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Research Article

Amelioration of Mercury Toxicity Induced Oxidative Stress by *Aloe vera* and N-Acetylcysteine (NAC) in Rat Brain

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Abstract

Mercury compounds are bio-accumulative and toxic pollutants. Neurotoxicity is one of the many deleterious consequences of inorganic mercury toxicity. We investigated the toxicity potential of mercury chloride ($HgCl_2$) in promoting oxidative stress and its subsequent amelioration by *Aloe vera* and NAC treatment by employing a rat model. Rats were equally divided into six groups. Three groups of rats were exposed to inorganic mercury ($HgCl_2$ - 0.25 mg/kg/day) via the oral route for 21 days. Two out of three groups of rats receiving inorganic mercury were also given N-Acetylcysteine (NAC) [30 mg/kg] and *Aloe vera* [400 mg/kg] respectively for 21 days. Three control groups were made; first that didn't receive any treatment, second that received only NAC and third that was treated with only *Aloe vera.* We studied the effects of chronic exposure to mercury chloride in promoting neurodegeneration in adult rats.

Deposition of mercury in brain tissues and parameters indicative of oxidative stress were determined. Mercury treated rats showed increased lipid peroxidation along with reduced glutathione and decreased antioxidative enzyme activities of superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase and glutathione-S-transferase. These observations were further confirmed by our histopathology studies. It was concluded that both NAC and *Aloe vera* were effective in ameliorating the oxidative stress, functional impairments and histopathological changes induced by $HgCl_2$ toxicity in rat brain.

Keywords: *Mercury Chloride; Aloe vera; N-Acetylcysteine; Oxidative Stress; Neurotoxicity*

Introduction

Heavy metal contamination and toxicity is being recognized in large parts of the developing world, particularly in India and China [1]. Mercury is a rare non-transition metal that comes third in the list of most toxic elements on this planet by the US government agency. Anthropogenic activities such as agriculture, mining, discharge and incineration of industrial waste water contribute to the pollution caused due to this element. Mercury vapor can be released into the environment naturally through volcanic eruptions or from natural sinks like the ocean but also through human activities, such as burning of coal or waste [2]. Toxicity, biological impact and clinical outcomes of mercury compounds depend on their chemical forms [3]. Average whole-body half-life of mercury is 40 days. Several clinical cases due to inorganic mercury exposure in humans are reported in the literature. Inorganic mercury is used in drug formulations, dermatologic lotions and germicide solutions. Artisans get exposed to inorganic mercury during gold mining [4].

Inorganic mercury can damage several tissues such as kidney [5], liver [6], gastrointestinal tract [3], cardiovascular system [7] and reproductive system [8]. Neurotoxicity has also been reported as an important health concern due to toxicity of inorganic mercury. Majority of studies on the neurotoxicity are carried out with experimental models of different cerebral development stages (gestational, pre-natal or postnatal period) [9], due to the immaturity of the blood- brain barrier (BBB). Not many studies are reported in the literature on the effects of inorganic mercury in adults on account of its sparing lipid soluble nature, low absorption and passage through BBB. However, few reports on the effects of mercury in adult organisms [10] revealed its deposition in the brain parenchyma resulting in functional aberrations. Presence of large amounts of polyunsaturated fatty acids in nerve cell membranes make brain cells susceptible to attack by free radicals and hence to lipid peroxidation [11]. Increased levels of free radicals (especially nitric oxide) are found in both brain and serum of animals exposed to inorganic mercury [12,13]. *In vitro* studies show that diminished mitochondrial activity and lowered intracellular ATP levels form the molecular basis of the acute toxicity to inorganic mercury [13]. However, the exact mechanism of alterations in the redox status effecting energy metabolism in the brain is still not clear.

Endogenous antioxidant mechanisms operative in cells include molecules like glutathione and several enzymes such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX), as well as the enzymes involved in the recycling of GSH, and generation of NADPH [14]. Factors that deplete cells of GSH and other thiols create oxidative stress inside the cell that is counteracted by cells by elevating antioxidant enzymes activities such as glutathione-S–transferases and glutathione peroxidases that conjugation reactions and catalyze elimination of hydroperoxides, respectively [15].

