Research Paper

# The Potential Effects of Sodium Bromide, Calcium Carbonate, and Potassium Nitrate against Aluminum Phosphide Poisoning in the Heart and Lung Tissues of Rats: Focus on Oxidative Stress

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## ABSTRACT

**Background:** Aluminum phosphide (AlP) exposure can cause fatal poisoning due to severe oxidative damage. The current study evaluated the effects of sodium bromide (NaBr), calcium carbonate ($CaCO_3$), and potassium nitrate ($KNO_3$) on ALP-induced cardiac and lung injuries and determined the oxidative stress markers.

**Methods:** Sixty-six male Wistar rats were allocated into 11 groups: Normal control, ALP group (40 mg/kg body weight AlP was administered by oral gavage), ALP + Low dose of $CaCo_3$, ALP + High dose of $CaCo_3$, ALP + Low dose of $KNO_3$, ALP + High dose of $KNO_3$, ALP + Low dose of NaBr, ALP + High dose of NaBr, High dose of $CaCO_3$, High dose of $KNO_3$, and high dose of NaBr.

**Results:** Administration of $CaCO_3$ and NaBr reduced ALT, MDA, and SOD levels and increased TAC levels in the serum and lung tissue.

**Conclusion:** $CaCO_3$ and NaBr may be promising and potential options for managing and treating AlP toxicity.

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## Introduction

One of the most dangerous poisonings leading to death is caused by the ingestion of Aluminium phosphide (AlP), which is common in countries where its availability is not narrowly restricted [1, 2]. Because of its highly toxic properties, AlP is reported to be a suicidal agent in many cases [3]. Despite accidental and intentional morbidity and mortality from exposure to AlP having been reported in several epidemiological reports [4], effective antidotes have not been developed yet [5].

Several organs, such as the heart and lungs, are primarily affected by AlP, which results in the rapid onset of poisoning symptoms, including restlessness, palpitation, refractory shock, cardiac arrhythmias, pulmonary edema, dyspnea, and cyanosis [5]. Specifically, myocardial injury has been observed in cases of poisoning with AlP, associated with hypotension, myocarditis, bradycardia, acute congestive heart failure, and arrhythmias [4, 6]. Moreover, pulmonary injury and edema have been documented following ingestion of AlP or exposure to phosphine gas [7, 8], leading to dyspnea, respiratory failure, and acute respiratory distress syndrome [9].

The toxicity of AlP results from phosphine gas, which is produced in contact with air or moisture [5]. Phosphine is considered a powerful reducing agent that disrupts metabolic processes by inhibiting cellular enzymes, particularly cytochrome c oxidase, thereby leading to cellular hypoxia [10, 11]. In addition, experimental and clinical studies have reported that cellular injury is accompanied by increased levels of cellular peroxides and superoxide radicals [12, 13].

Several therapeutic options, such as potassium permanganate, coconut oil, sodium bicarbonate, and activated charcoal, have been suggested to manage the toxicity of ALP [5]. Considering the inefficiency of currently available therapeutic approaches and the higher mortality rate despite resuscitative measures, there is an urgent need to find effective antidotes and alternative strategies to reduce ALP toxicity [14]. Several experimental and human studies have investigated the effect of various substances on AlP toxicity. However, the effectiveness of these antidotes requires further studies [15].

Phosphine is a nonpolar compound with very low solubility in water, which limits the replacement of its hydrogen atoms. Consequently, due to the presence of a non-bonding electron pair on the phosphorus atom, phosphine tends to form a dative bond to undergo chemical transformation. A dative bond, also known as a coordinate covalent bond, involves the donation of a pair of electrons from one atom into the empty orbital of another atom [16]. In the molecular structure of phosphine, phosphorus acts as an electron donor through its lone pair of electrons. Based on the theoretical framework of this study, suitable compounds for dative bond formation must possess an empty orbital capable of accepting this lone pair, particularly in a humid environment. Therefore, the potential effects of three non-toxic, positively charged inorganic compounds, including sodium bromide (NaBr), potassium nitrate (KNO3), and calcium carbonate (CaCO3), were investigated in this study.

