



Review Article

Repair Activity Impaired by Arsenic: Recovery by Phytochemicals

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ABSTRACT

Reactive oxygen species result in oxidative damage, which is well documented to play a role in various diseases, including cancer. DNA repair mechanisms of the cell help to cope with such damages; however when these pathways get impaired, genomic instability and cancers result. Ground water contamination with arsenic is a global problem. Exposure to arsenic results in generation of reactive oxygen species, damage of DNA and inhibition of repair machinery. These mechanisms are highly relevant for the development of carcinogenesis. Chemotherapeutic drugs used in cancer therapy are mostly DNA damaging agents. However they show various toxic side effects and in many cases, drug resistance results. Thus, novel means of therapy needs to be developed to tackle the calamity. Phytochemicals or active ingredients of plants may be explored in this context. They have known mechanisms of action and are potent anti-carcinogenic agents. In addition to all these, they are relatively non-toxic, easily available, and inexpensive, show anti-oxidant and DNA repair activities. Use of phytochemicals may thus open new avenues in the fight against this dreadful disease.

Keywords

Cancer,
arsenic,
DNA damage,
NER,
BER, repair,
phytochemicals

Introduction

Cancer burden all over the world is on the rise. Carcinogenesis is not a single process, but involves multitude of mechanisms. Three main three steps are initiation, promotion and progression, which act in concert to contribute to the malignant transformation. Oxidative stress plays a pivotal role in the initiation of the events. Enhanced generation of Reactive Oxygen Species (ROS) can originate from

exogenous sources like environmental agents, pharmaceuticals, industrial chemicals etc. However endogenous sources like mitochondria, peroxisomes, and inflammatory cell activation can have equal contribution in this regard (Klaunig *et al.*, 2010). They can affect the intrinsic antioxidant defence mechanism of the cell which is insufficient to overcome the ROS burden. ROS production disrupting the

antioxidant balance often culminates to damage macromolecules like proteins, lipids and DNA (Uttara *et al.*, 2009). Steady-state quasi-equilibrium of a cell may get perturbed due to damage in DNA. Consequentially it results in activation and amplification of several pathways controlling cell growth and division (Moron *et al.*, 2011). Manifestations that can counter the adverse effect of DNA damage are DNA repair, DNA damage checkpoints, transcriptional response, and apoptosis (Sancar *et al.*, 2004). Metal ions interact with DNA and nuclear proteins, leading to damage and conformational changes, which may also aid in carcinogenesis. Among the exogenous factors that harm DNA, protein and lipid are some metals, including heavy metals. People quite often are environmentally or occupationally exposed to these dangerous elements. Cadmium, cobalt, lead, arsenic, mercury, chromium etc are some of the metals worth mentioning. They affect cellular components including cell membrane, mitochondria, lysosome, endoplasmic reticulum, nuclei and eventually alter metabolism, detoxification and damage repair system. They interfere with the repair machinery *vis a vis* cause damage to the genetic material. Owing to the high toxicity, these elements find a place among those responsible for public health hazards (Tchounwou *et al.*, 2012).

Arsenic and cancer

Water is essential for sustenance of life. But, water can cause a plethora of health hazards, due to the presence of several toxic substances as a pollutant. The lurking poison Arsenic (As), a well known toxicant, poses major threat to human health. Arsenic is a naturally occurring tasteless, colourless, odourless metalloid widely distributed in the environment and a variety of occupational settings. Arsenic is ubiquitously present in