Antioxidants, therefore are emerging as popular therapeutic agents against diseases caused due to oxidative stress. Studies confirm that N-acetylcysteine (NAC) supplementation has been effective in reversing the depletion of glutathione such conditions [5,16]. Furthermore, NAC also has reducing and antioxidant properties due to its nucleophile nature and as a donor of -SH group, making it an excellent scavenger of ROS [17].

For ages, plants have been used as valuable sources of medicinal compounds that have been used of the treatment of many illnesses, neutralization and elimination of environmental toxicants [18,19]. *Aloe vera* (AV) is one such therapeutic medicinal food plant of *Aloe* species [20]. More than 75 potentially active constituents have been identified in the plant including vitamins, minerals, saccharides, amino acids, anthraquinones, enzymes, lignin, saponins, and salicylic acids. Few reports have suggested that *Aloe vera* as a functional food that plays a significant role in protecting against oxidative stress. It is believed to reduce cell-damaging processes during stress condition and minimizes biochemical and physiological changes in the body [21]. The role of *Aloe vera* in protecting neurotoxic damages induced by metal toxicity has not been evaluated and examined so far.

Material and Methods

Animals

30 healthy Wistar male rats weighing between 180 - 200 gm were used for the present studies. The animals were procured from animal house, IGNOU, New Delhi. All the animals were housed in polypropylene cages and were kept at room temperature maintained at (25 ± 2°C) with a 12-hr light/dark cycle. The rats were fed standard rat pellet diet and provided water *ad libitum*. Experiments were performed as per the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), India and approved by the Institutional Animal Ethical Committee (Reg No-175/GORE/S/14), Government of India.

Chemicals

All the chemicals used in the present study were of analytical grade and purchased from Sigma, Himedia, Qualigens, Merck, SISCO research Laboratories and Loba Chemie, India. NAC was obtained from Hi Media, India. Herbal plant *Aloe vera* was procured from Indian Agricultural Research Institute (IARI), Pusa Road, New Delhi.

Experimental plan and induction of mercury toxicity

The rats were allowed to acclimatize to the local conditions for one week. The rats were randomly segregated into six groups each having 5 animals. The animals were fasted overnight before giving them the following treatments:

- **Group 1**: Control rats.
- **Group 2**: $HgCl_2$ treated (0.25mg/kg body weight).
- **Group 3**: NAC treated (30 mg/ kg body weight).
- **Group 4**: $HgCl_2$+ NAC treatment.
- **Group 5**: *Aloe vera* (400 mg/ kg body weight).
- **Group 6**: *Aloe vera* + $HgCl_2$ treatment.

The body weights of the individual animals were recorded regularly. All the experiments were performed on the 22nd day.

On 22nd day, blood samples were collected from the animals after overnight fasting for the estimation of mercury. The animals were sacrificed by cervical dislocation. Sciatic nerve and brain were removed, rinsed in ice cold isotonic saline (0.9% w/v NaCl), blotted dry, weighed and stored at -20ºC for further analysis.

Preparation of PMS

10% tissue homogenate prepared in 0.05 M phosphate buffer (pH = 7) was centrifuged at 2000 rpm for 10 minutes. Supernatant obtained was again centrifuged at 10000 rpm for 20 minutes for separation of post mitochondrial supernatant (PMS). PMS was collected and stored at -20ºC for further biochemical analysis.

Preparation of *Aloe vera* gel powder

Aloe vera gel was prepared by the method of Jha., *et al*. (2019) [20] with slight modifications. Healthy and fresh leaves were collected and washed under running water followed by washing with double distilled water. The upper layer epidermis of leaf was removed and gel was collected and homogenized. It was centrifuged and mixed with 95% ethanol and left for 5 days with occasional shaking. After 5 days, ethanol and aqueous extracts were removed by incubating at 36ºC. The filtrate was collected and evaporated to dryness under reduced pressure in a rotary evaporator and after that it was lyophilized to obtain the *Aloe vera* gel powder extract.

Estimation of mercury

Levels of mercury were measured in serum samples using induced couple-mass spectrometry [22].

