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Biotoxins Mediated DNA Damage and Role of Phytochemicals in DNA Protection

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Abstract

The DNA is reported to be consistently damaged by both endogenous processes and external insults thereby posing a serious threat to the cell survival. Exposure of DNA from living systems to different biotoxins is believed to lead DNA damage and a variety of genetic disorders. However, only meager information is available in this context. Keeping in view the knowledge gap, we have endeavored to present an updated account on this subject with special reference to the amelioration by herbal products.

Keywords: Xenobiotics; DNA damage; Toxins; Oxidative; Nicotine

Introduction

Xenobiotics are often defined as small organic molecules that are “foreign to life”. DNA is consistently damaged by both endogenous processes and external insults thereby posing a challenge to the cell survival [1-3]. Generally, the genomes of all the living organisms, including animals and plants, are stable. Because of constant exposure of the genome to various xenobiotics, the DNA gets damaged. This event can produce a variety of genetic disorders which might be inherited from one generation to the other [4,5] The DNA damaging potential of xenobiotics has been reported well by several workers. While the impact of biotoxins on DNA has been described by only a small number of workers, the results however, have been inconclusive. Keeping in view the knowledge gap, we have endeavored to present an updated account on this subject with special reference to their mechanism(s) of action for DNA damage. For instance, Ochratoxins which are a group of mycotoxins produced by some Aspergillus species and some Penicillium species act as potential nephrotoxins and renal carcinogens. Ochratoxin A (OTA) has been reported to DNA-strand breaks in liver, kidney, and spleen of treated animalsand a similar degree of DNA damage was observed in rats treated with Ochratoxin A (OTB) [6].

Biotoxins are the substances which are produced by living organisms. The living organism can be a plant or an animal. Generally, toxin are metabolic byproducts of animals and plants. Natural compounds such as plants products and human hormones can also act as toxins.

These toxins enter into the body of an organism through several routes of exposure such as dermal contact, inhalation, ingestion, injection or accident. These chemicals may cause membrane damage, protein dysfunction, DNA impairment, disorder of metabolism. They may negatively modulate signaling pathways, and cause mutagenicity as well as cell death (**Table 1**) [7,8].

Table 1 List of some Biotoxins and their effects on DNA.

S.No.	Biotoxins	Effects on DNA	Reference
1	Mitomycin C	Damage of DNA in rice	[9]
2	Nicotine	DNA damage in different human epithelial and non-epithelial cells	[10]
3	Sanguinarine	Inhibits tumor promotion by damaging DNA	[11]
4	T-2 Mycotoxin	Hepatic DNA fragmentation	[12]
5	Berberine	Inducing oxidative DNA damage	[13]
6	chelerythrine	DNA damaging effects against mouse leukemic cells and primary mouse spleen cells	[14]
7	Deoxyamphimedine	Enhanced toxicity in cells sensitive to single or double strand DNA breaks	[15]
8	Nitrosobenzene,	Induced NADH plus Cu(II)-mediated DNA cleavage frequently at thymine and cytosine residues.	[16]
9	YM155	Generate DNA damage through intercalation with DNA	[17]
10	Domoic acid	Induced direct DNA damage	[18]

Mechanism of DNA damage by biotoxins

Toxins induce their effects by distorting the DNA structure through breakage of hydrogen bonds between two complementary base pairs involved in stabilization of DNA

strands. In order to maintain the genome integrity, it is necessary to repair the DNA damage with the help of DNA repair machineries. Any abnormality in DNA repair mechanism can result in genomic instability. The cross-linking agents such as mitomycin C and aromatic compounds, fungal and bacterial toxins, metabolic products such as free radicals or reactive oxygen/nitrogen species (ROS/RNS) play crucial role in DNA damage [19]. Free radical induced DNA damage in living organisms by a variety of mechanisms. These include DNA base and sugar products, single- and double-strand breaks, 8,5′-cyclopurine-2′-deoxynucleosides, tandem lesions, clustered sites and DNA-protein cross-links (**Figure 1**) [20].

Oxidative stress and DNA damage

The mechanisms of oxidative DNA damage have not been elucidated properly. However, the oxidative DNA damage mediated by Fenton reactions has been reported to be the most acceptable hypothesis. Free radicals, commonly known as reactive oxygen species, contain one or more unpaired electrons in their outer most orbital. Excessive production of free radicals results in depletion of antioxidants *in vivo* and causes an imbalance between free radicals and the antioxidant defenses of the body, which results into generation of oxidative stress mediated DA damage.

The 8-hydroxydeoxyguanosine (8-OHdG) is the most common biomarker of oxidative DNA damage by chemical carcinogens in which oxidation of a specific base i.e., guanosine in DNA causes increase in the level of hydroxydeoxyguanosine (8-OHdG). These oxidative chemical species may cause deamination of cytosine converting it into uracil or may remove an individual base generating apurinic/apyrimidinic (AP) sites into DNA (**Figure 1**) [21].