both organic and inorganic forms, the later being more toxic than the previous one. Natural processes like weathering of rocks, emissions from volcano and a variety of anthropogenic activities resulted in mobilisation of arsenic into the environment. Some industrial and agricultural processes also contribute to this calamity. Cumulatively these factors make arsenic a disastrous ground water contaminant (Roy *et al.*, 2014). Arsenic contamination of groundwater has become a worldwide menace. The reason behind mixing of arsenic with the ground water and food chain is mainly because of its association with rocks, sediments and soil. Excess level of arsenic may be the cause of serious health issues. Therefore the World Health Organisation (WHO) set a safety level of arsenic in drinking water, which is 10 µg/ml (Huq *et al.*, 2006). Beyond this safe limit, adoption of remedial measures is very important. Arsenic also causes several problems at the cellular level; DNA damage, sister chromatic exchange (SCE), gene amplification, aneuploidy, clastogenicity, mutagenicity may be the aftermath of arsenic exposure (Tchounwou *et al.*, 2003). Oxidative stress to DNA may be recognised as a mechanism underlying carcinogenic effects of arsenic (Biswas *et al.*, 2010a). Generation of ROS leads to oxidative DNA adducts comprising base modification, deoxyribose oxidation, single-strand or double-strand breakage, and DNA-protein cross-links (Cadet *et al.*, 1997). Carcinogen-DNA interaction results in damage to the genetic material and leads to the initiation stage of carcinogenesis. Cell identifies and corrects damage to the DNA molecules by the inherent repair process. An active DNA repair process is therefore of tremendous importance to maintain the integrity of DNA. Failure to repair the damage and evasion of programme cell death (apoptosis)

are the foundation stones of malignant transformation.

Involvement of repair mechanism in cancer:

DNA damages include covalent changes in structure of DNA and non covalent structural changes including base-pair mismatches, loops and bubbles arising from a string of mismatches. Covalent changes are repaired by DNA repair and recombination means. Non-covalent alterations on the other hand get repaired by mismatch pathways. To counteract the harmful effects of DNA damage, cells have developed a specialized DNA repair system, which can be subdivided into several distinct mechanisms based on the type of DNA lesion. These processes include base excision repair (BER), mismatch repair, nucleotide excision repair (NER), and double-strand break repair, which comprise both homologous recombination and non-homologous end-joining (Sancar *et al.*, 2004).

Of the two forms of arsenic present in the environment, organic forms are comparatively safer for human consumption. Inorganic arsenic by virtue of its interference with repair process contributes to the development of cancer. Repair potential in a population drinking arsenic contaminated water was hampered in contrast to the population drinking safe water (Roy *et al.*, 2011). Impairment of the DNA repair capacity is one of the main mechanisms of carcinogenesis. Pentavalent organic arsenic, dimethylarsenic acid (DMA) inhibits DNA repair in human alveolar cells, leading to prolonged DNA damage. The damage in DNA normally gets repaired by excision repair pathway. Two main excision repair pathways are BER and NER. Arsenic induces ROS, which is

predominantly repaired by BER mechanism (Martinez *et al.*, 2011). Expression of repair enzymes like Poly (ADP-ribose) polymerase 1 (PARP1), DNA β polymerase, X-ray repair cross-complementing protein1 (XRCC1) and DNA ligase III, involved in BER pathway get impeded by arsenic. Bulky DNA adducts are efficiently repaired and removed by NER pathway (Andrew *et al.*, 2006) which has been found to be inhibited by arsenic as well (Roy *et al.*, 2011). Reports suggest that this inhibition of repair machinery is attributable to generation of ROS by arsenic (Shen *et al.*, 2013). Chronic exposure to elevated arsenic in drinking water resulted in diminished expressions of excision repair cross-complementing (ERCC1) and xeroderma pigmentosum (XPB and XPF), proteins involved in NER pathway (Andrew *et al.*, 2003). Nonhomologous end joining (NHEJ) repair modality is present in eukaryotic cells and this is facilitated by DNA-dependent protein kinase (DNA-PK). Some other proteins involved in this pathway are XRCC4-ligase IV complex, which functions in the ligation step of repair. Reports show that chronic exposure to arsenic leads to diminished expression of DNA-PKcs, both at the protein and genetic level (Okayasu *et al.*, 2003). Arsenic not only is genotoxic, but influences the genotoxicity of other DNA damaging agents and that too by impairment of repair activities. Therefore repair mechanism plays a pivotal role in maintaining genomic stability and hence prevention of cancer. Arsenic interrupts the whole repair mechanism, promoting carcinogenesis. The guardian of genome, p53 has a direct impact on cell cycle regulation, which is required for DNA repair machinery. Exposure to arsenic leads to down-regulation of p53 at the protein and genetic level, as a consequence of which the repair of DNA damage gets interrupted (Shen *et al.*, 2013). All these facts