Biochemical analysis

The following biochemical parameters were studied to determine the effect of mercury on oxidative stress parameters and antioxidant defenses along with the beneficial effect of NAC and *Aloe vera.*

Lipid peroxidation (LPO)

Lipid peroxidation level in the brain was measured by the method of Ohkawa., *et al.* (1979) [23] as thiobarbituric acid reactive substances (TBARS). The reaction mixture was prepared with 100 µl of the sample and 200 µl of 10% of SDS. Then 1.5 ml of acetate and 1.5 ml TBA were added to the reaction mixture and contents were mixed followed by incubation in the boiling water bath at 90ºC for 60 minutes. The reaction mixture was removed from the water bath and cooled at room temperature. 5 ml of butanol:pyridine mixture (15:1) was added in the reaction mixture. The samples were mixed and centrifuged at 3000 rpm for 10 minutes. Absorbance of the supernatant was measured at 532 nm. The results were expressed as nmoles MDA/mg protein.

Reduced glutathione (GSH)

Elman method [24] was followed to measure GSH content in brain tissue using Elman's Reagent (DTNB) as a coloring reagent.

Glutathione-S-transferase (GST) (EC 2.5.1.18)

The glutathione-S-transferase activity was determined spectrophotometrically by method of Habig., *et al.* (1981) [25].

Superoxide dismutase (SOD) (EC 1.15.1.1)

Superoxide dismutase was assayed by the method of Dhindsa., *et al.* (1981) [26].

Catalase (CAT) (EC 1.11.1.6)

Catalase was estimated in post mitochondrial supernatant by the method of Caliborne (2018) [27]. Catalase activity was calculated in terms of nmoles of H_2O_2 consumed/min/mg protein using molar extinction coefficient of 43.6×10^3 M^{-1} cm^{-1}.

Glutathione peroxidase (GPx) (EC 1.11.1.9)

GPx activity was determined by the method of Mohanndas., *et al.* (1984) [28]. The enzyme activity was expressed as nmoles of NADPH oxidized/min/mg protein by using molar extinction coefficient 6.22×10^3 M^{-1} cm^{-1}.

Glutathione reductase (GR) (EC 1.8.1.7)

Carrlberg and Mannervik (1985) [29] method was followed to determine GR activity. Value of 6.3 M^{-1} cm^{-1} was used as the extinction coefficient of NADPH and the enzyme activity was expressed as nmol NADPH oxidized/min/mg protein.

Protein estimation

Protein levels were estimated using Lowry's method by taking readings at 660 nm [30].

Histopathology

Histopathological studies in cerebral cortex of rat brain tissues were carried out by performing routine hematoxylin and eosin staining.

Biostatistics

The results are presented as mean ± SE of the studied group. Statistical analyses of the results were performed by one-way analysis of variance (ANOVA). Tukey-Kramer multiple comparisons test was used between various treated groups. Values with $p < 0.05$ were considered statistically significant.

Results

Rats treated with mercury chloride showed increased lipid peroxidation (Figure 1A) as indicated by significantly higher levels of TBARS in mercury chloride treated group ($p < 0.05$) in comparison to the control group. However, the level of TBARS were almost restored when *Aloe vera* and NAC were supplemented as shown by the significant decrease with $p < 0.001$ and $p < 0.05$ for *Aloe vera* and NAC, respectively. The levels of reduced glutathione (GSH) were found to decrease ($p < 0.001$) in mercury chloride treated group in comparison to the other group (Figure 1B). The content of reduced glutathione was also significantly recovered following treatment with *Aloe vera* ($p < 0.001$) and NAC and ($p < 0.001$), respectively when compared to mercury chloride groups.

