Cadmium Induced Lung Toxicity and The Protective Role Of Selenium In Adult Male Albino Rat

Thesis
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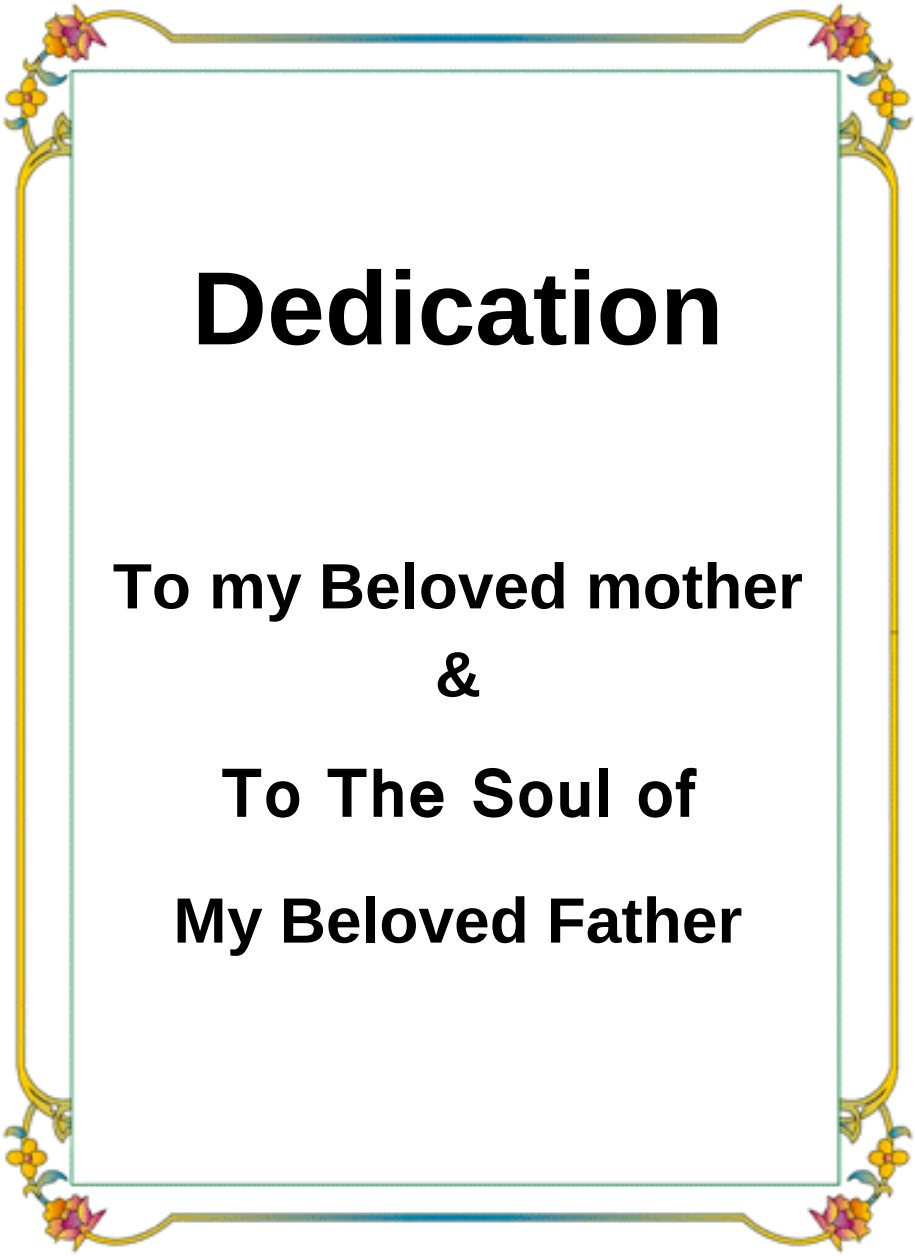

Dedication

To my Beloved mother

&

To The Soul of

My Beloved Father

بسم الله الرحمن الرحيم

قالو سبحانك لا علم لنا إلا ما علمتنا إنك أنت العليم الحكيم

صدق الله العظيم

سورة البقرة الأية ٣٢

Introduction

Cadmium (Cd) is an environmentally widely dispersed and highly toxic heavy metal that has been classified as human carcinogen ***(Shin, et al., 2004).***