cumulatively suggest that more than one mechanism may toil to alter the repair machinery, contributing to toxicity and therefore cancer.

Arsenic, epigenetics and cancer:

Epigenetics involves study of cellular and physiological features that get passed on to the daughter cells without causing any changes in the DNA sequence; thereby altering long-term transcriptional activity, leading to changes in expression of genes. One of the mechanisms of induction of tumorigenesis by arsenic is through epigenetic modulations like methylation of DNA (Reichard and Puga, 2010). It was thought that Methylation of Arsenic is a detoxification reaction, but later on it was found to be more dangerous than the toxic inorganic forms. Inorganic arsenic and its methylated forms are reported to have an inhibitory effect on NER. Trivalent forms of arsenic are more effective in inhibiting the above process than their pentavalent counterparts as pentavalent arsenic on entering the cell gets reduced to trivalent forms. Trivalent forms of arsenic are responsible for most of the observed biological effects (Shen *et al.*, 2013). Arsenic upregulates the expression of epidermal growth factor receptor (EGFR) resulting in phosphorylation of the component of mismatch repair namely proliferating cell nuclear antigen (PCNA). The carcinogenic potential of arsenic is attributed to inactivation of mismatch repair system (Kim *et al.*, 2014). Some other epigenetic changes like histone modifications are also involved in the process of development of malignancy (Shen *et al.*, 2013). Histone deacetylase (HDAC) inhibitors are reported to influence DNA repair mechanisms. Inhibition of HDAC leads to acetylation of histones and transcription factors such as p53, GATA-1

and estrogen receptor-alpha. Some inhibitors of HDACs like vorinostat (suberoylanilide hydroxamic acid or SAHA), trichostatin A, valproic acid may cause nausea, vomiting, anorexia, fatigue, thrombocytopenia, neutropenia, anemia, cardiac toxicity, neurological disorder etc. Natural plant products may aid in this problem.

Phytochemicals in remediation:

Chemical compounds that are present in plants are called phytochemicals, which are abundantly present in fruits, vegetables, herbs, beans, grains, spices, beverages and other plants. These are non-nutritive part, imparting protective and preventive role against diseases (Sarkar *et al.*, 2014). Phytochemicals are very often stud with antioxidant properties and therefore very efficient to protect against oxidative damage. Some examples are flavonoids, flavones, isoflavones, anthocyanidins, carotenoids, polephenols, isothiocyanates, allyl sulphides (Roy *et al.*, 2014). In addition to this, phytochemicals are also known to boost the immune system and possess anti-cancer (Sarkar *et al.*, 2014), anti-inflammatory and anti-bacterial properties. They may also act as stimulators of the enzymatic and replicatory machinery of the cell. Phytochemicals, apart from all these properties are very effective in reversal of DNA damage and an enhancer of damage repairing capacity (Liu, 2004). There is a link between tissue necrosis and carcinogenesis with impaired anti-oxidant system associated DNA damage in arsenic exposed humans, which can be efficiently reverted by amla (*Emblica officinalis*). Superoxide dismutase (SOD), catalase and non-protein soluble thiols which are inhibited by arsenic may get restored by amla (Singh *et al.*, 2014).