KNO3 is commonly used as a food preservative, and emerging evidence suggests that it also exhibits antihypertensive properties. Moreover, several studies have highlighted its potential antioxidant effects, including the enhancement of superoxide dismutase activity and the upregulation of mitochondrial function-related proteins such as mitochondrial aldehyde dehydrogenase and superoxide dismutase [17]. CaCO3 nanoparticles represent a class of materials that have garnered significant attention in recent biomedical research due to their diverse applications, such as drug delivery systems, encapsulation of bioactive compounds, and enzyme immobilization [18]. NaBr participates in a variety of oxidative processes as a source of bromine in both electrochemical and chemical reactions via the generation of bromine radicals or hypobromous acid as potent oxidizing agents [19, 20].

This study was performed to assess the impact of NaBr, CaCO3, and KNO3 on oxidative stress and histopathological changes in the heart and lung tissues of rats induced by acute ALP toxicity.

## Materials and Methods

### Ethical issues

Animals were strictly treated according to the previously published protocols (Guide for the Care and Use of Laboratory Animals of the National Institute of Health (8th edition, 2011)). All of the procedures and protocols were approved by the ethics committee of Tabriz University of Medical Sciences (No: IR.TBZMED.VCR.REC.1399.473).

### Animal housing and experimental protocol

Sixty-six male Wistar rats (weighing 200-250 g) were maintained under controlled conditions (12h: 12h light-dark cycle at 22 ± 2°C). All of the animals had ad libitum access to food and water. Following

accommodation to the environment, rats were randomly allocated into 11 groups as follows: 1. Normal control group received distilled water; 2. ALP group received 40 mg/kg body weight Aluminium phosphide; 3. ALP + Low dose of calcium carbonate (ALP + CaCO3-L); 4. ALP + High dose of calcium carbonate (ALP + CaCO3-H); 5. ALP + Low dose of potassium nitrate (ALP + KNO3-L); 6. ALP + High dose of potassium nitrate (ALP + KNO3-H); 7. ALP + Low dose of sodium bromide (ALP + NaBr-L); 8. ALP + High dose of sodium bromide (ALP + NaBr-H); 9. High dose of calcium carbonate (CaCO3-H); 10. High dose of potassium nitrate (KNO3-H); and 11. High dose of sodium bromide (NaBr-H). ALP was administered by oral gavage (17 mg ALP dissolved in 1cc of distilled water per rat) in ALP-received groups.

## Treatment with sodium bromide, calcium carbonate, and potassium nitrate

Twenty minutes after ALP gavage, NaBr, CaCO3, and KNO3 were administered by the gavage route at low (L) and high (H) doses in experimental groups. The dosage of the compounds was determined based on relevant chemical reactions and stoichiometric calculations. Once the baseline dose for each of the three compounds was established, the animal models receiving each compound were divided into two groups: one group received a high dose (twice the baseline dose). In contrast, the other group received a low dose (half the baseline dose). Table 1. Administered doses of candidate antidotal agents in experimental animalspresents the baseline, low, and high doses of the three chemical compounds.

## Serum and tissue sampling

Retro-orbital sinus blood sampling was carried out 3 hours after the ALP injection. The samples were then centrifuged for 5 min at 10000 g; serum samples were frozen and stored at −20°C until analysis [21]. Tissue sampling was done 24h after ALP administration. Briefly, animals were euthanized using an overdose of Xylazine and Ketamine. After decapitation, the heart and lung tissues were quickly removed and placed in 10% formalin for histological analysis. A part of the lung tisues was froze at −80°C and kept for molecular analysis.

## Histopathological examination

The lung and heart tissue samples were routinely fixed in 10% buffered formalin, embedded in paraffin, sectioned at about 5 µm, and stained with hematoxylin and eosin (H&E). The tissue sections were studied by a light microscope (Olympus-CH30, Japan). Microscopic analyses were performed as previously described [22] with some modifications. Four microscopic scores were considered for all parameters, consisting of normal (0), mild (+1), moderate (+2), and severe (+3). In the heart, the evaluated criteria comprised vascular congestion, hemorrhage, inflammation (pericarditis/myocarditis/endocarditis), hyaline degeneration, and necrosis. In the lung tissue, the evaluated criteria included pulmonary edema, vascular congestion, hemorrhage, inflammation (pneumonia), and necrosis.