Phytoremediation of DNA damage

There are some plant products which are shown to possess DNA damaging potential. Recent findings suggest an active role of nicotine. It is the major tobacco alkaloid present in tobacco and causes carcinogenesis. Nicotine exhibits tumor promoting potential by causing DNA damage in different human epithelial and non-epithelial cells [10]. An alkaloid, sanguinarine, isolated from a wild plant, *Argemone mexicana*, has been shown to cause chromosomal aberration, micronucleus formation and DNA damage by comet assay in mouse model *in vivo* system. Sanguinarine is reported to inhibit the activity of epidermal histidase leading to the increase in the levels of keratin formation and tumor promotion.

In this study, the effects of microcystins (MCs)-containing cyanobacteria extract (CE) on damage of DNA in rice was studied in which significant DNA damage was observed in rice seedlings after exposure to CE [9]. T-2 Mycotoxin is a trichothecene mycotoxin. It is a naturally occurring mold byproduct of Fusarium spp. It is a fungus which is toxic to humans and animals. Treatment of fasting mice with a single dose of T-2 toxin (1.8 or 2.8 mg/kg body weight) by oral route has been shown to lead to 76% hepatic DNA fragmentation (**Figure 1**) [12].

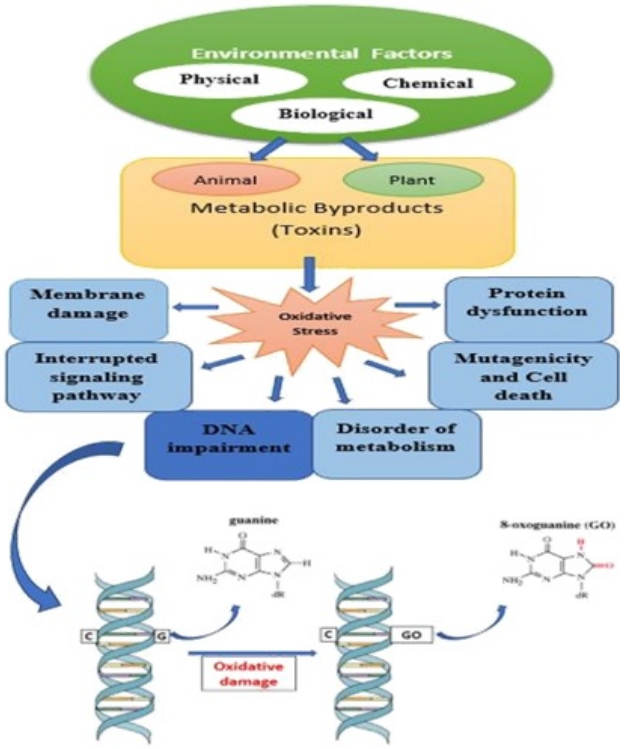

Figure 1 Toxins mediated alterations in DNA structure and the mechanism of DNA damage. The accumulation of biotoxins is believed to generate free radicals which primarily act on the 8th position of the guanosine changing it into 8hydroxy or 8oxoguanosine responsible for DNA damage.

Discussion

Antioxidants are usually the free radicals neutralizing and reducing agents such as vitamins, carotenoids, flavones, flavonoids and polyphenols, which scavenge the reactive oxygen species (ROS) and inhibit the chain reaction by initiated by them. DNA damage inhibition by the methanolic extract of *C. carandas* leaves has been demonstrated. The aqueous extract of *Ganoderma lucidum* occurring in South India have demonstrated significant antioxidant property and revealed the potential to protect DNA from radiation mediated damage. These findings were suggestive of the possibility of using the medicinal extracts containing flavones, polyphenols, flavonoids, terpenes, tannins and alkaloids as alternative therapeutics in treatment of cancer. Arecoline, an alkaliod constituent of Areca nut has been used in treatment of oral and pharyngeal cancers. In addition to their free radical quenching potential, the plant products help chelate heavy metals and protect the DNA from damage. Also, some vitamins such as Vitamin C and E have been shown as quenchers of free

radicals and therefore they inhibit the DNA damaging properties of xenobiotics in the living cells [22,23].

Natural products such as vitamins, phytochemicals and alpha-lipoic acid has been reported to minimizing the adverse effects of toxins. It has been reported that natural products chelate with toxins and increase the excretion of bio-toxicants outside from the body, the process helps in less accumulation of toxins into the body (blood and tissues). Thus it is evident that natural compounds with both chelating and antioxidant activities could be good candidates for mitigating several adverse effects of toxins such as DNA damage and carcinogenesis [24].

Conclusion

Genotoxicity induced by both the man-made chemicals and those produced by living systems need to be properly addressed by application of safer and cost effective antidotes. The use of phytochemicals in this context can offer a potential option. However, lot of work is required to be carried out in this direction to reap the optimum benefit.

Conflicts of interests

The authors declare that they do not have any conflict of interests.

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