Original Article

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Experimental study of cerium oxide nanoparticles (CeNP) against malathion induced lung oxidative toxic stress in rats

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ABSTRACT

Regardless of toxicity of nanoparticles, cerium oxide nanoparticles (CeNPs) are emerging as a multi-functional agent for biomedical purposes. On the other hand, Organophosphorus pesticides, like malathion, are inevitably found in the environment. The common involving pathway CeNPs and malathion share is oxidative stress. Therefore, we conducted this study to find the possible neutralizing or synergistic effects of CeNPs on oxidative stress responses in malathion-induced toxicity by intraperitoneal (IP) injection. In this experimental study, 40 Wistar male rats with the weight range of 200-250 g were randomly selected and divided into eight groups. Group1 (control, normal saline), group2 (100 mg/kg/day malathion /IP), group3 (15 mg/kg/day CeNPs/IP), group4 (30 mg/kg/day CeNPs /IP), group5 (60 mg/kg/day CeNPs /IP), group6 (100 mg/kg/day malathion+15 mg/kg/day CeNPs /IP), group7 (100 mg/kg/day malathion+30 mg/kg/day CeNPs /IP) and group8 (100mg/kg/day malathion+60 mg/kg/day CeNPs /IP). After 4 weeks of treatment, the levels of lipid peroxidation (LPO), total antioxidant capacity (TAC), total thiol molecules (TTM) and activity of catalase (CAT) in lung tissue were measured. All data were analyzed by SPSS V16 and One way ANOVA with Tukey post hoc test. The results demonstrated that CeNPs caused significant increases in LPO and TAC, in a dose-dependent-manner. For TTM level, none of the groups presented any significant change compared to control. Significantly decreased levels of CAT, also, were seen in all treatment groups. Surprisingly, all animals of group 8 died. Worth of noting, groups receiving combined CeNPs and malathion showed severe responses for these parameters. These results discovered that CeNPs induces oxidative stress parameters and ROS production, especially combined with malathion in lung tissue. Groups receiving both CeNPs and malathion displayed synergistic toxic properties. LPO, TAC and CAT seem to be better parameters for measuring CeNPs-induced responses. Further investigations are required to shed light on clear mechanisms involved.

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Keywords
Cerium oxide nanoparticle,
Lung,
Oxidative Stress,
Rat,
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INTRODUCTION

Organophosphorus compounds are known to be one of the most widely utilized pesticides all over the world. Residual amounts of these pesticides can be detected in the

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water, soil, vegetables and other food products [1]. Among such compounds, malathion [O,O-dimethyl-S-(1,2-dicarbethoxy-ethyl) phosphorodithioate] is known to be the most extensively used organophosphate pesticides in agriculture, industry, medicine and public health issues [1-3]. Wide application of malathion, however, brings potentially hazardous impacts on human toxicity [3]. Induction of oxidative stress has been represented as the main mechanism of malathion toxicity in subchronic exposition [4]. Oxidative damage predominantly occurs by increasing in the production of reactive oxygen species (ROS), which during the reactions with biological molecules such as lipids, proteins and nucleic acid are generated [5]. ROS are highly reactive and unstable particles with unpaired electron(s) which attack to nearby molecules to get another electron, resulting in damaged molecular structures and inhibiting cellular functions [5].

There are so many hydrophobic pesticides, like malathion, that bind strongly to biological membranes, particularly phospholipid bilayers of cells, and are capable of damaging the membranes by induction of lipid peroxidation (LPO) [6-9]. In another words, oxidative stress can be described as an imbalance between the body antioxidant defense system and the production of free radicals [44]. If the latter conquers the former, or by any other reason antioxidant defense falls into decreased state, a condition of oxidative stress will be developed, that might cause long-term problems [10]. Moreover, the vital role of lung in facing ROS in daily life and its susceptibility to the variety of diseases cannot be denied [11].

