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Research article

Protective effects of natural antioxidant supplementation on cadmium induced toxicity in albino mice

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Keywords: Cadmium (Cd), garlic extract (GE), tomato extract (TE) and antioxidants.

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Abstract

Objectives: Cadmium (Cd) is a widespread industrial and environmental pollutant that may cause harmful effects on humans and animals. It can cause dysfunction of different body organs. The present study has been undertaken to evaluate the protective efficacy of natural antioxidants (garlic + tomato) against cadmium induced toxicity in brain and kidney of albino mice. **Materials and methods:** Albino mice were divided into different groups: **(1)** control mice, **(2)** animals were administered Cd (6 mg/kg bw) orally, **(3)** animals were given a Cd followed by a daily dose of garlic (100 mg/kg bw) + tomato (50 mg/kg bw) extract orally, **(4)** mice were given a Cd singly and were kept for 15 days and then given garlic (100 mg/kg bw) + tomato (50 mg/kg bw) extract for next 15 days. **Results and conclusion**: Results showed a significant elevation in LPO levels with decreased activity of SOD, CAT and GST in Cd intoxicated groups at 15 and 45 days post treatment. With garlic + tomato supplementation, a significant reversal in the oxidative stress enzymes was observed and also restored the biochemical changes in brain and kidney tissue. It was concluded that garlic + tomato prevented the Cd induced damage and this might be due to strong antioxidant potential of their components.

Introduction

Heavy metals are natural components of the earth's crust and are considered as constant environmental pollutants since they cannot be degraded or destroyed easily [1]. Cadmium (Cd) is one of the toxic heavy metal and its increased concentration in the agricultural soils is known to come from the application of phosphate fertilizers, sewage sludge, waste water and pesticides [2].

Cd exposure generates free radicals such as superoxide radicals, hydroxyl radicals and nitric oxide [3]. Liver, kidney and brain tissues are highly susceptible to oxidative damage due to their high utilization of oxygen and poorly developed antioxidant defense mechanism [4]. Free radical accumulation in animals is harmful to tissue types in many organs, including the brain and spinal cord [5].

The kidney has been considered as the critical organ for Cd toxicity [6]. Cadmium-induced kidney injury is primarily characterized by proximal tubular dysfunction [7]. The cytotoxic action of Cd mainly occurs in the tubules and particularly in the renal glomeruli [8]. Cadmium exposure causes alterations in the neurotransmitter level of brain affecting behavior of both neonatal and adult animals [9]. Various workers suggest Cd is neurotoxic but the exact mechanisms involved in the neurotoxicity are poorly understood [10]. Oxidative stress has been proposed as a method for Cd toxicity in a number of tissues such as kidney [11], liver [12] and brain [13].

Antioxidants have been reported to prevent oxidative damage by reacting with free radicals, chelating the catalytic metals and also by acting as oxygen scavengers which remove the excessive free radicals generated from human body [14].

Garlic (*Allium sativum*) is one of the studied plants, with a long history of therapeutic use and its health benefits have been extensively reported [15]. It exhibits antioxidant properties due to rich organo-sulfur compounds [16]. Garlic contains several enzymes, 17 amino acids, minerals such as selenium and holds at least 33 organosulfur compounds which are responsible both for garlic's pungent odour and its many medicinal properties [17].

Tomato (*Lycopersicon esculentum*) is a source of antioxidants [18] and can be used as a food additive for fortification and stabilization [19]. It is among a group of plants reported to synthesize metal chelating proteins, peptides, phytochelatins (PC) and other heavy metal binding complexes analogous to metallothioneins when exposed to heavy metal ions [20]. These proteins thus help to prevent cellular damage by capturing the metals [21]. Lycopene is a major carotenoid present in tomatoes and a highly potent antioxidant that provides protection against integral tissue damage caused by reactive oxygen species [22].

Thus, an attempt has been made to assess the protective as well as therapeutic potential of garlic and tomato on cadmium induced toxicity in brain and kidney of albino mice.

Experimental

Materials and methods

Animals

Swiss albino mice weighing 20-25g were procured from CRI, Kasauli. They were kept and acclimatized to the laboratory conditions for 15 days under optimal conditions of light and temperature. They had *ad libitum* access to tap water. The animals were handled with humane care in accordance with the guidelines of the 'Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA)', India and all experimentation procedures were approved by Institutional Animal Ethical Committee (Reg No. 107/99/CPCSEA/2014-33).