Lifestyle and healthy diet are key players in the aetiology of cancer. Polyphenols (like luteolin and quercetin), carotenoids (like β -carotene, lutein and lycopene) and extracts of *Salvia* species are reported to induce strand breaks rejoining. Flavonoids and vitamin C & E help to promote the repair activity against oxidative DNA damage. DNA repair capacity has been found to be enhanced upon consumption of kiwifruits. BER activity was also increased by anti-oxidant rich plant products (Ramos *et al.*, 2011). Resveratrol present in red wine is another nutraceutical rich in anticancer properties. It is reported to reduce DNA damage in breast cancer cells (Leung *et al.*, 2009). Phytochemicals present in diet affects the epigenome, thus triggering DNA damage and repair mechanisms. Inhibition of histone acetyl transferase (HAT) also induces double strand break repair. A diet deficient in folate is known to interrupt genomic stability (Rajendran *et al.*, 2011). Cruciferous vegetables like cabbage, broccoli, cauliflower etc are rich sources of glucinolates which get hydrolyzed to form isothiocyanates and indoles (Rajendran *et al.*, 2011). Sulphoraphane and phenethylisothiocyanate (PEITC) are reported to positively influence the mRNA levels of ERCC4 and ERCC5, two NER genes (Gross-Steinmeyer *et al.*, 2010). Certain active compounds like chlorophyllin, ellagic acid, and theaflavin, present in green leaves, fruits and tea respectively have been found to enhance the DNA repair enzymes 8-oxoguanine glycosylase 1 (OGG1), xeroderma pigmentosum D (XPD), xeroderma pigmentosum G (XPG), and x-ray repair cross complementing group 1 (XRCC1) (Kavitha *et al.*, 2013). Quercetin and rutin, two polyphenols exert their repair activity via non-enzymatic repair mechanism (Tan *et al.*, 2009). The active ingredient in tomato is lycopene. Lycopene finds importance in the

treatment of oxidative stress-induced cell death and that is achieved by prevention of loss of DNA repair protein Ku70 (Seo *et al.*, 2009). Vitamins are good for health. Good source of Vitamin A, Vitamin C, niacin and polyphenolic compounds are some fruits like peaches and nectarines. Intake of these in diet modulates the DNA repair activities and as a result ameliorates the level of oxidative stress induced DNA damage (Croteau *et al.*, 2010). Endogenous oxidative damage may be reduced by ellagic acid, present in raspberry by enhancement of DNA repair. Dietary ellagic acid is highly effective in reducing baseline hepatocellular oxidative DNA damage partly via enhanced DNA repair. Red raspberry, a natural source of ellagic acid, is more efficacious than pure ellagic acid and also causes up regulation of DNA repair enzymes, making it a suitable candidate for nutritional intervention. Both berries and ellagic acid significantly reduce hepatic oxidative DNA damage, suggesting their usefulness in other hepatic pathologies in which oxidative mechanisms are implicated (Aiyer *et al.*, 2008). Results suggest that an increased intake of fruits might modulate the efficiency of DNA repair, resulting in restoration of DNA damage.

Natural inhibitors of HDACs like isothiocyanates (ITCs), curcumin, indole-3-carbinol, anacardic acid, allium compounds, selenium, epigallocatechin-3-gallate (EGCG), resveratrol, quercetin, isoflavones etc (Rajendran *et al.*, 2011), contribute to the activation of repair process. Indole 3 carbinol increases repair of DNA by regulating various proteins involved in the repair pathway (Rogan, 2006). β -cryptoxanthin, β -carotene, lutein and lycopene increased rejoining of strand breaks (Lorenzo *et al.*, 2009, Fillon *et al.*, 1998, Torbergsen and Collins, 2000). *Azadirachta indica* (neem), *Ocimum sanctum*