## Measuring cardiac enzymes

The extent of myocardial injury was assessed by measuring serum cardiac enzymes, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), and creatine kinase-MB isoenzyme (CK-MB) by commercially available kits and using a biochemical autoanalyzer following the manufacturer's protocol [23].

## Measuring oxidative status in the lung tissue

To assess the effects of sodium bromide, calcium carbonate, and potassium nitrate on oxidative status, we measured the levels of SOD, GPx, TAC, and MDA in the lung samples. Briefly, the tissues were homogenized and lysed in protein lysis buffer (150 mM NaCl, 0.1% SDS, 50 mM Tris-HCl, two mM EDTA, 1% NP-40) and then centrifuged at 12,000 rpm for 20 min at 4°C. The levels of SOD and GPx were measured in the collected supernatants using appropriate kits according to the manufacturer's instructions [24]. Results were expressed in units/mg of protein.

The content of lung MDA was also measured as previously described [25]. For this purpose, total

**Table 1.** Administered doses of candidate antidotal agents in experimental animals

| Antidotes | Baseline dose | Low dose | High dose |
|---|---|---|---|
| NaBr | 45 mg/250 g rat | 22.5 mg/250 g rat + 5 cc DW | 90 mg/250 g rat + 10 cc DW |
| $CaCo_3$ | 22.5 mg/250 g rat | 11.25 mg/250 g rat + 5 cc DW | 45 mg/250 g rat + 10 cc DW |
| $KNO_3$ | 605 mg/250 g rat | 302.5 mg/250 g rat + 5 cc DW | 1210 mg/250 g rat + 10 cc DW |

protein content was calculated using the BCA kit. Protein lysates were mixed with phosphoric acid (1%), and after adding buffer, thiobarbituric acid (0.67%), the samples were kept in boiling water for 45-50 min. Then, samples were centrifuged at 1000 g for 10 min, and the MDA-thiobarbituric acid adduct was detected at 570 nm. MDA levels were expressed as Nm/mg protein.

Total antioxidant activity (TAC) was calculated by monitoring peroxidase activity and production of the blue-to-green solution after the addition of ABTS [26]. The ODs were read at 600 nm, and the final concentration was calculated and expressed as µM/mg protein.

### Statistical analysis

Data analyses were performed using SPSS software version 20 (SPSS Inc., Chicago, IL). The normally distributed data were analyzed using one-way analysis of variance (ANOVA) with post hoc Turkey's test and stated as mean ± standard error of the mean (SEM). Non-parametric tests (Kruskal-Wallis H and Mann-Whitney U) were used for pathological lesions (semiquantitative data) between the various groups. A $P<0.05$ was considered significant.

## Results

Histopathological findings in the heart tissue are presented in Table  and Figure 1. Briefly, the ALP group and ALP plus treatment groups showed mild hemorrhage and vascular congestion compared to the control group. However, no significant changes were found in antidote-receiving groups as compared with the ALP group.

The histopathological findings in Table 3. Pathological findings of the lung sections (n = 5) and Figure 2 show that all the ALP-receiving groups showed significant histopathological lesions in the lung tissue, including edema, vascular congestion, hemorrhage, inflammation, and necrosis. However, the most severe lesions were found in the lung tissue of ALP, ALP-KNO3-H, and ALP-KNO3-L groups.

### The levels of cardiac enzymes in the serum

As shown in Figure 3A, serum ALT levels were significantly ($P<0.001$) increased in the ALP group compared with the control group. However, ALT levels were significantly ($P<0.01$) reduced in the ALP-NaBr-L group as compared to the ALP group.

AST levels were significantly ($P<0.05$) increased in the ALP group compared with the control group. Moreover, the levels of this variable were significantly ($P<0.05$, $P<0.001$) increased in ALP and antidote-receiving groups compared with the control group. Antidotes did not affect the levels of AST compared to the ALP group (Figure 3B).

Data analysis also showed that serum levels of LDH were significantly ($P<0.05$) increased in the ALP group compared with the control group. The results showed no significant changes in LDH levels in antidote-received groups compared to the ALP group (Figure 3C).