Chemicals

Cadmium chloride ($CdCl_2$) was bought from S.D FINE CHEM LIMITED, Mumbai. It was dissolved in double glass distilled water and administered orally to mice. Garlic and Tomato was obtained from the local market. Fresh garlic extract was prepared by the method of Iwalokun *et al.* [23] and tomato extract was prepared by the method of Salawu *et al.* [24] and administered orally to mice.

Experimental design

The mice were divided into following groups: **Group I –** animals were given kept as control. **Group II** – Animals were administered a single dose of 6 mg/kg bw of cadmium orally. **Group III** – Animals were given an acute dose of 6 mg/kg bw of cadmium followed by a daily dose of GE (100 mg/kg bw) + TE (50 mg/kg bw) for 15days. **Group IV** mice were administered Cd on the initial day and were kept for 15 days and then were given GE+ TE extract for next 15 days. Autopsies were done on 15 and 30 days post treatment.

Brain and kidneys were excised, freed of adipose tissue, blotted dry so as to remove blood and were preceded for biochemical studies.

Biochemical analysis

Brain and kidney homogenates were prepared with the help of tissue homogenizer in 3 ml of phosphate buffer and used for estimation of antioxidant enzymes. Lipid peroxidation was measured as malondialdehyde a thiobarbutaric acid reacting substance, using the method of Wilbur *et al.* [25]. SOD activity was determined by the method of Das *et al.* [26]. The catalytic activity (CAT) was estimated from the rate of decomposition of H_2O_2 by the method of Aebi [27]. GST activity was determined by the method of Habig *et al.* [28].

Statistical analysis

The data was analyzed by using Student's *t*-test followed by ANOVA.

Results and discussion

Lipid peroxidation (LPO)

Malondialdehyde (MDA) is considered as a most popular bioindicator of oxidative damage to cells and tissues [29]. MDA content showed an extremely significant increment in brain ($p<0.001$) and kidney ($p<0.0001$) of Cd treated mice in comparison to control (Figure 1). At 15 days, GE+TE treated group showed a statistically significant decrease in MDA content in brain ($p<0.0001$) and kidney ($p<0.01$) of mice. A non significant decrement in brain and a significant ($p<0.0001$) decrease in kidney were observed in GE+TE group at 30 days post treatment as compared to Cd treated group.

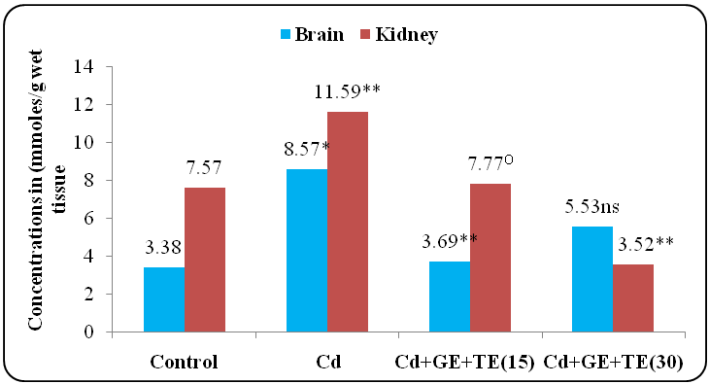

Figure 1. MDA content in brain and kidney tissue of all the treated groups. Control vs Cd, Cd vs Cd+GE+TE. ** p<0.0001, *p<0.001, O p<0.01, NS p>0.05.

Cd may induce oxidative damage by (i) enhancing the production of ROS [30] i.e. hydroxyl radicals [31], superoxide anions, nitric oxide and hydrogen peroxide [32] (ii) by decreasing the biological activities of some antioxidant enzymes such as SOD and CAT [33] which play an important role in antioxidant profile and in scavenging of free radicals (iii) by metal complex decompartmentalization [34].

Increase in MDA levels in brain and kidneys are in confirmation with the results of other workers [35-42].

In this study, Cd induced higher LPO in kidneys as compared to brain. This could be due to different bio-kinetic pattern of its distribution in various tissues [43]. Kidney, due to its capacity to produce metallothionein, was believed to influence the uptake, distribution and toxicity of Cd which induced oxidative stress and resulted in LPO [44].