(holy basil) and *Withania somnifera* (winter cherry) possesses phytonutrients that increase O(6)-Methylguanine-DNA methyltransferase (MGMT) expression and activity. *Emblica officinalis* (gooseberry), *Ocimum basilicum* (common basil) and *Mentha viridis* (spearmint) are also reported to increase levels of MGMT. It is an enzyme that helps to repair DNA damage. Curcumin, silymarin, genistein, epigallocatechin-3-gallate and resveratrol also helps to enhance MGMT activity (Niture *et al.*, 2006). Green pepper, mushrooms, brussel sprouts, cruciferous vegetables and leguminous sprouts also play an important role in repair of damaged DNA. NADPH oxidase has a key role in stress responses and subsequent repair process of the cell (Jiang *et al.*, 2011). Capsaicin, derived from capsicum has been reported to diminish the NADPH oxidase activity in carcinoma differentially, with no harmful effect on normal cells (Bley *et al.*, 2012).

Beverages are an intricate part of the daily life and culture. Tea, the second most popular beverage in the world, is an infusion of the dried leaves of the *camellia sinensis* in water. Polyphenols in tea possessing antioxidant properties may aid in counteracting the damage induced by arsenic by quenching ROS and increasing antioxidant enzymes expression. (Sinha *et al.*, 2010). Both green and black tea are capable of combating the arsenic disaster (Sinha *et al.*, 2003). Arsenic exposure causes loss of repair potential which can be restored by tea polyphenols via induction of repair enzymes (Sinha *et al.*, 2005).

Spices do not lag behind so far as antioxidant and repair activities are concerned. Curcumin is an age old Indian spice imparting taste, colour and flavor to the cuisine, which aids in many home remedies against various ailments. Initiation

of arsenic induced cancers may be counteracted by curcumin as it induces repair enzymes at both protein and genetic levels (Roy *et al.*, 2011). A field trial conducted in West Bengal, India revealed the potential of curcumin against arsenic induced genotoxic effect. Decrease in DNA damage, ROS generation, lipid peroxidation and increasing anti-oxidant activity (Biswas *et al.*, 2010b) are some of the mechanisms responsible for this action. *Origanum compactum*, commonly known as oregano, finds use in many recipes, contains high amounts of carvacrol. It possesses high antioxidant property and DNA repair potential. Fushimi sweet pepper is reported to enhance repair against pyrimidine dimers induced by ultraviolet rays (Nakamura *et al.*, 2000). Suppression of nucleotide glycation by glyoxalase I has a protective role on DNA repair. Detoxification is achieved by glyoxalase I, which catalyses the isomerisation of the spontaneously formed hemithioacetal adducts between GSH and 2-oxoaldehydes (such as methylglyoxal) into S-2-hydroxyacylglutathione. Fennel, a spice having a characteristic odour and taste that adds taste to the gourmet increases the activities of antioxidant enzymes (Singh and Kale, 2008). DNA-PKcs play an active role in NHEJ DNA repair pathway and also in programmed cell death. The phytochemical thymoquinone, found in the plant *Nigella sativa* acts on DNA-PKcs, which mediate the repair process by phosphorylating various DNA binding proteins (like p53, DNA ligase IV) and transcription factors including Fos, Jun, myc, Oct1, NF-kappa B, and RNA polymerase H (Gurung *et al.*, 2010).

Maintenance of genomic integrity and stability is of supreme importance in the development of carcinogenesis. Most of the anti-cancer drugs elicit their activity by damaging DNA of the cancer cells, but, at

the same time they target normal cells as well, causing severe toxicity to the individual and imparting severe undesirable side effects. DNA damage is caused by exposure to several chemicals, radiation; arsenic is one such metalloid, which has a serious impact on health. Plant derived molecules which are rich in disease fighting properties are normally free from toxicity. There has been a fountain of phytochemicals and they are paramount in these respect. These molecules are unique as they are cheap, acceptable to the society, can prevent damage, potentiate repair activity and differentially target cancer cells and therefore may serve as an arsenal against many disastrous situations. They seem to promote health in an orchestrated, but not yet fully understood way. These nutraceuticals therefore require more research to establish their place in cancer management.

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