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Posted Date: 2 September 2024

doi: 10.20944/preprints202409.0040.v1

Keywords: brain toxicity; diazinon; oxidative stress

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Investigation of the Protective Effect of Gallic Acid on the Toxicity of Diazinon-Induced Mitochondrial Damage and Oxidative Stress in the Brain of Mice

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Abstract: Background and Purpose: Oxidative stress is an important factor in the pathogenesis of neurological problems. One of the compounds causing oxidative stress is diazinon. In the present project, the protective role of gallic acid compound in reducing oxidative stress in brain tissue of mice exposed to diazinon was investigated. Method: In this study, eight groups of six series of mice including the first group (control) of normal saline, the second group of diazinon (40 kg/mg) as IP, three groups of diazinon with gallic acid (50, 100, 200 kg/mg), was prescribed as a single dose and for 24 hours. The atropine + pralidoxime group was also evaluated as a standard treatment group. At 24 hours after the last dose, the animals were sacrificed and brain tissue was examined to assess oxidative stress parameters, including glutathione content, protein carbonyl content, lipid peroxidation, reactive oxygen species (ROS) and mitochondrial function in mitochondria isolated from brain tissue. Results: The results of this research showed that oxidative stress biomarkers increased significantly ($P<0.001$) in the diazinon group compared to the control group. Oxidative stress was significantly reduced in the groups receiving gallic acid at a dose of 200 and 100 kg/mg of diazinon compared to the diazinon group. Conclusion: The results of the present study show that diazinon causes damage to brain tissue by inducing oxidative stress. Therefore, according to the reduction of oxidative stress by gallic acid compound, it can be concluded that this compound can protect against brain toxicity caused by diazinon in animal model by stimulating antioxidant and radical scavenging pathways.

Keywords: brain toxicity; diazinon; oxidative stress

1. Introduction

Diazinon is an organophosphate insecticide that inhibits the enzyme acetylcholinesterase and can cause severe acute poisoning, including headache, nausea, neurological effects and even death (36, 37). Acute poisoning may result in supranuclear palsy and opsoclonus due to cholinergic enhancement (37). Chronic exposure to diazinon has been associated with an increased risk of certain cancers, although the evidence is mixed (38). Exposure to this toxin can occur by dermal absorption, inhalation or ingestion, resulting in persistent neurological, skeletal and endocrine effects (36). Diagnosis of poisoning is based on history of exposure, symptoms such as miosis and fasciculation, response to treatment and reduction in blood cholinesterase activity, and in some cases permanent complications such as polyneuropathy and central nervous system symptoms may occur (39). The initial treatment approach for diazinon poisoning includes the use of atropine to counteract the effects of acetylcholine and pralidoxime chloride to restore blood cholinesterase levels (40). While pralidoxime has shown efficacy in the treatment of several organophosphorus poisonings, including diazinon, its efficacy varies in different combinations (39). Supportive measures such as intravenous

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fluids, oxygen and prompt gastric lavage are important (40). Studies have shown that exposure to diazinon reduces the activity of antioxidant enzymes, increases oxidative stress parameters and also causes blood abnormalities in mice (42).

Gallic acid (GA) is a phenolic compound that is widely distributed in various plants and foods and has significant medicinal properties. This compound has neuroprotective effects against neurodegeneration and oxidative stress (54). In addition, GA has potent anti-inflammatory activities, primarily through modulation of the MAPK and NF-kB signaling pathways, as well as reducing the release of inflammatory mediators (55). The strong antioxidant properties of GA contribute to its protective role in oxidative damage diseases, including cancer and cardiovascular disease (56). With specific effects attributed to its unique chemical structure, its cytotoxicity against cancer cells has been demonstrated (57). Despite its promising therapeutic potential, further clinical studies are needed to confirm its efficacy and safety in human application (56).

The aim of this study was to investigate the effect of gallic acid on the treatment of diazinon-induced toxicity in mouse tissues compared to standard treatment.