Furthermore, the levels of CK showed significant ($P<0.05$) alteration in the ALP group compared with the control group. The levels of this enzyme also showed a significant increase ($P<0.05$ to $P<0.001$) in ALP-KNO3-L, ALP-KNO3-H, ALP-CaCO3-L, ALP-CaCO3-H, and ALP-NaBr-L groups in comparison to the control group (Figure 3D).

**Table 2.** Pathological findings of the heart sections (n = 5).

| | Lesions* | | | | |
|---|---|---|---|---|---|
| Groups | Vascular congestion | Hemorrhage | Inflammation | Hyaline degeneration | Necrosis |
| Control | 0 | 0 | 0 | 0 | 0 |
| ALP | +1 | +1 | 0 | 0 | 0 |
| ALP-$KNO_3$-L | +1 | +1 | 0 | 0 | 0 |
| ALP-$KNO_3$-H | +1 | +1 | 0 | 0 | 0 |
| ALP-$CaCo_3$-L | +1 | +1 | 0 | 0 | 0 |
| ALP-$CaCo_3$-H | +1 | +1 | 0 | 0 | 0 |
| ALP-NaBr-L | +1 | +1 | 0 | 0 | 0 |
| ALP-NaBr -H | +1 | +1 | 0 | 0 | 0 |

*Normal (0), Mild (+1), Moderate (+2), and Severe (+3)

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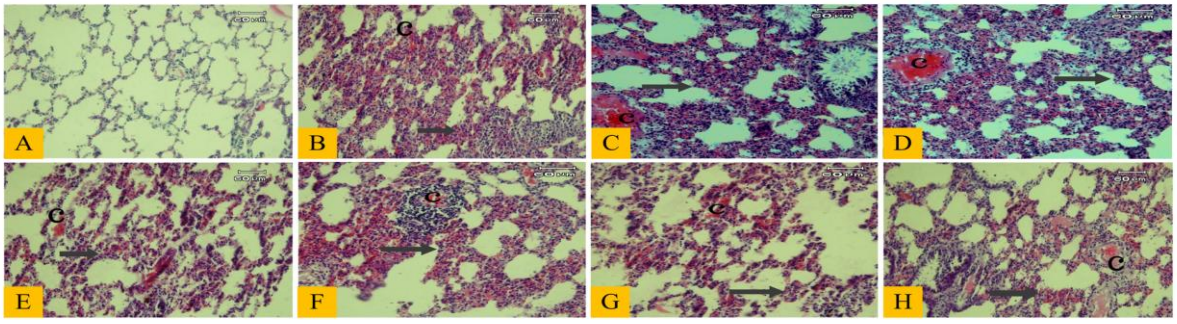




**Figure 1.** Hematoxylin and eosin-stained lung specimens. A: normal control group with a normal structure B: ALP-control group. C: ALP-$KNO_3$-H group, D: ALP-$KNO_3$-L group, E: ALP-$CaCo_3$-H group, F: ALP-$CaCo_3$-L group, G: ALP-NaBr-H group, and H: ALP-NaBr-L group. All treated groups presented vascular congestion (c) associated with the thickening of alveolar walls and infiltration of inflammatory cells (arrows).

## The levels of stress oxidative markers in the lung tissue

As shown in Figure 4, the MDA levels in lung tissue were significantly (P<0.05) increased in the ALP group compared with the control group. However, results showed a significant (P<0.05) reduction of MDA in the lung tissue of ALP+CaCO3-H and ALP+NaBr-H groups compared with the ALP group.

## Measurement of antioxidants, Enzymes, and TAC in the lung tissue

According to our data, AlP intoxication significantly (P<0.05, P<0.001) decreased the levels of lung GPx compared to the control rats. In addition, the levels of GPx significantly reduced (P<0.05 to P<0.001) in groups that received ALP and were treated with CaCO3, KNO3, and NaBr in comparison to the control group (Figure 5A).