Nowadays, nanomaterials have been chosen to meet the different requisites in an extent range including medical and industrial goals [12]. Cerium oxide nanoparticle (CeNPs) has gained its own place in applications for fuel cells, phosphor/luminescence, solar cells, oxygen pumps, gas sensors and acting as catalysts [12-14]. In line with this, for biomedical purposes, CeNPs were exhibiting antioxidant properties [15-17]. The unique ability to self-regeneration and switching, based on the physiological environment, between cerium (3+) and cerium (4+) oxidation states enables CeNPs to scavenge free radicals such as superoxide, hydrogen peroxide, and hydroxyl and nitric oxide [15]. Furthermore, it has been exploited as a mimicking catalase agent [16, 18] and is recognized to be non-toxic [15,18-21].

On the other hand, some concerns has raised according to the published reports about CeNPs toxicity [22-27], which with regards to oxidant/antioxidant effect of CeNPs, explains the controversial usage of this nanoparticle. There is still a lot to be understood [14, 28-29] and function of CeNPs needs to be determined much more closely. This study was conducted to find the possible neutralizing or synergistic effects of CeNPs on oxidative stress responses in malathion-induced toxicity by intraperitoneal (IP) injection.

MATERIALS AND METHODS

Preparation of cerium oxide nanoparticles

To evaluate the different doses for each group, based on average body weight of rats (220 g), CeNPs were suspended in deionized water. A sonication time of 10 minutes was considered. To avoid the separation of the particles and precipitation, suspension of particles was immediately prepared and vortexed vigorously, before each injection.

Chemicals

The CeNPs (30 nm, US Research Nanomaterials, Inc company), used in this study, were obtained from Notrino company. Dithiononitrobenzoic acid (DTNB), malathion, ethylenediamine tetraacetic acid (EDTA), phosphate buffer solution (PBS), tetraethoxypropane (MDA), trichloroacetic acid (TCA), 2-thiobarbituric acid (TBA), n-butanol and 2, 4, tris base, H2O2, tripyridyl-s-tiazine (TPTZ) were purchased from Sigma Co.

Animals and experimental design

This study was an experimental one. All measures in this work were approved by the Ethics Committee of Vice-Chancellor for Research & Technology of Hamadan University of Medical Sciences. Forty male adult Wistar rats (weighing 200-240 g) were purchased from Pasteur Animal Breeding Center of Tehran and maintained in polypropylene cages under standard conditions of 12/12-h light and dark cycles at room temperature (25 ± 2°C). Rats had freely access to distillated water ad libitum. After one week acclimation, animals were randomly divided into 8 groups (each containing 5), as described below:

Group 1: Control, normal saline , Group 2: 100 mg/kg/day malathion , Group 3: 15 mg/kg/day CeNPs , Group 4: 30 mg/kg/day CeNPs , Group 5: 60 mg/kg/day CeNPs, Group 6: 100 mg/kg/day malathion + 15 mg/kg/day CeNPs, Group 7: 100 mg/kg/day malathion + 30 mg/kg/day CeNPs , Group 8: 100 mg/kg/day malathion + 60 mg/kg/day CeNPs. Handling and IP injection of all groups for the entire 4 weeks of the treatment were done by an expert laboratory technician.

Homogenizing the lung tissues

At the noontime of the twenty-ninth day, rats were sacrificed. Their lungs were quickly separated and rinsed with PBS (pH = 7.5). Tissues were all quickly dried and homogenized with 10 mL PBS (pH = 7.5), using a homogenizer.

Measurement of thiobarbituric acid reactive substances (TBARS)

The cellular LPO products in homogenized lung tissue samples were evaluated by measuring thiobarbituric acid reactive substances represented as the extent of malonedialdehyde (MDA) productions during reaction activated by acid-heating protocol. After diluting the samples with 1.5 mL TCA (20 % w/v) and centrifuging in 3000g, the precipitation was mixed with 1.5 mL H2SO4 (0.05 M) and 1.5 mL TBA (0.2 % w/v). Then, it was incubated for 45 minutes in boiling water bath. After passing time, 2 mL n-butanol was added to each solution, followed

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by cooling and centrifuging. The absorptions were, eventually, recorded at 532 nm. A standard curve of tetraethoxypropane was used to find the concentrations [17].