2. Material and methods

To evaluate the brain-protective effect of gallic acid on the brain mitochondria of exposed mice, six groups of mice were selected, each group consisting of six mice. The pralidoxime group received diazinon poison, pralidoxime and atropine, and the gallic acid group, which included three subgroups, received diazinon poison and gallic acid at concentrations of 50, 100 and 200 mg/kg. Mice were acutely poisoned with 0.5 LD50 of diazinon, and after 15 minutes treatments were started, including gallic acid, pralidoxime and atropine (standard treatment).

3-1-2 groups tested

Group 1. The control group, which received normal saline.

Group 2. The group that received diazinon at 40 mg/kg.

Groups 5, 3, 4 received different doses of gallic acid (50, 200 and 100 mg/kg) 15 minutes after diazinon administration.

Group 6 received standard treatment with atropine and pralidoxime 15 min after diazinon administration.

2-3 Ethical considerations

For two weeks prior to the experiments, the animals were kept in separate standard cages with a 12-hour light/12-hour dark cycle, access to food and water, and a temperature of 22 ± 2 degrees C for environmental adaptation. At the end of the treatment period, the animals were anaesthetized with ketamine/xylazine and operated on, and all ethical aspects of the study were followed. Brain tissue was then removed and used.

3. Results

The results obtained based on the method mentioned in the third chapter were determined as follows in this study.

1-4 The results of investigating the effect of gallic acid on mitochondrial glutathione content of mouse brain tissue exposed to diazinon poison

According to the analysis, the amount of glutathione in the Diazinon group has decreased significantly compared to the Control group ($p<0.001$).

The amount of glutathione in the gallic acid 100 and 200 mg/kg group increased significantly compared to the diazinon group ($p<0.001$). Also, the gallic acid 200 group had no significant difference with the atropine and pralidoxime group in glutathione content.

Gallic acid 50 groups did not have a significant increase in glutathione compared to diazinon group (Figure 1).

 doi:10.20944/preprints202409.0040.v1

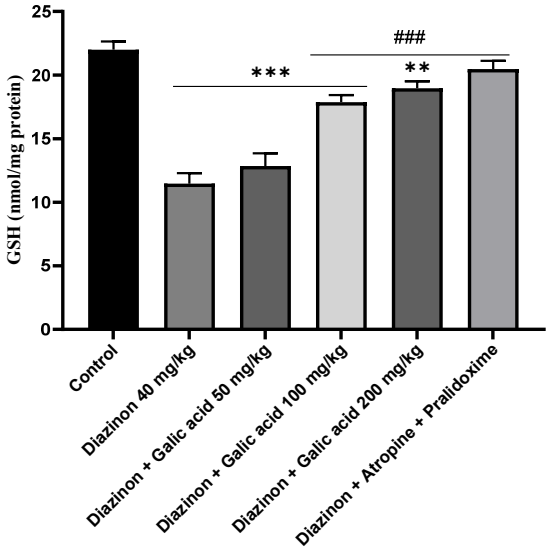

Figure 1. Determining the effect of gallic acid on the mitochondrial glutathione content of rat brain tissue exposed to diazinon. * Significant difference with control group p<0.001***, p<0.01**, p<0.05 *. # Significant difference with diazinon group p<0.001##, p<0.01##, p<0.05#

2-4 The results of investigating the effect of gallic acid on lipid peroxidation of mitochondria in rat brain tissue exposed to diazinon poison

According to the analysis, the amount of MDA in the Diazinon group increased significantly compared to the Control group (p<0.001).

The amount of MDA in the 100 and 200 mg/kg gallic acid group was significantly reduced compared to the diazinon group (p<0.001). Also, the gallic acid 100 and 200 group had no significant difference with the atropine and pralidoxime group in MDA content.

Gallic acid 50 groups did not have a significant increase in MDA compared to diazinon group (Figure 2).