Significant quantities of cadmium compounds are used in several industries, and a large number of workers are potentially exposed to toxic levels of the metal ***(Waalkes, 2000)***. Workers are exposed to cadmium through smelting and refining of metal ores; during electro-plating & welding, burning coal and during the manufacture of batteries, paints and plastic stabilizers. On the other hand the general population is exposed to cadmium through cigarette smoke and contaminated food, water and air. Certain food contains low level of cadmium such as row potato, fish, shellfish, liver and kidney ***(Waalkes, et al., 1992).***

Cadmium has an extremely long biological half life which essentially makes it a cumulative toxin ***(Ostrowski, et al., 1999).***

Cadmium is ranked seventh on the "Top 20 Hazardous Substances Priority List" by the Agency for Toxic Substances and Disease Registry and the United Sates Environmental Protection Agency ***(Fay and Mumtaz, 1996).***

Cadmium compounds are considered to be a potential human carcinogen, and has been classified by the International Agency for Research on Cancer as a type I human carcinogen. The main target organs of cadmium-induced carcinogenicity are

the lungs, testis, prostate and hematopoietic system ***(Grasseschi, et al., 2003).***

Even though the toxic effects of Cd compounds have been studied for many years, inconsistent results have been obtained about their mutagenic and carcinogenic properties. The mechanism of metal induced carcinogenesis is still unknown. One possible mechanism of cadmium-induced carcinogenicity includes the mediation of mutagenic DNA damage, as demonstrated by chromosomal aberrations, DNA-protein cross links ***(Liu and Jan, 2000).***

Another possible pathway of Cd genotoxicity may be due to direct DNA-metal interaction ***(Valverde, et al, 2001).***

Although cadmium-induced mutagenicity and carcinogenicity are a multifactorial processes, oxidative mechanisms are believed to be of prime importance ***(Stohs, S.J. and Bagchi, D., 1995)***. Therefore, several reports have indicated that the mutagenicity of cadmium is associated with intracellular reactive oxygen species (ROS) ***(Chao and Yang, 2001).***

Lung is a primary target organ of systemic exposure to cadmium because Cd is mainly absorbed through the inhalation of industrial pollution and tobacco smoke, resulting in the accumulation of this metal in the lung. Systemic administration of this metal revealed the lung as a significant site of its deposition. Lung toxicity includes acute inflammation, edema

and chronic bronchitis as well as cancer ***(Kataranovski, et al., 2009).***

Selenium is an essential trace mineral that has a variety of functions. It activates antioxidant enzymes, which play a role in preventing cell damage. Some medical information suggests that selenium may help in preventing certain cancers, but better studies are needed. Selenium seems to stimulate antibodies after you receive a vaccination. It also may protect the body from the poisonous effects of heavy metals and other harmful substances ***(Woldarczyk, et al., 2000***). Fish, red meat, grains, eggs, chicken, liver, and garlic are all good sources of selenium. Meats produced from animals that ate grains or plants found in selenium-rich soil have higher levels of selenium ***(Karabulut-Bulan, et al, 2008).***

Woldarczyk, et al., (2000) mentioned that selenium may have a protective role against cadmium toxic effects. However the mechanism is not quite recognized, they reported that selenium and cadmium form a non-toxic high molecular weight complex in blood, moreover it was also found that selenium promotes cadmium excretion.

The single cell gel electrophoresis (SCGE) or comet assay is technically simple, effective, fast, cheap, sensitive, and accurate method which investigates DNA damage in all mammalian cell types without need for cell culture. It was applied in testing novel chemicals for genotoxicity and monitoring environmental contamination with genotoxins. Also

it is a reliable genotoxicity test for detection of DNA damage in tissues of experimental animals ***(Moller, 2005).***

AIM OF THE WORK:

Aim of the present work is to study the hazardous effect of cadmium on the structure of lung tissue and to evaluate its genotoxicity using the comet assay (single cell gel electrophoresis) as well as studying the possible protective role of selenium.

