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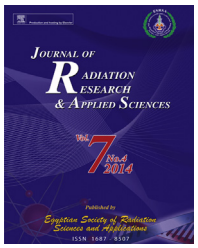

Combined effect of arsenic trioxide and radiation on physical properties of hemoglobin biopolymer

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ABSTRACT

Arsenic trioxide (As_2O_3) has been recently established as one of the most effective drugs for the treatment of patients with acute promyelocytic leukemia. However, it was widely used in therapeutic of many kinds of cancer by combining it with ionizing radiation. Thus, the purpose of the present study was to explain the combined effect of As_2O_3 and gamma irradiation on hemoglobin (Hb) structure. Measurements using fourier transform infrared (FTIR) and UV-visible spectra were done. This study included five groups: control, irradiation with single dose of gamma irradiation of 5 Gy, intraperitonial injection with single dose of 10 mg/kg body weight of As_2O_3, As_2O_3+5 Gy and 5 Gy+As_2O_3. The results reported that the absorbance of secondary amide, amide I and amide II of all groups were lowerd than control, whereas the absorbance of amide III and amide IV for As_2O_3 and 5 Gy followed by As_2O_3 injection has been increased. For UV-visible spectra, As_2O_3 injection decreased the absorbance of globin-heme and soret bands and increased β, α and 630 bands compared with control. On injection with As_2O_3 followed by 5 Gy showed a decrease in globin-heme, soret, β and α bands and increase in 630 band. Moreover, 5 Gy followed by As_2O_3 demonestrated a decrease in globin-heme, β, α and 630 bands and an increase in soret band, also the ratio of α/β showed an increase in absorbance compared with control. The results concluded that 5 Gy followed by As_2O_3 showed some sort of repair in the structure of rats hemoglobin rather than injection with As_2O_3 and 5 Gy both individually.

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1. Introduction

Arsenic agents have been used as anti-cancer agents in traditional Chinese medicine (Antman, 2001). Also, Usage of As_2O_3 in therapy has been approved by the U.S. Food and Drug Administration (FDA) (Zhu, Chen, Lallemand-Breitenbach, & De Thé, 2002), it is reported to be an effective inducer of apoptosis in certain cancer cells including acute promyelocytic leukemia (APL), other myeloid leukemic cells, osephageal, prostate and ovarian carcinomas (Maeda et al., 2001; Shen, Shen, Cai, Hong, & Zheng, 2000; Uslu et al., 2000). Ionizing radiation is one of the most common radiotherapy techniques used for cancer patients. Thus, for first time one of the important points in the development of a new anti-cancer drug is the understanding of the combined effect of As_2O_3 and gamma irradiation on hemoglobin structure. Although, several studies have been worked in arsenic, one of them was given by (Mishra & Flora, 2008) in India and Bangladesh who showed the chronic exposure poisoning of arsenic caused by contaminated drinking water in rats this led to oxidation stress in blood and brain. Another, Mallick, Mallick, Guha, & Khuda-Bukhsh (2003) who studied the effect of intraperitoneal injection of As_2O_3 of mice on alanine amino transferase (ALT) and aspartate amino transferase (AST) activities and reduced glutathione (GSH) in blood and liver. One advantage of As_2O_3 is its capability to penetrate into the subcellular compartments of living cells (Bacquart, Deves, & Ortega, 2010). Also arsenic interact not only with the DNA molecules, but also with different proteins and important enzymes with the cell, the most reactive trivalent form of arsenic has a preference for SH groups present in various essential compounds. Trivalent arsenicals have a binding affinity for the cysteine residues present on cellular protein molecules (Zhou et al., 2006). Also, Iriyama et al. (2012) explained the analysis of total arsenic concentration and speciation, of blood and bone marrow from acute promylocytic leukemia patient, were performed by inductively coupled plasma mass spectrometry (ICP-MS) and high performance liquid chromatography (HPLC), respectively. Lastly, Raja (2013) who studied the combined effect of various low doses of As_2O_3 and ionizing radiation on MTLn3 cells, and demonstrated that As_2O_3 was able to generate apoptosis in these cells; however, in low doses treatment with As_2O_3 caused rapid cell proliferation. Although ionizing radiation alone had no effect on cell proliferation, when combined with the low concentration treatment of As_2O_3 which alone had no effect, cellular proliferation was stimulated. Thereby, arsenic acted on cells through a variety of mechanisms, influenced numerous signal transduction pathways and resulted in a vast range of cellular effects that include apoptosis, growth inhibition, promotion or inhibition of differentiation and angiogenesis (Miller, Schipper, Lee, Singer, & Waxman, 2002; Rossman, 2003). Arsenic induced responses vary depending on cell type, dose and its chemical form. Arsenic trioxide was detected as an active compound in an ancient Chinese therapy for leukemia and is currently under review in clinical approval process (Chou & Dang, 2005).