Antioxidative enzyme activities also changed following treatment of animals with mercury chloride as compared to the control group. Catalase (CAT) activity was significantly reduced ($p < 0.0001$) in brains of animals exposed to mercury chloride groups (Figure 2A). Treatment with *Aloe vera* ($p < 0.05$) and NAC ($p < 0.05$) resulted in the significant increases in the activity of this enzyme when compared

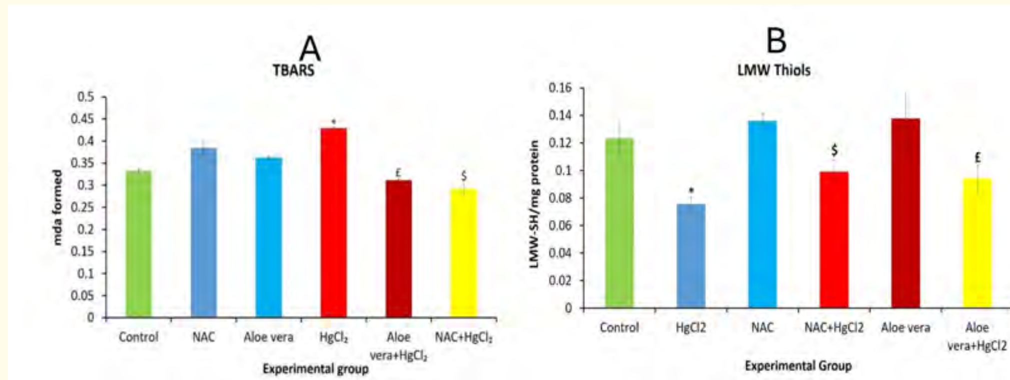

Figure 1: *Level of TBARS (A) and reduced glutathione (B) in brain of rats in different experimental groups (N = 6 in each group and *p < 0.05 control vs $HgCl_2$, $ p < 0.05 NAC + $HgCl_2$ vs $HgCl_2$, £ p < 0.05 Aloe vera + $HgCl_2$ vs HgCl2).*

to the mercury chloride groups. However, activity of GR in mercury chloride treatment group showed a significant increase with $p < 0.001$ (Figure 2B) which decreased significantly under the effects of *Aloe vera* ($p < 0.001$) and NAC ($p < 0.001$).

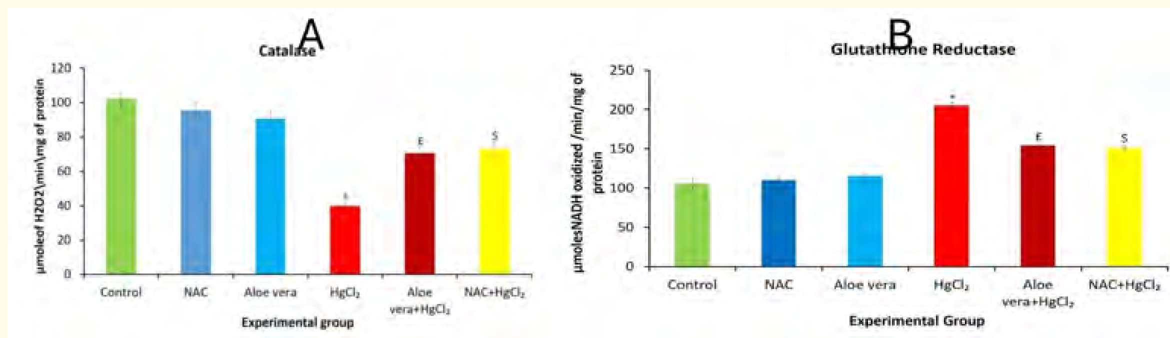

Figure 2: *Catalase (A) and glutathione reductase (B) activities in brain of rats in different experimental groups (N = 6 for each group and *p < 0.0001 control vs $HgCl_2$, $ p < 0.05 NAC+ $HgCl_2$ vs $HgCl_2$, £ p < 0.05 Aloe vera +$HgCl_2$ vs $HgCl_2$).*

The enzymatic activities of glutathione peroxidase (GPx; Figure 3A) ($p < 0.0001$), superoxide dismutase (Figure 3C) and glutathione S- transferase (Figure 3B) in mercury chloride administered group showed significantly decline ($p < 0.001$) when compared to the control animals. Treatment with *Aloe vera* and NAC restored the activities of all these enzymes with significant increases ($p < 0.001$) in each case when compared to mercury chloride groups.

These *in vivo* studies therefore strongly point towards the ameliorative role of NAC and *Aloe vera* against $HgCl_2$ toxicity and suggest their possible application as chemoprophylactic agents against hazardous exposure to inorganic mercury in occupational or industrial setups.