Brain is thought to be vulnerable to oxidative stress due to high oxygen consumption, presence of high concentrations of polyunsaturated fatty acids and nondegenerative nature of neurons, which may lead to various neurodegenerative diseases [45]. Further, it may be due to its poor antioxidant defense system [46].
The combination of both AGE and ATE afforded more amelioration resulting in significant decline in the MDA content in the tissues. This may be due to the antioxidant properties of garlic and tomato which limited the oxidative injury in the tissues. Further, it was observed that the attenuation was more prominent in the protective group III than that of therapeutic group IV.

Antioxidant enzymes: Superoxide Dismutase (SOD)

SOD is an enzymatic antioxidant that catalyses detoxification reactions of toxic oxygen metabolites [47]. Cd treatment significantly reduced SOD activity in brain and kidney ($p<0.0001$) of mice in confirmation with that of control values (Figure 2). GE+TE treated group showed a non significant increment in both (brain and kidney) of mice at 15 days post treatment. In the therapeutic group IV, a significant ($p<0.001$ increase in brain but a non significant increase in kidney SOD content was observed in comparison to toxic group II.

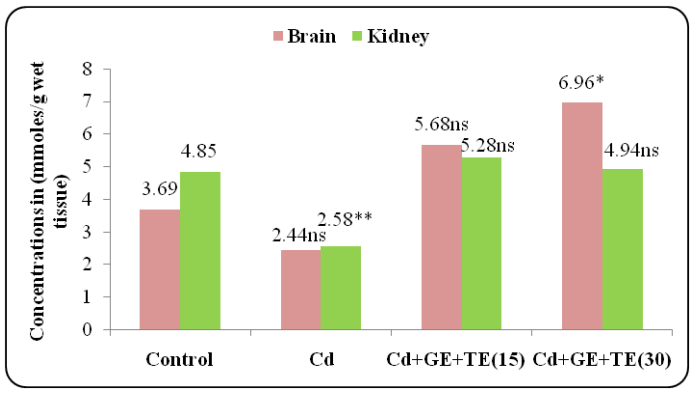

Figure 2. SOD activity in brain and kidney tissue of all the treated groups. Control vs Cd, Cd vs Cd+GE+TE. ** $p<0.0001$, *$p<0.001$, ^{NS} $p>0.05$.

The decrease in SOD content in Cd treated group was also observed by other workers [48-51, 41, 42]. Casolino *et al.* [52] demonstrated that SOD activity is strongly inhibited by Cd, probably by interacting with metal moieties of SOD (Cu, Zn or Mn) and thus reducing its activity. Alternatively, Cd may change the protein conformation by interacting with the enzyme, thereby converting its functional activity [53].
The ability of Cd to produce oxidative stress in brain cells has been reported due to the induction of ROS, by the interaction of Cd^{2+} with mitochondrial sites, leading to the breakdown of mitochondrial potentials that result in the reduction of intracellular GSH and decrease in CAT and SOD levels [54]. The detoxification of ROS in brain involves the cooperative action of the intracellular antioxidant enzymes i.e. SOD, CAT and GPx [55]. This decrease in the antioxidant activity of brain resulted in the accumulation of free radicals and increased LPO level which caused oxidative damage to the brain tissue [10].
The combination groups showed significant increment in SOD activity in case of both protective and therapeutic groups. This might be due to the additive effect of both the antioxidants which showed protection against oxidative stress. Similarly, more amelioration was observed to be in brain as compared to kidney.

Catalase (CAT)

CAT activity was significantly ($p<0.001$) reduced in brain and kidney of Cd treated group in comparison to control values (Figure 3). An extremely statistically significant ($p<0.0001$) elevation in brain and kidney CAT level was observed in GE+TE treated group III. A significant reduction in CAT activity was observed in brain ($p<0.001$) and kidney ($p<0.0001$) of group IV as compared to Cd treated group. The increase was more in group III.

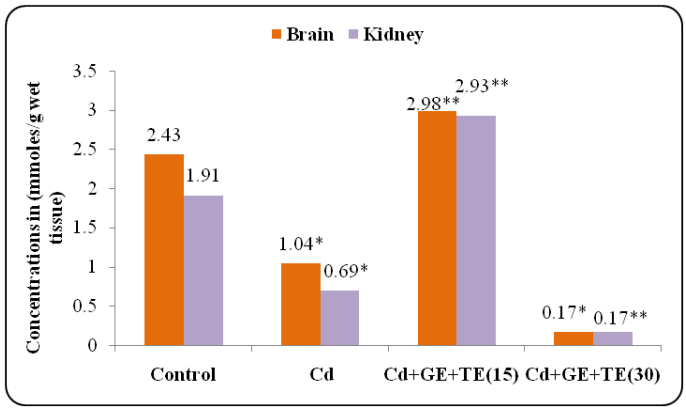

Figure 3. CAT activity in brain and kidney tissue of all the treated groups. Control vs Cd, Cd vs Cd+GE+TE. ** $p<0.0001$, *$p<0.001$.