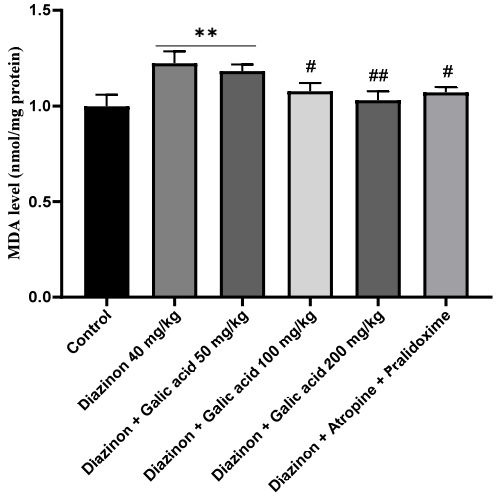

Figure 2. Determining the effect of gallic acid on the mitochondrial MDA content of rat brain tissue exposed to diazinon. * Significant difference with control group p<0.001***, p<0.01**, p<0.05 *. # Significant difference with diazinon group p<0.001##, p<0.01##, p<0.05#

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3-4 The results of investigating the effect of gallic acid on the mitochondrial carbonyl protein content of rat brain tissue exposed to diazinon toxin.

According to the analysis, the amount of protein carbonyl in the Diazinon group has increased significantly compared to the Control group ($p<0.001$).

The amount of protein carbonyl in the gallic acid 100 and 200 mg/kg group was significantly reduced compared to the diazinon group ($p<0.001$). Also, the gallic acid 100 group had no significant difference with the atropine and pralidoxime groups in the carbonyl protein content.

Gallic acid 50 groups did not have a significant increase in the amount of protein carbonyl compared to the diazinon group (Figure 3).

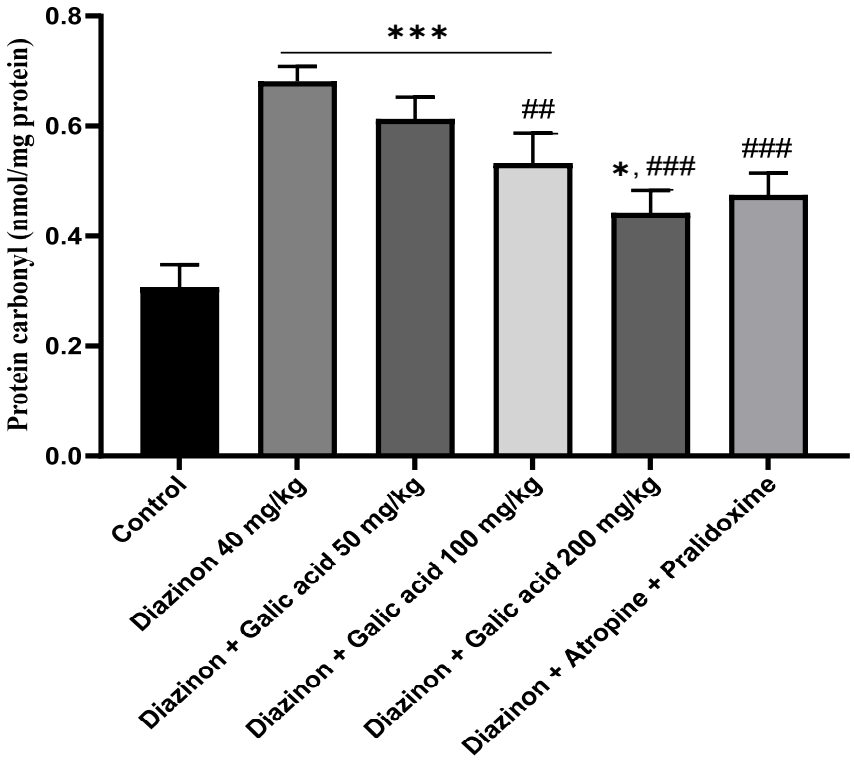

Figure 3. Determining the effect of gallic acid on the mitochondrial carbonyl protein content of rat brain tissue exposed to diazinon. * Significant difference with control group $p<0.001$***, $p<0.01$**, $p<0.05$ *. # Significant difference with diazinon group $p<0.001$##, $p<0.01$##, $p<0.05$#

4-4 The results of investigating the effect of gallic acid on the amount of mitochondrial ROS in the brain tissue of mice exposed to diazinon poison

According to the analysis, the amount of ROS in the Diazinon group increased significantly compared to the Control group ($p<0.001$).

The amount of ROS in the 100 and 200 mg/kg gallic acid group was significantly reduced compared to the diazinon group ($p<0.001$). Also, the gallic acid 100 group had no significant difference with the atropine and pyralidoxime groups in the carbonyl protein content.