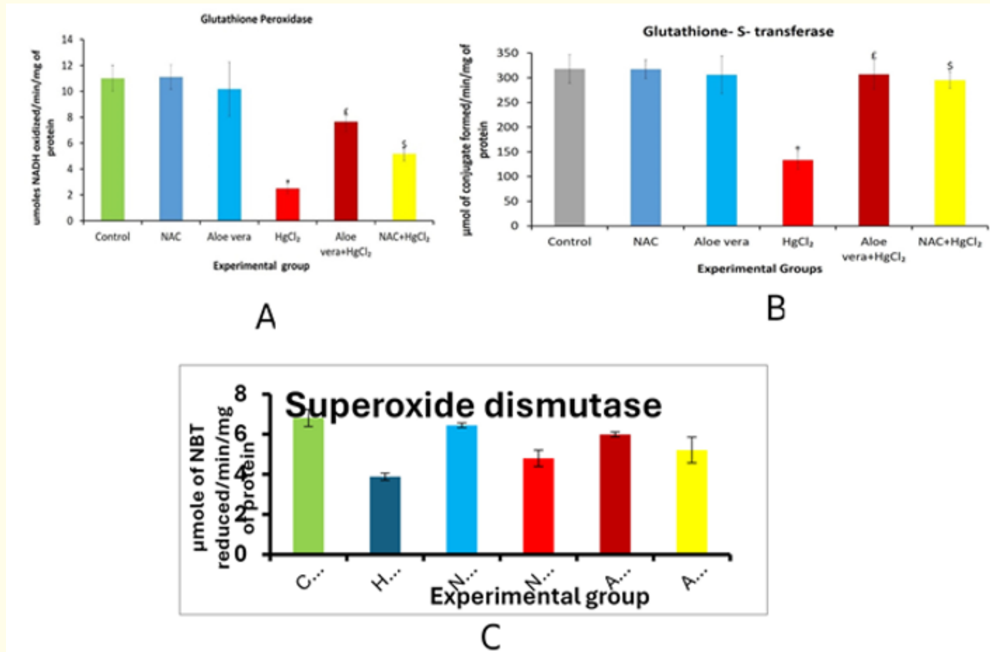

Figure 3: *Glutathione peroxidase (A), GST (B) and SOD (C) activities in brain of rats in different experimental groups (N = 6 for each group); Figure 3A (*P < 0.0001 control vs $HgCl_2$, \$ p < 0.001 NAC+ $HgCl_2$ vs $HgCl_2$, £ p < 0.001 Aloe vera +$HgCl_2$ vs $HgCl_2$); Figure 3B (*P < 0.0001 control vs $HgCl_2$, \$ p < 0.001 NAC+ $HgCl_2$ vs $HgCl_2$, £ p < 0.001 Aloe vera +$HgCl_2$ vs $HgCl_2$) and Figure 3C (*P < 0.0001 control vs $HgCl_2$, \$ p < 0.05 NAC+ $HgCl_2$ vs $HgCl_2$, £ p < 0.05 Aloe vera +$HgCl_2$ vs $HgCl_2$).*

Histopathological observations

Perivascular and pericellular edema or any neuron degeneration was absent in the control group indicating healthy neurons. In mercury treated groups, very mild perivascular and pericellular edema was seen along with degeneration of astrocytes including ischemic neuronal injury (Figure 4).

Discussion

Toxic metals (heavy) such as mercury are extensively present in environment as a result of the anthropogenic actions. Looking at their ill effect on human health, there is a need to characterize the parameters that could predict their toxicity with better sensitivity, specificity and variability. Differential toxicity of mercury compounds is determined by their physical and chemical properties that affect their absorption, distribution, metabolism and excretion in the affected organism. Inorganic form of mercury; mercury chloride ($HgCl_2$) is a wide spread environmental pollutant which is absorbed and distributed in several human tissues. In fact, small fractions of absorbed $HgCl_2$ have been shown to cross the brain-blood barrier and the placenta [31]. Farina., *et al.* (2004) [17] has reported prolonged exposure to many toxins including heavy metals such as mercury may cause permanent abnormalities affecting different parts of brain. Studies suggest that oxidative stress particularly in the mitochondria could be a common mechanism underlying the toxicity induced by many heavy metals such as Fe, Mn and Hg toxicity [22]. Mercury is undergoes redox cycling reactions and generates reactive species such as superoxide ions and nitric oxide in biological systems [33]. Therefore, *in vivo* animal models are essential to understand the precise mechanism of heavy metal toxicity in human and its clinical outcomes.