There were no significant differences in the catalase

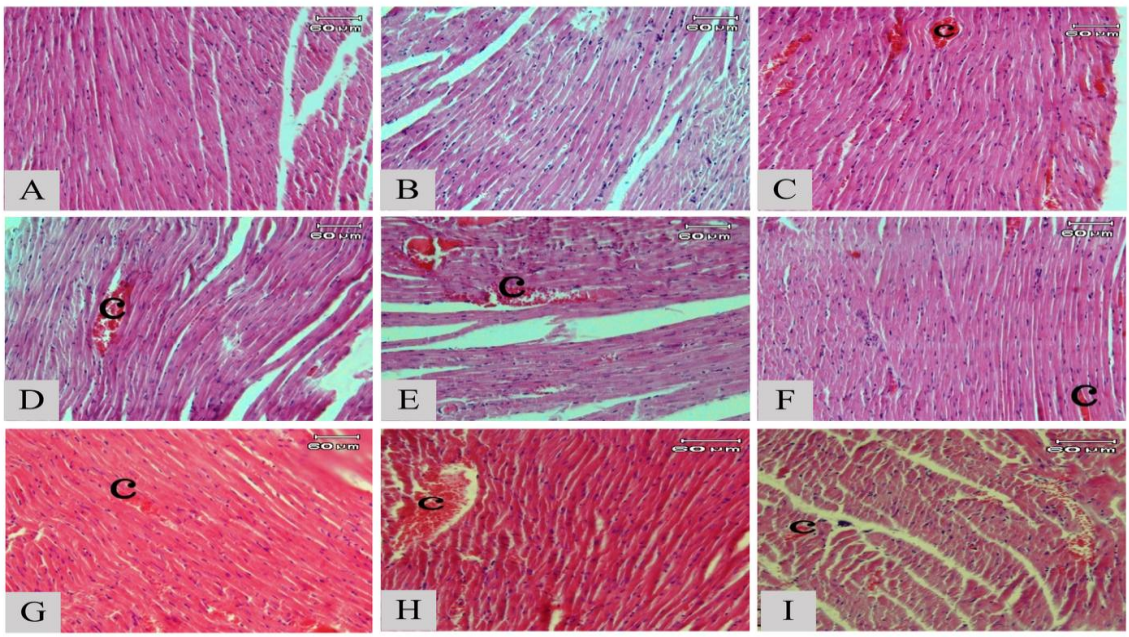




**Figure 2.** Photographs of a heart specimen in different groups. A, B: normal control group with a normal structure. C: ALP-control group. D: ALP-$KNO_3$-H group, E: ALP-$KNO_3$-L group, F: ALP-$CaCo_3$-H group, G: ALP-$CaCo_3$-L group, H: ALP-NaBr-H group, and I: ALP-NaBr-L group. There was mild vascular congestion (c) in all poisoned and treated groups with no significant difference.