Gallic acid 50 groups did not have a significant increase in glutathione compared to diazinon group (Figure 4).

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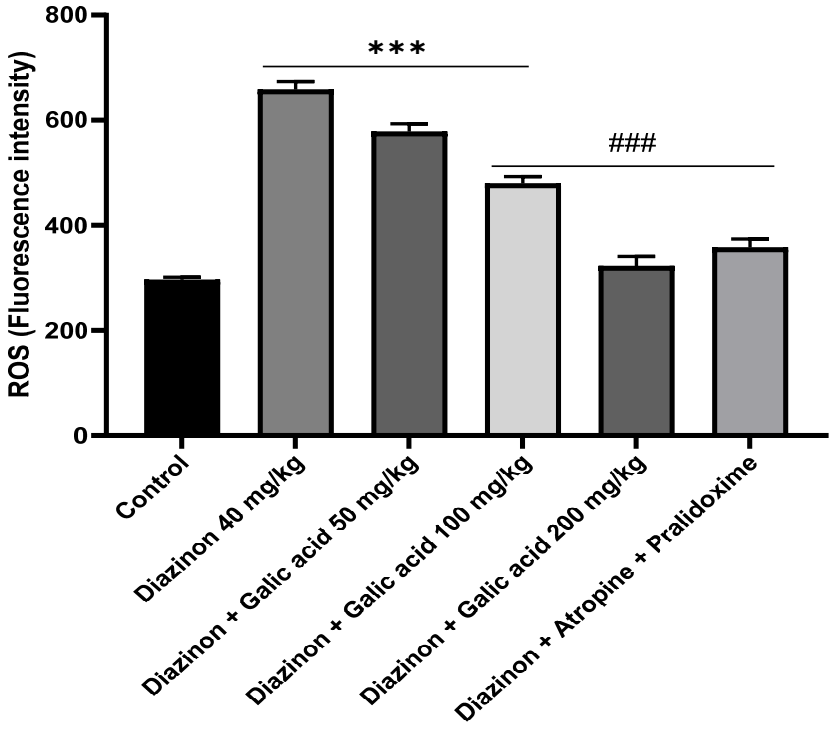

Figure 4. Determining the effect of gallic acid on the amount of mitochondrial ROS in the brain tissue of rats exposed to diazinon. * Significant difference with control group p<0.001***, p<0.01**, p<0.05 *. # Significant difference with diazinon group p<0.001##, p<0.01##, p<0.05#

4-5 The results of investigating the effect of gallic acid on the mitochondrial function of mice brain tissue exposed to diazinon poison

The findings of this study showed that the mitochondrial function was significantly reduced in the group receiving diazinon, while after receiving doses of 200 and 100, 50 mg/kg of gallic acid, it was reduced compared to the control group. It is noteworthy that the greatest increase in mitochondrial function was related to the dose of 200 mg/kg.