Total antioxidant capacity (TAC)

The reduction of Fe3+ to Fe2+ in the biological samples was assayed as the indicator of TAC. Thereafter, by the formation of complex between Fe2+ and TPTZ, the maximum absorbance of blue color solution, at 593 nm, was measured [30].

Total thiol molecules (TTM)

By calorimetric method of Hu and Dillard and using DTNB (Ellman's reagent) as the reagent of the reaction, the lung homogenates TTM, in a manner briefly as this, were determined: 1 mL of tris buffer (250 mM and EDTA 2 mM, pH= 8.2) was mixed well with 50 µL of each sample. Afterwards, with adding 20 µL DTNB, absorbance were measured again at 412 nm [31].

Catalase (CAT) activity

The activity of CAT was gained by absorbance decrease in 240 nm for each sample, in a reaction medium comprising H2O2 (10 mM) and sodium phosphate buffer (50 mM, pH = 7.5). One unit of the enzyme was considered as one mol H2O2 as the substrate consumed per minute. Altogether, specific activity was then expressed as unit per milligram protein [32].

Statistical analysis

All results were expressed as the Mean ± SE for each group. Statistical analysis was performed, by SPSS.16 software, using one-way analysis of variance (ANOVA), as followed by post hoc Tukey test. The differences were considered significant if p value was less than 0.05 ($p< 0.05$).

RESULTS

CeNPs and malathion effects on the rats' general health

During the experiment, all rats of 60 mg/kg group died, but in other groups no missing was observed. Meanwhile, some clinical signs of illness in malathion group were seen as salivation, lacrimation, head shaking, spasms of the muscles, weight loss and poor mobility. Also, these signs had the most manifestations in groups of combined CeNPs and malathion. However, there was less presentation of those symptoms in rats treated with only CeNPs.

LPO

As can be seen from Fig. 1, CeNPs with dose of 15 mg/kg in comparison with the control group caused a significant increase in lung LPO (p value = 0.004). Also, in accordance with that, LPO contents were found to have significant increase in the groups of CeNPs 30 mg/kg (P = 0.013), CeNPs 60 mg/kg (P = 0.013), CeNPs 15 mg/kg plus malathion (P< 0.001, with the highest TBARS level in all treated groups) and CeNPs 30 mg/kg plus malathion (P = 0.047), all compared with the control group.

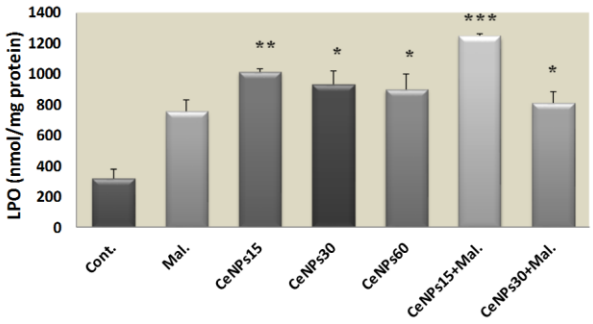

Figure 1. Lipid peroxidation (LPO) in lung tissue of rats. *Significantly different from control group at $p < 0.05$. **Significantly different from control group at $p < 0.01$. ***Significantly different from control group at $p < 0.001$. Cont, Control; Mal, malathion; CeNP, Cerium oxide nanoparticles.

To our surprise, the elevated level of LPO of lung tissue in the treatment group of malathion alone, however, compared to the control group was not statistically significant (P= 0.134).

TAC

Combination of malathion with CeNPs and malathion alone led to a significant increase in total antioxidant capacity level in lung homogenates of groups treated with malathion alone (P = 0.009), 15 mg/kg CeNPs plus malathion (P< 0.001, with the highest TAC level in all treated groups) and 30 mg/kg CeNPs plus malathion (P = 0.014), as compared to the control group shown in Fig 2. In line with this, significant increase was, furthermore, seen in TAC level of CeNPs 60 mg/kg group (Fig. 2). Moreover, CeNPs 15 mg/kg plus malathion group indicated significant increase compared to the group of CeNPs 30 mg/kg (P = 0.042).