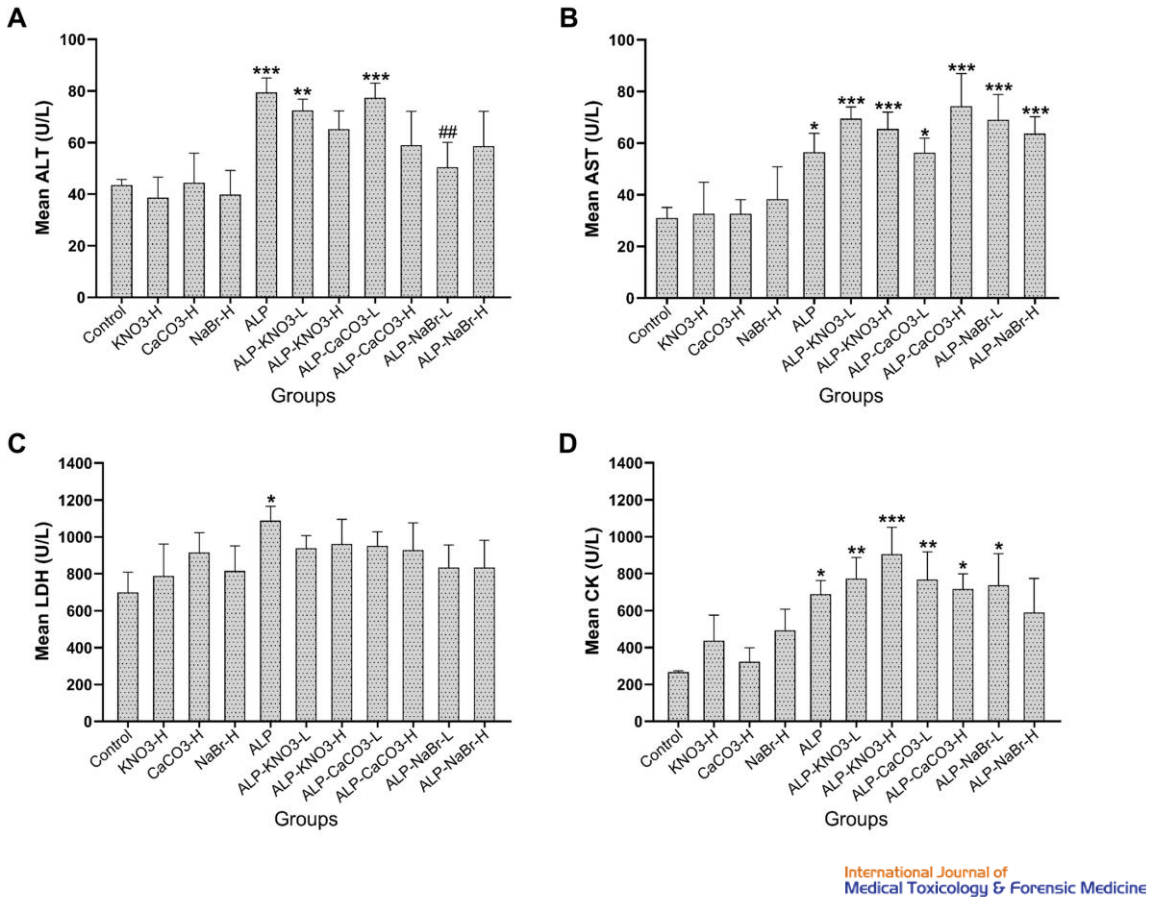


**Figure 3.** Measuring the levels of MDA in the lung tissue of experimental groups. Data are expressed as means ± SEM (n = 8). *, P<0.05 versus control; #, P<0.05 versus ALP based on Tukey's post hoc analysis.

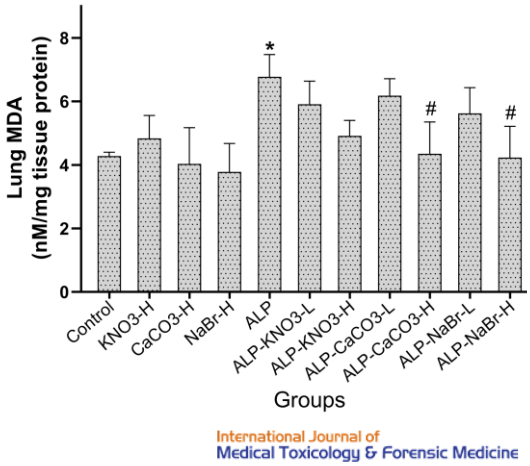


**Figure 4.** Measuring the serum levels of ALT (A), AST (B), LDH (C), and CK (D) in experimental groups. Data are expressed as means ± SEM (n = 8). *, P<0.05 versus control; **, P<0.01 versus control; ***, P<0.001 versus control; ##, P<0.01 versus ALP based on Tukey's post hoc analysis.

levels among experimental groups (Figure 5B).

Moreover, SOD levels showed no significant changes in the ALP group. However, ALP+CaCO3-L, ALP+CaCO3-H, and NaBr-H groups showed significant (P<0.05) increases as compared with the ALP group (Figure 5C).

We also noted that lung TAC was significantly (P<0.05) reduced in the ALP group. Treatment with CaCO3 and NaBr increased the levels of TAC in ALP+CaCO3-H and ALP+NaBr-H groups compared to the ALP subjects (Figure 5D).