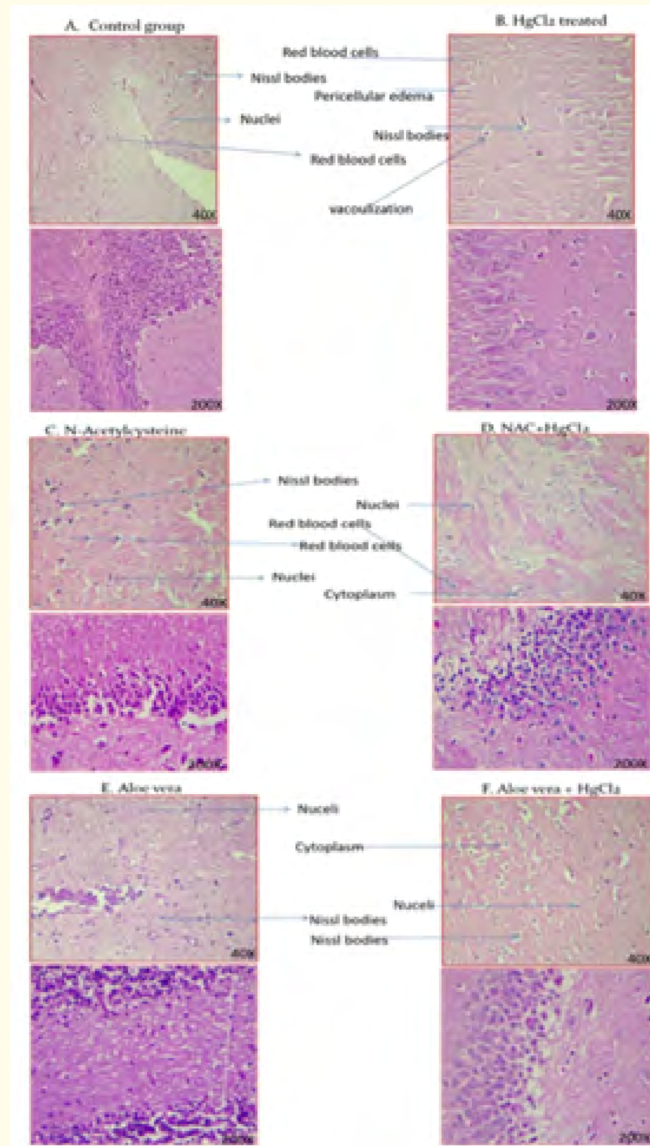

Figure 4: *Histopathological observation in brain of Wistar rats: A- Control group; B- $HgCl_2$ treated; C- NAC treated; D- NAC+ $HgCl_2$ treated; E- Aloe vera and F- Aloe vera + $HgCl_2$ treated.*

In our studies, rats exposed to mercury have much higher mercury content in comparison to controls [22]. These results are in corroboration with earlier studies by Oriquat., *et al*. (2012) that also showed higher levels of mercury in the whole blood of mercury chloride treated rats [31]. They also reported levels of mercury in the brain within range of 4.67 - 3.68 µg/gm. Moreover, the rapid interconversion of the inorganic forms into the organic forms suggests that toxicity of mercury is complex.

Brain tissue has high rate of oxidative metabolism and is especially sensitive to the alterations in the redox status. Membranes in brain such as neuronal membranes, myelin sheath and synaptic membranes are exceptionally rich in polyunsaturated fatty acids making these susceptible to attack by free radical leading to damage caused by lipid peroxidation [34]. In fact, brain is reported to have highest MDA

levels among the tissues examined in mercury-treated animals [35]. Our results are also in agreement with these observations. Mercury promotes lipid peroxidation resulting in cell membrane damage [36]. This may obstruct the permeability the blood brain barrier complex of the brain. Moreover, Gstraunthaler., *et al*. (1983) reported that Hg^{2+} reacts with thiol groups (-SH), thus depleting intracellular thiol pool, especially GSH causing cellular oxidative stress [37]. As lipid peroxidation plays a major role in necrosis and cellular death, accelerated lipid peroxidation in brain could explain the significant death of both neurons and astrocytes caused by $HgCl_2$.

