine (8-hydroxydeoxyguanosine, 8-OHdG) acts as one of the key biomarkers of oxidative damage to DNA by chemical xenobiotics. These chemical species may also cause deamination of cytosine thereby converting it into uracil. Also, these free radical species have been experimentally demonstrated to remove a base from DNA generating a basic (apurinic/apyrimidinic; AP) site into it [11]. Other mechanisms involved in DNA damage depend on the type of sources for DNA damage. For example, the ROS and RNS induce oxidative base modifications as discussed above, infra-red (IR) radiation typically leads to single-strand breaks (SSB) and double-strand breaks (DSB), DNA alkylation leads to adduct and inter-strand crosslink (ICL) formation, and UV triggers the formation of thymidine dimmers [12,13].

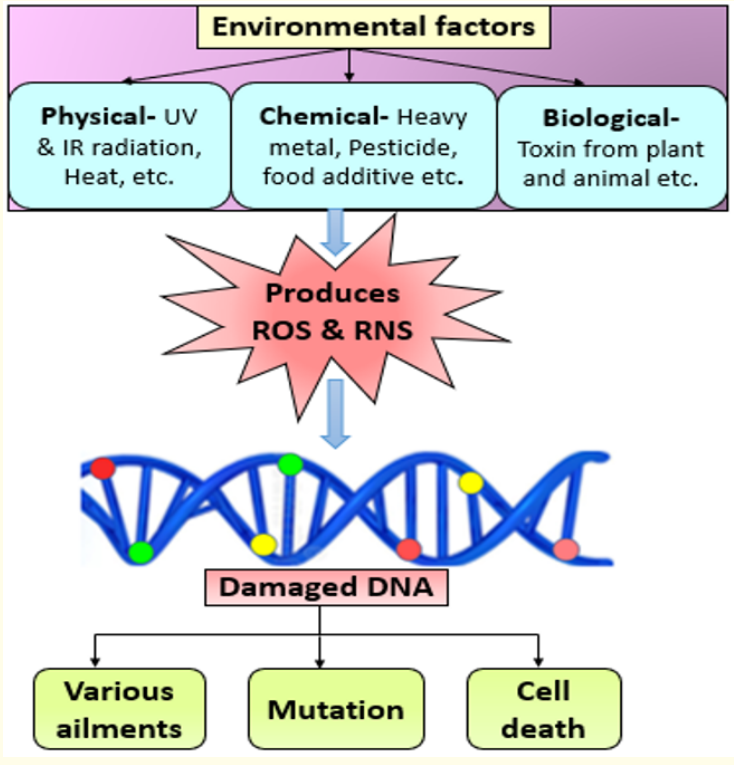

Figure 2: *Overview of environmental factors mediated DNA damage.*

Environmental toxicants

The environmental DNA-damaging agents are placed in three different categories: (1) physical DNA damaging agents, (2) chemical DNA damaging agents, and (3) biological DNA damaging agents. The physical agents such as UV and IR radiations have been reported to produce ROS which tends to damage cellular systems including DNA. The UV radiation has an electromagnetic spectrum spanning from 200 to 400 nanometers, which is further subdivided into UV-A, UV-B and UV-C. UV-C radiations are usually blocked by the atmospheric ozone layer; whereas UV-A and UV-B exhibit abilities to each on the earth and hence are considered responsible for causing serious DNA damage. In addition, the exposure of the living subjects to high temperature or heat may also cause DNA damage [14].

The stock of chemical agents causing DNA damage constitutes many heavy metals including lead, arsenic, mercury and cadmium, responsible for DNA damage through generation of double strand breaks (DSBs) [15]. These chemicals inhibit the biochemical functions of certain key proteins from different DNA repair pathways [16]. On the other hand, the pesticides being indiscriminately used in farming and health practices have been observed to induce mutation, DNA damage and chromosomal alterations [17,18]. Copper exists in the nucleus and is closely associated with chromosomes and DNA bases. It has been reported that double strand breaks of DNA can be activated by copper in association with the pesticides such as fluoxastrobin and imazamox [19]. The industrial chemicals such as fluoroalkyl substances, brominated flame retardants and butadiene emitted from rubber factories, dichloroethane an industrial solvent, vinyl chloride and hydrogen chloride from plastic manufacturing plants are reported to seriously damage DNA since they affect the repair machinery involved in fixing DNA aberrations. The food additives such as coloring agents like Red no 40 (Allura red Ac), Yellow no 5 (Tetrazine) and Yellow no 6 (sunset yellow) have been reported to act as carcinogenic agents. Some Nitrate and Nitrite chemicals (Food preservatives) used against bacterial growth are reported as highly toxic and carcinogenic agents [20]. In addition, some cross-linking agents such as mitomycin C and cisplatin; alkylating agents, aromatic compounds, fungal and bacterial toxins are also reported to have DNA damaging potential [21].