## Discussion

In the current study, we established the protective effects of CaCO3, KNO3, and NaBr in an acute AlP toxicity model in rats by evaluating histopathological parameters, cardiac enzymes, and oxidative stress biomarkers in the serum and lung tissues. We found severe histopathological lesions in the lung tissue of the ALP receiving groups. However, necrosis was not observed in the groups treated with NaBr and CaCO3, and hemorrhage was absent in the high-dose calcium carbonate group, indicating improvement in at least some histopathological parameters. AlP intoxication increased the level of ALT, AST, LDH, and CK enzymes. However, NaBr at a low dose could reduce

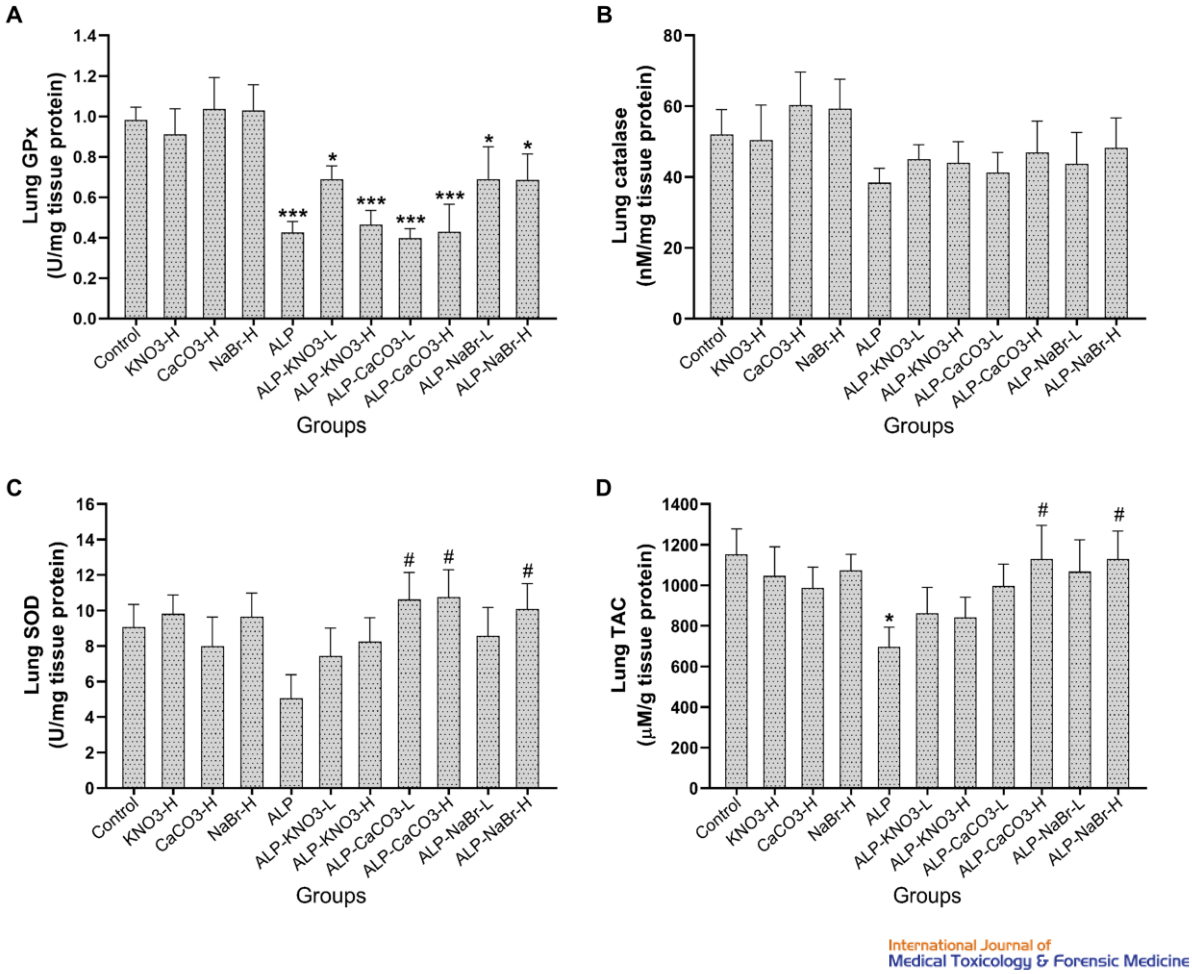


**Figure 5.** The levels of GPx (A), Catalase (B), SOD (C), and TAC (D) in the lung tissue of experimental groups. Data are expressed as means ± SEM (n = 8). *, P<0.05 versus control; ***, P<0.001 versus control; #, P<0.05 versus ALP based on Tukey's post hoc analysis.