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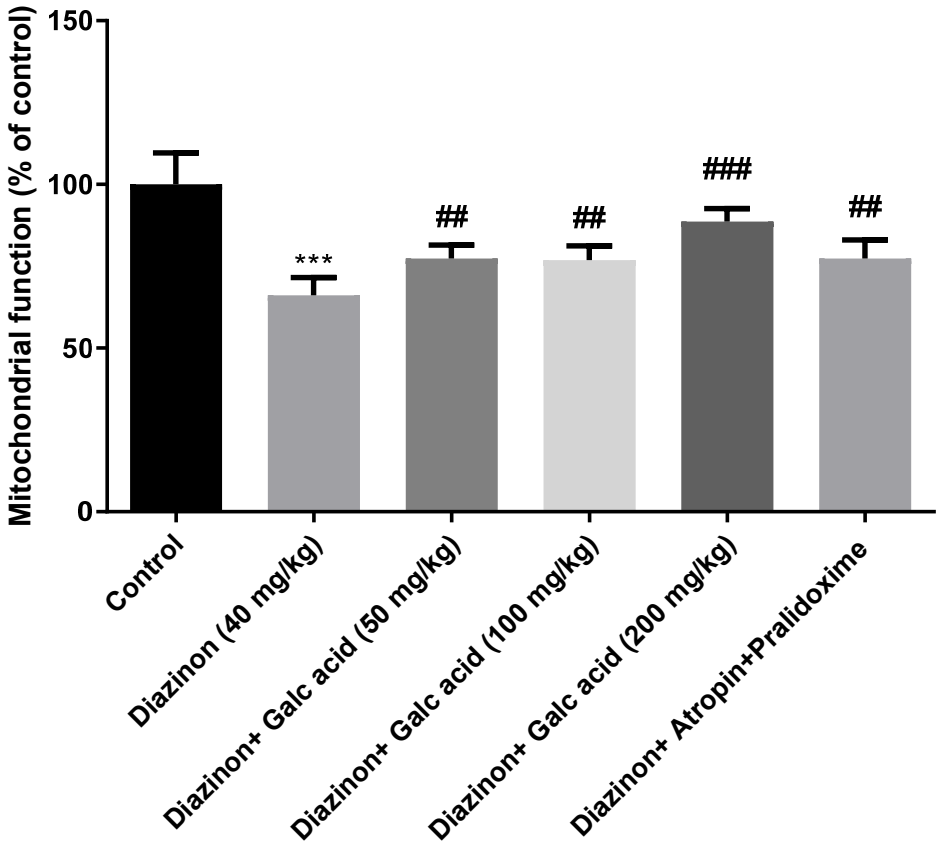

Figure 5. Determining the effect of gallic acid on the mitochondrial function of rat brain tissue exposed to diazinon. * Significant difference with control group p<0.001***, p<0.01**, p<0.05 *. # Significant difference with diazinon group p<0.001##, p<0.01##, p<0.05#

4. Discussion

The study was conducted to investigate the protective effect of gallic acid on the toxicity caused by diazinon in the mitochondria of mouse brain tissue.

According to the results of the present project, diazinon has significantly increased the oxidative stress parameters in the mitochondria of mouse brain tissue. These results are consistent with previous studies. Studies have shown that exposure to diazinon leads to an increase in lipid peroxidation and lactate dehydrogenase, a decrease in glutathione, and a change in the activity of antioxidant enzymes such as catalase and superoxide desmutase in the brain, heart, spleen, liver, and kidneys (71-71), (74). These effects are dose-dependent and vary between mouse strains, with Wistar rats showing higher sensitivity than Norway rats (71). Diazinon-induced oxidative stress can lead to tissue damage and organ dysfunction, especially in the kidneys (72). Exposure to diazinon significantly decreases the activity of antioxidant enzymes, increases markers of oxidative stress, and causes hematologic changes in mice (42). It also affects liver function and increases serum levels of ALT, AST, and ALP (75, 76). The use of antioxidants such as N-acetylcysteine may partially reduce diazinon-induced oxidative stress by scavenging reactive oxygen species and inducing glutathione synthesis (74). One of the primary pathways of diazinon in neurotoxicity involves inhibition of acetylcholinesterase (AChE), which leads to the accumulation of acetylcholine (ACh) in synapses, which disrupts normal neurotransmission and can lead to neurotoxicity (77, 78). However, the neurotoxic effects of diazinon go beyond cholinesterase inhibition, and oxidative stress and neuroinflammation have been implicated as important factors in its neurotoxicity (79, 80). Oxidative stress is a critical mechanism through which diazinon exerts its neuroprotective effects. Diazinon

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exposure has been shown to induce the production of reactive oxygen species (ROS), which lead to lipid peroxidation and damage to cellular components, including DNA and proteins (80, 81). This oxidative damage can trigger apoptotic pathways in neuronal cells, as studies show increased apoptosis in neuronal cell lines following diazinon exposure (82). In addition, alterations of neurotrophic factors and their signaling pathways have been observed, which may impair neurogenesis and neuronal survival (83).

5. Conclusion

In general, the results of the present study show that diazinon has the potential to cause damage in the mitochondria of the brain tissue by causing oxidative stress. In this study, the oxidative damage caused by diazinon was reduced by administering gallic acid, which is a compound with antioxidant properties.

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