Antioxidants remove free radical intermediates and protect against oxidative damage. Antioxidant enzymes like SOD, CAT, GST and GPx counter oxidative stress by scavenging the free radical. At lower concentrations of mercury, these enzymes remove toxic electrophiles helping the cell maintain its internal environment. However, acute exposure of high doses of mercury causes decreased activity of anti-oxidative enzymes and increased LPO [44]. Our results also corroborate with these studies, since we also found higher levels of lipid peroxidation, alterations in SOD, GPx and CAT activities along with histopathological damage in the brain tissues. The decreased activities of SOD, CAT and GPx in the tissues of $HgCI_2$ treated rat may be due to the inhibition of these enzymes by H_2O_2 [38]. Furthermore, formation of reactive oxygen species within the membrane affects the metabolic activity of brain leading to decrease in the activity of antioxidative enzymes and therefore an increase in the lipid peroxidation products [39].

SOD is family of metalloenzyme, which are synthesized in response to oxidative stress. Underlying mechanism involves conversion of harmful and reactive superoxide free radicals by addition or removal of electrons resulting in the less harmful species like oxygen or hydrogen peroxide. Mercury is thought to inhibit SOD by covalently binding to the cysteine residues at its active site [40] which are involved in the detoxification of metals [41]. Others report increased production of reactive oxygen species may alter the SOD structure and hence inhibit its activity [42]. Since this enzyme neutralizes reactive oxygen species, therefore, regardless of the underlying mechanism, SOD inhibition may contribute to the enhanced oxidation observed in mercury-exposed rats. The alteration in the activity of antioxidative enzymes along with SOD results in a number of deleterious effects due to accumulation of superoxide radicals and H_2O_2.

Catalase plays a significant role in protecting cells from oxidative stress [22] by removing hydrogen peroxide which is toxic to the cells. Glutathione peroxidase (GPx) catalyzes the oxidation of GSH to GSSG, at the expense of H_2O_2, thereby helping cell getting rid of toxicity due to hydrogen peroxide. Enzyme GST is a phase II enzyme that plays a key role in cellular detoxification of xenobiotics, electrophiles and reactive oxygen species through their conjugation to GSH. Mercury inhibits the activities of these antioxidant enzymes; catalase, superoxide dismutase and glutathione peroxidase [38].

Levels of GPx activity following treatment of mercury intoxicated brain tissue with NAC and *Aloe vera* were found to increase to almost normal levels suggesting the protective role of these two agents in mercury toxicity. GR (Glutathione reductase) is an important enzyme that catalyses conversion of oxidized form of glutathione, GSSG to its reduced form GSH with NADPH as a reducing cofactor. Our studies revealed increased GR activity in the brain following $HgCl_2$ exposure under *in vivo* as well as *in vitro* conditions. This increase may be related to the direct oxidative effects of mercury on endogenous GSH, which leads to an increase in GR activity. It was evident that NAC and *Aloe vera* treatment to mercury exposed rats significantly restored the changes caused by mercury chloride toxicity due to increased antioxidant activities (enzymatic and non-enzymatic system). Such observations clearly marked that NAC and AV have neuro-protective activity against brain injury induced by $HgCl_2$ [43]. During the recovery span, the level of LPO content in the brain tissue was found to be near normal level in NAC and *Aloe vera* (AV) treated on mercuric chloride intoxicated rats. Administration of NAC and AV treatment normally decreases the production of LPO in brain tissue of mercury intoxicated rat, which in turn might protect the system against the toxic manifestation of OH radical and H_2O_2. Many studies have also suggested that an enhanced level of LPO content was significantly decreased in mercury intoxicated brain mainly due to administration of NAC and it may exert a stabilizing action on brain cell membrane [44].

Competing Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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