TTM

The results of TTM are interesting in different aspects. Fig. 3 shows that after the entire 4 weeks of our study and

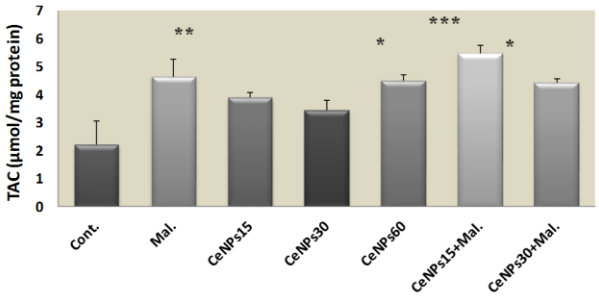

Figure 2. Total antioxidant capacity (TAC) in lung tissue of rats. *Significantly different from control group at $p < 0.05$. **Significantly different from control group at $p < 0.01$. ***Significantly different from control group at $p < 0.001$. Cont, Control; Mal, malathion; CeNP, Cerium oxide nanoparticles.

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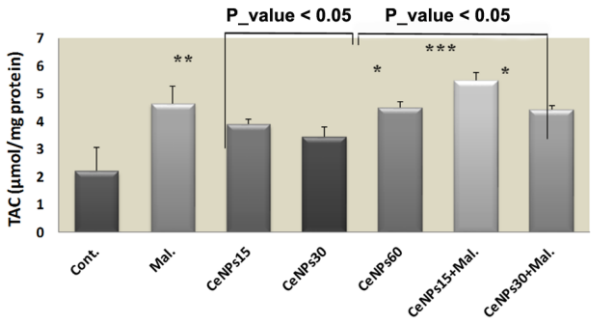

Figure 3. Total thiol moleculs (TTM) in lung tissue of rats. Significant different TTM levels are elucidated .Cont, Control; Mal, malathion; CeNP, Cerium oxide nanoparticles.

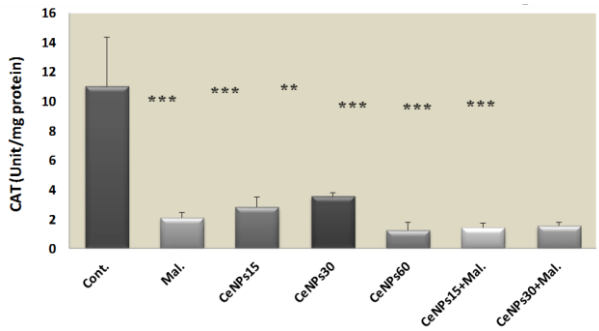

Figure 4. Catalase activity (CAT) in lung tissue of rats. **Significantly different from control group at $p < 0.01$. ***Significantly different from control group at $p < 0.001$. Cont, Control; Mal, malathion; CeNP, Cerium oxide nanoparticles.

measurement of total thiol molecules in lung of the animals, no significant changes were produced in any group, in comparison with the control. Malathion group showed reduced TTM levels about half of the control. The level of TTM in group of 15 mg/kg CeNPs was almost as the same as that of control group. It can be highlighted in the Fig. 3 that dose of 30 mg/kg CeNPs showed a significant increase compared to malathion group ($P = 0.023$). Also, this increase was significant ($P = 0.021$) for group of CeNPs 30 mg/kg plus malathion. Although malathion group resulted in a considerable reduce in TTM level, but it was not statistically significant ($P = 0.826$). Similarly, considerable but not significant change (this time increased level of TTM) in CeNPs 30 mg/kg group ($P = 0.317$) was observed, compared to the control group.

CAT activity

Interestingly, by subchronic injection of CeNPs and malathion, in all of the treated groups CAT activity of rat lung tissue, as described in Fig. 4, was detected significantly decreased: malathion ($P< 0.001$), CeNPs 15mg/kg ($P< 0.001$), CeNPs 30 mg/kg ($P = 0.001$), CeNPs 60 mg/kg ($P< 0.001$), CeNPs 15 mg/kg plus malathion ($P< 0.001$) and CeNPs 30 mg/kg plus malathion ($P< 0.001$).