Cadmium

Cadmium (Cd) is a highly toxic heavy metal that is naturally present in the environment. Pure Cd is a soft, silver-white metal; however, it is unusual to find it in its pure form. It is commonly found in combination with other elements such as oxygen (cadmium oxide) or sulphur (cadmium sulphate) ***(Oberdorster, 1992).***

One of the most important problems that humanity expected to face in this century is environmental pollution. Cadmium is a particularly dangerous pollutant due to its high toxicity and great solubility in water. It has been classified as human carcinogen ***(Waalkes, et al., 1992).***

Kalcher, et al., (1993) stated that cadmium is present in tobacco with concentration determined by soil Cd concentration in the region where tobacco is grown. A single cigarette contains 1-2 mcg of Cd, so that exposure to environmental cigarette smoke may be a significant source of inhaled Cd.

Significant quantities of cadmium compounds are used in several industries, and a large number of workers are potentially exposed to toxic levels of the metal. Workers are exposed to cadmium through smelting and refining of metal ores; during electro-plating & welding, burning coal and during the manufacture of batteries, paints and plastic stabilizers. On the other hand the general population is exposed to cadmium through cigarette smoke and contaminated air, water and food. Certain food contains low level of cadmium such as raw potato,

fish, shellfish, liver and kidney. Meat, fish, and fruits generally contain up to 50 µg Cd/kg fresh weight, whereas vegetables, potatoes, and grain products may contain up to 150 µg Cd/kg fresh weight. Also, natural processes, such as erosion of rocks, volcanic eruptions, and forest fires, as well as, the burning of fossil fuels and use of sewage sludge as fertilizer, can result in an increased exposure risk to humans ***(Wahba, et al., 1993).***

The U.S. Environmental Protection Agency (EPA) suggested that a safe level of Cd in drinking water is 5 ppb (parts per billion) and in food is 15 ppm. The EPA believed that this level of exposure to Cd will not produce any of the health problems associated with Cd. Occupational Safety and Health Administration (OSHA) workplace air limit: 100 micrograms/m3 as cadmium fumes and 200 micrograms/m3 as cadmium dust ***(Stohs and Bagchi, 1995).***

Cadmium is ranked seventh on the "Top 20 Hazardous Substances Priority List" by the Agency for Toxic Substances and Disease Registry and the United Sates Environmental Protection Agency ***(Fay and Mumtaz, 1996).*** It has an extremely long biological half life (10-20 years) which essentially make cadmium a cumulative toxin. It is stored primarily in the kidneys; also liver and lung are important sites of toxication ***(Ostrowski, et al., 1999).***

Jeong, et al., (2001) stated that cadmium inhibited gap junctional intercellular communication (GJIC) in rat liver epithelial cells treated with 200µm CdCl2 for 14 days.

Moreover, they found that Cd reduced the number and function of gap junctions per cell.

Swiergosz-Kowalewska, (2001) had reviewed the toxicological effect of Cd on vital organs after acute and chronic exposures and had reported the incidence of nephropathies, hepatic necrosis, osteoporosis, and carcinogenesis.

Cell stress response is usually modulated at the molecular level via two mechanisms. The first is the synthesis of cell stress proteins or heat shock proteins (HSP) which assist protein folding and translocation. The second mechanism ensures the synthesis of proteases and hydrolytic components for degradation of damaged and short lived proteins. Cadmium induces the expression of several stress genes. It increases the expression of heat shock protein (HSP70). The relationship between cadmium and induction of cell stress gene expression is non-linear and affected by cadmium concentration and duration of exposure ***(Al-Khedhairy, et al., 2001).***

Kocak and Akcil (2006) mentioned that adult Wistar albino rats treated with 15 ppm $CdCl_2$ in drinking water for 4 weeks showed shortened prothrombin time and activated partial thromboplastin time. This indicated the presence of hypercoagulable state during chronic Cd intoxication, and hence increased the risk of thrombosis.

Cadmium exposure is known to cause endoplasmic reticulum (ER) stress, cellular damage and cell death. Moreover,

apoptosis occurred in $CdCl_2$ exposed human renal cells was due to activation of cell death signal transduction pathways ***(Komoike , et al., 2012).***