Study of FTIR for Hb functional groups as a result of combined effect of As_2O_3 and 5 Gy gamma irradiation was taken in the interest. Hb functional groups are five groups; secondary amide (3250–3300 cm^{-1}) N–H stretch in resonance with amide II overtone, amide I (1640–1660 cm^{-1}) mainly C=O stretch, amide II (1480–1575 cm^{-1}) N–H bend in plane and C–N stretch, amide III (1400–1600 cm^{-1}) and amide IV (1300–1400 cm^{-1}) (Potter, Hazzard, Choc, Tucker, & Caughey, 1990). The component of amide I (α, β, random and turn) determined at wavenumber 1654, 1626, 1640 and 1682 respectively (Damian & Canpean, 2005). The amide III and amide IV originate from the bending vibrations of $-CH_2$ and $-CH_3$ groups of amino acids in the protein side chains (Dong, Huang, & Caughey, 1992; Surewicz & Mantch, 1996). Only amide bands I-III are used for investigation protein secondary structure (Bandekar, 1992; Barth & Zscherp, 2002; Dousseau & Pezolet, 1990; Krimm & Bandekar, 1986). In the amide I region (1700–1600 cm^{-1}), each type secondary structure gives rise to a somewhat different C=O stretching frequency due to unique molecular geometry and hydrogen bonding pattern (Kong & Shaoning, 2007). The most sensitive spectral region to the protein secondary structural components is the amid I band (1700–1600 cm^{-1}), which is due almost entirely to the C=O stretch vibrations of the peptide linkages (Krimm & Bandekar, 1986).

UV-visible absorption spectroscopy showed that Hb exhibited intense absorption wavelengths above 320 nm; the absorption spectrum of Hb biopolymer characterized by globin-heme, soret, β, α bands. The band for globin-heme at 340 nm refers to non-covalent bond between globin's histidine and heme irons, for β-band at 542 nm refers to Iron–Nitrogen in porphyrine, and for α at 578 nm (heme–heme interaction band) (Zijlstra, Buursma, & Meeuwsen-van der Roest, 1991), strong absorptions occur near 400 nm and this peak region is known as the soret band (Denninghoff, Chipman, & Hillman, 2007; Faber et al., 2004). The soret band is characteristic of hematoporphyrin proteins (Murray, 2003; Nelson & Cox, 2005).

2. Materials and methods

2.1. Chemical

Arsenic trioxide (powder As_2O_3) was obtained from Sigma Aldrich code A1010, p code 1001268737, reagent plus®, ≥99% have molecular weight of 197.84 g/mol, appearance of white solid. As_2O_3 was dissolved in H_2O by continues stirring and kept at 4 °C as a stock solution.

2.2. Animals

Rats weighting 130 ± 20 g were kept in cages under routine light and dark system and freely provided with fresh water, they were divided into five equal groups of ten rats each: group (1): control group, group (2): irradiated group, group (3): injected group with As_2O_3, group (4): irradiated group and injected group and group (5): injected and irradiated group. Group (3) taken intraperitoneally single dose of 0.1% As_2O_3 10 mg/kg body weight, group (4,5) taken single dose of 5 Gy after/before 2 h from injection, rats were scarified after 24 h.