DISCUSSION

The present study established administration of CeNPs induces oxidative stress parameters and ROS production, especially combined with malathion in lung homogenate. Malathion toxicity in lung homogenate seemed to be caused by oxidative stress. Also, oxidative stress was decreased by the treatment with CeNPs (Figs. 1 to 4).

ROS generated by malathion significantly reduced the levels of cellular antioxidants [33]. In this study we focused on the lung tissue, owing to its continuously and increasingly hazard of facing reactive derivatives of oxygen with the exogenous or endogenous sources

CeNPs have been applied in a variety of purposes from biomedical to industrial activities [34]. Likewise, because of limited and a very low absorption of nanoparticles' inhalation exposure and oral administration in animals, approximately 100% excreted in the feces [35-36], IP injection seems to be an appropriate approach to investigate the effects in a better setting.

This work was undertaken to determine whether CeNPs could attenuate some of the toxic effects of malathion [100 mg/kg/day = 1/20 LD50 [37] or a synergistic role can be found, in Wistar male rats treated for 4 weeks. During the experiment, all of the rats in group of 60 mg/kg CeNPs plus malathion died, which was explained as a primary sign of severe combined toxicity of CeNPs and malathion both together, before testing parameters. In comparison to the three groups receiving CeNPs alone, clinical signs of illness observed in other groups treated with malathion alone or combined with different doses of CeNPs were more severe.

As seen in Fig 1, groups with three different doses of CeNPs (15, 30 and 60 mg/kg) and combined injection of CeNPs and malathion confirmed significantly increased levels of MDA as a marker of LPO and cell membrane damage, among which the highest MDA level and cellular damage belongs with the combination of CeNPs 15 mg/kg plus malathion. Supporting this results, in previous studies it was found that MDA level in malathion exposed groups has increased [5, 38-40]. As discussed above, it is hypothesized that the missed group (CeNPs 60 mg/kg plus malathion) could not tolerate the oxidative damage which might have resulted in death. The lung is the first organ to come in contact with inhaled toxic chemicals especially organophosphate. OP insecticides can cause adverse effects in various organs such as the lungs [41]. Also, our results demonstrated that administration of malathion alone or with CeNPs led in significantly increase for TAC levels (Fig 2). This results are in the same line with findings reported previously and one explanation can be suggested that subchronic treatment in the present study confers the compensatory mechanisms activated through the effects of CeNPs and malathion on related progenitor cells. By regarding this results it seems reasonable to say that in subchronic treatment via overproduction of antioxidants, body is capable of defending against ROS. Presumably, as reviewed in publications of other researchers [14, 42], the aggregation of nanoparticles in part might play an essential role in development of toxicity. Thus, only in high

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concentrations (such as dose of 60 mg/kg in this study) increase in TAC levels, induced by toxic properties of CeNPs and potentially ROS, would occur. Interestingly, like MDA levels, combination of CeNPs 15 mg/kg plus malathion led in the highest level of TAC response. Additionally, from rats treated with CeNPs alone, only 60 mg/kg group revealed significant increase in TAC levels. Worthy of note, group received CeNPs 30 mg/kg displayed less increase and probably less response because of milder toxicity.

TTM was assayed as an indicator of protein oxidation. Interestingly, results of TTM, in comparison with other parameters of study, in all treatment groups revealed no significant correlation, compared to the control group in this subchronic design. Also, except 30 mg/kg CeNPs group others displayed decreased levels. Even though CeNPs 30 mg/kg caused a considerable (but not significant) increase, it is presumed that antioxidant enzymes containing thiol molecules such as glutathione are not affected as the same as other studied factors and there seems to be another mechanisms strongly involved in the alteration of TTM. From other side, LPO and TAC levels in lung tissues were changed significantly after subchronic treatment, suggesting that LPO and TAC is more affected by CeNPs and malathion exposure rather than protein oxidation. Possamai et al. showed similar finding only for malathion alone [1].