Biological factors are mainly secondary metabolites or metabolic products including free radicals such as ROS or RNS synthesized by animals and plants both. Some plant products like nicotine, an alkaloid present in tobacco induce carcinogenesis. It has potential of tumor promotion by inducing DNA damage in different epithelial and non-epithelial cells of human [22]. Sanguinarine (an alkaloid) obtained from a weed, *Argemone mexicana,* has been shown to act as a potential genotoxic agent. It has been shown to induce chromosomal aberrations, formation of micronucleus and damage of DNA in mouse model by comet assay. Sanguinarine acts as a potential inhibitor to the activity of epidermal histidase. As a consequence, two major events take place i.e. (i) the elevation in the levels of keratin formation and (ii) the promotion of tumor [23,24].

Phytochemicals as protective agents

Antioxidants are usually the free radicals neutralizing and reducing agents such as vitamins, carotenoids, polyphenols and trace metals (Zn, Mo), which scavenge ROS and inhibit the chain reactions initiated by them. DNA damage inhibition by the methanolic extract of *C. carandas* leaves has been reported. The aqueous extract of *Ganoderma lucidum* occurring in South India contains significant antioxidant property and the potential to protect DNA from radiation/chemical mediated damage. These findings were suggestive of the possibility of using the medicinal plants extracts containing flavones, polyphenols, flavonoids, terpenes and alkaloids as alternative therapeutics in treatment of cancer. Arecoline, an alkaloid constituent of *Areca* nut has been used in treatment of oral and pharyngeal cancers. The plant products chelate heavy metals and thus protect the DNA from damage induced by them. In addition, some vitamins such as Vitamin C and E have been shown to act as quenchers of free radicals and therefore, they inhibit their DNA damaging properties in the living cells [25-27]. Using the Chinese hamster lung fibroblast cells (CH V-79), Chakraborty., *et al.* (2004) evaluated the ability of some natural products including, curcumin, resveratrol, indole-3-carbinol, and ellagic acid to alter the DNA damaging ability of the alkylating carcinogen *N*-methyl-*N*'-nitro-*N*-nitrosoguanidine (MNNG).In cell culture, they have reported that the preincubation of cells treated with any of these compounds offered protection from MNNG mediated DNA damage, which indicated their true chemo-preventive function [28].

Eulophia nuda, a vital medicinal plant is used by local healers in India. Deferent solvents including aqueous, methanol, aqueous–methanol and acetone has been used for preparation of extracts and assessed for protection of Fenton's reagent mediated DNA damage. All

the extracts have been reported to protect the DNA from hydroxyl radical induced damage. The aqueous-methanolic extracts have been reported to be the best in protection of DNA against free-radicals induced damage [29].

In a study using radioprotective properties of curcumin and rhizome extract of tropical ginger have been investigated. Both two extracts have been reported to exhibit protective nature against radiation-induced damage to the plasmid pBR322 and rat bone marrow cells' DNAs by using agarose gel and single cell gel electrophoreses [30]. The eggplant commonly known as brinjal, belongs to the family Solanaceae. Its antigenotoxic effect has been studied which has demonstrated its inhibitory potential against urethane-induced mutagenicity. Furthermore, the protection of oxidative DNA damage by eggplant extracts in human lymphocytes using the single-cell gel electrophoresis (comet) was also investigated [31]. The available reports confirm that medicinal plants contain lot of antioxidants, they can act as therapeutic supplements to protect DNA from oxidative stress mediated consequences [32].

Conclusion

This review article illustrates the issues concerning varied aspects of natural and synthetic environmental factors mediating DNA damage in different organisms including humans as demonstrated as a flow chart in figure 1. It has been attempted to include the possible mechanisms involved in this important cascade of events. An updated account of plant extracts/plant-based principles exhibiting protection potential have also been added. The information presented in this article may be useful to a wide range of audiences including researchers, health workers, students, teachers, environmentalists and policy makers so as to design and develop strategies to protect humans and animals from carcinogenic impacts of varied physical, chemical and biological agents known for their genotoxic properties.

Author Contributions

NS wrote the review article prepared and assembled the figure; BS has critically organized and revised the manuscript by incorporating significant reports.

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Conflicts of Interest

The authors declare no conflict of interest.

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