Many workers [56-59, 41, 42] also reported similar decrease in CAT content in toxic group. This decline in CAT activity is attributed to the possibility of high production of ROS and their increased intracellular accumulation which exceed the detoxification capacity of antioxidant enzymes resulting in subsequent development of tissue injury [60].
The decrease in CAT content could result from iron deficiency due to cadmium intoxication as iron acts as a composing element for the interaction between Cd and catalase [61]. According to Jamakala and Rani [59], CAT levels get decremented progressively due to high accumulation of H_2O_2 in the tissues; thereby more peroxidation of lipids is favoured in Cd treated mice.
Cd was shown to exert a direct inhibitory effect on SOD and CAT activities via cadmium-enzyme interaction with

a resultant perturbance of enzyme topography critical for catalytic action [52].

The combination of both garlic and tomato extract treatment resulted in significant increase in CAT activity in protective group only. This might be due to the positive effects of sulfur compounds of garlic along with the tomato lycopene, a strong carotenoid which reversed the CAT levels to the normal value. The therapeutic group showed less amelioration in CAT levels.

Glutathione-S-Transferase (GST)

A statistically significant ($p<0.0001$) decrease was observed in GST activity in brain and kidney of Cd treated group in comparison to control (Figure 4). In group III, GE+TE showed a significant ($p<0.0001$) increase in GST level in both tissues. Similarly, in group IV also showed a significant ($p<0.001$) increment in GST level as compared to Cd treated group. This elevation was more prominent in group III.

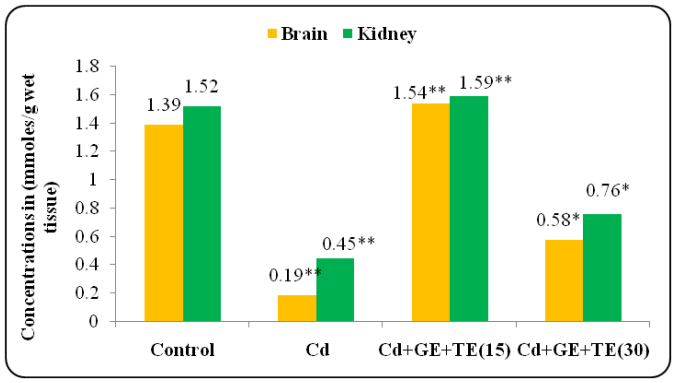

Figure 4. GST activity in brain and kidney tissue of all the treated groups. Control vs Cd, Cd vs Cd+GE+TE. ** p<0.0001, *p<0.001.

Other workers [44, 56-59, 41, 42] also observed a similar decrease in GST activity after Cd treatment.

The decrease in the GST concentration might be due to the effect of Cd on GSH because of its high affinity to this molecule where a sulfhydryl acid, an amino acid and two carboxylic acid groups as well as two peptide linkages represent reactive sites for metals [59]. Reaction of metals like Cd with glutathione, might lead to either the formation of complexes or the oxidation of glutathione [62]. Moreover, this decline in the action of each of them would induce free radical production, thus injuring the corresponding tissues [63].

GST activity was restored after garlic and tomato treatment and showed increment in GST activity in groups III and IV. It may be related to the antioxidant as well as antimutagenic properties of their constituents such as lycopene and organosulfur compounds respectively. Being lipophilic, lycopene is easily absorbed, taken up by the liver and from there it gets easily transported to different tissues of the body [64] and is further reported to cross blood brain barrier [65]. More amelioration was observed in case of protective study.

Conclusion

It can be concluded from the present research work that cadmium intoxication resulted in severe toxic effects in the brain and kidney of albino mice as mirrored by oxidative stress markers. These antioxidants individually proved effective to a certain level. Both Garlic and tomato supplementation counteracted this toxicity more effectively due to their synergistic action which showed more satisfactory and encouraging results. So, more of the natural antioxidants should be included in the daily diet to combat the deleterious effects of heavy metals.

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Conflict of interest

There is no conflict of interest regarding the publication of the research article.

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