In this study, activity of CAT enzyme was investi-gated as an antioxidant enzyme activity biomarker of primary defense against oxidative damage [43], by converting H2O2 produced as ROS free radicals to water and then blocking free radical-mediated damage. For CAT activity, all treatment groups showed significant decrease, which can be taken as a suitable biomarker for oxidative stress status. In contrast, Akhgari et al. has mentioned that by 4 weeks malathion administration activity of CAT in erythrocytes and liver was increased [44]. However, the reduced CAT activity may be resulted from the accumulation of the H2O2 and O-2 . Therefore, Loss of CAT activity will cause oxygen intolerance and triggers lots of deleterious reactions in the body [45]. As like TAC and TTM tests, CeNPs with dose of 30 mg/kg were detected with less decrease in CAT levels, promising less toxicity than other doses. Groups receiving both CeNPs (15 and 30 mg/kg) and malathion were seen with the greatest decreases in CAT level, suggesting this combination will cause the most severe damage in all assayed groups, in spite of the fact that rats receiving CeNPs 60 mg/kg plus malathion, due to potentially intolerable synergistic effects, were all dead. In this study by considering the highest responses of 15 mg/kg group in LPO and TAC tests and the most decreases in CAT activity of 30 mg/kg in groups treated with CeNPs alone, one can mention that CeNPs toxicity follows a dose-dependent-manner in this work. Some reports have claimed protective and antioxidant roles for CeNPs in lung and other tissues [16, 46-48]. Nonetheless, the results of this work are in agreement with that of previous studies having shown the pro- oxidant effects of malathion alone, whether in vivo or in vitro studies, especially in lung tissue [14, 49-50]; but for the first time this study reveals that using controversial CeNPs and malathion together, will cause much more deleterious behaviors over oxidative stress responses and CAT activity as an antioxidant enzyme, assayed in this study. Not only do not neutralize the toxic biological properties of malathion, but CeNPs also emerge their synergistic toxic and pro-oxidant function with malathion in rat lung tissue of male rats. One hypothesis can be stated as this: malathion-induced oxidative stress may decrease the cellular pH by destructing membranes of intracellular organelles. Reduced pH, described in other studies [49], is one of the main factors inducing harmful and pro-oxidant aspects of CeNPs.

In our study, only CeNPs with size of 30 nm were studied. Regarding discrepancy of results various methods of synthesis and shape [14,42], particle size [12,14,42,51-52], surface charge (also called zeta potential) [11,14,42,53-54] and agglomeration state [14,42] in different studies, were thought to be the reasons of varying range of pro- to anti-oxidant behavior. However, in the recent published paper of Pulido-Reyes et al. [55] only the percentage of Ce3+/Ce4+ surface content sites was determined to cause the anti- or pro- oxidant behavior, the less Ce3+ sites the less pro-oxidant status will be achieved.

CONCLUSION

Our results have demonstrated that (1) CeNPs with size of 30 nm and malathion may both be directly involved in induction of deleterious oxidative stress responses, including elevated levels of LPO and TAC in rat lung tissue. (2) CeNPs can act as SOD enzyme. Therefore, excess H2O2 produced may result in depletion of CAT activity. (3) Combined treatment of CeNPs and malathion provoked synergistic, more toxic and oxidative damage responses on above-mentioned parameters. The other oxidative stress responses, LPO and TAC measurements, seem to give more consistent re-sponses in the lung tissue examined rather than TTM after subchronic treatments. The toxic properties of CeNPs in groups treated with CeNPs alone, followed a dose-dependent- manner.

Further investigations using other oxidative stress and antioxidants parameters, different treatments periods (acute and chronic) after receiving CeNPs and malathion should be conducted to untangle and understand more aspects of CeNPs and its possible complementary properties with other chemicals.

CONFLICT OF INTEREST

The authors declare that this research does not have any conflict of interest with anyone or any institute.

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