**Table 3.** Pathological findings of the lung sections (n = 5)

| | Lesions* | | | | |
|---|---|---|---|---|---|
| Groups | Pulmonary edema | Vascular congestion | Hemorrhage | Inflammation | Necrosis |
| Control | 0 | 0 | 0 | 0 | 0 |
| ALP | +1 | +3 | +2 | +3 | +1 |
| ALP-$KNO_3$-L | +1 | +3 | +1 | +3 | +1 |
| ALP-$KNO_3$-H | +1 | +3 | +1 | +2 | +1 |
| ALP-$CaCo_3$-L | +1 | +2 | +2 | +2 | 0 |
| ALP-$CaCo_3$-H | +1 | +2 | 0 | +2 | 0 |
| ALP-NaBr-L | +1 | +2 | +1 | +2 | 0 |
| ALP-NaBr –H | +1 | +2 | +1 | +3 | 0 |

*Normal (0), Mild (+1), Moderate (+2), and Severe (+3)



the serum levels of the ALT enzyme. In addition, AlP administration led to increased MDA and reduced TAC levels in the lung tissue, which were reversed by high-dose administration of CaCO3 and NaBr. Besides, lung SOD levels were increased in ALP+CaCO3-L, ALP+CaCO3-H, and ALP+NaBr-H groups.

Histopathological changes such as vascular congestion, degeneration of hepatocytes, pulmonary edema, hemorrhagic pleural effusions, and mononuclear infiltration in the liver have been observed in AlP-poisoned patients [5]. In addition, dilated capillaries in the lung and alveolar thickening have been observed in these poisoned patients [27]. Furthermore, cardiac toxicity markers such as heart congestion, focal necrosis, subendocardial infarction,

edema, vacuolation of myocytes, and neutrophil and eosinophil infiltration have also been documented in AlP poisoning [28-30].

Previous studies have revealed that AlP induces significant alterations in oxidative stress biomarkers via disturbance in the electron transfer chain and antioxidant systems [31]. Oxidative stress has been proposed as one of the main mechanisms by which AlP exerts toxicity [32]. Multiorgan oxidative stress is accompanied by the inhibition of cytochrome oxidase and lipid peroxidation [2]. Non-competitive binding to the cytochrome oxidase results in cellular hypoxia and organ damage [33, 34]. In addition, animal model studies have shown that phosphine gas induces the extra-mitochondrial release of free radicals and lipid peroxidation in various organs via binding to cytochrome oxidase [12, 35]. Based on these data, organs with higher oxygen consumption, such as the lung and the heart, exhibit higher sensitivity to phosphine gas [36].

In line with our results, a study showed oxidative stress markers in the serum of AlP-poisoned patients. It established that elimination of phosphine five days after AlP ingestion could abolish oxidative stress by reversing the SOD, catalase, and MDA levels in the serum [13]. Animal and human studies have also shown that the level of LDH, a non-specific cardiac marker, increased in the serum of rats and humans intoxicated with AlP [37, 38]. Moreover, elevated CK levels have been reported in human-poisoned cases [39]. These data indicate that AlP could inhibit mitochondrial oxidative phosphorylation and shift cellular respiration into the anaerobic pathway [40].

It has been revealed that antioxidants could play an important role in reducing the effects of ROS caused by AlP [41]. Catalase, SOD, and GPx are necessary antioxidant enzymes in all tissues. It has been demonstrated that AlP decreases the levels of antioxidant markers such as TAC, CAT, and GPx [42]. In the rat model, the intragastric administration of AlP caused a significant decrease in ATP and an increase in cardiac MDA levels [43]. In addition, AlP-induced imbalance in oxidant/antioxidant status has been documented by reduced glutathione levels as a main antioxidant defense [5]. In another study, it has been demonstrated that MDA, SOD, and catalase levels were enhanced following ALP exposure, leading to lipid peroxidation and finally resulting in damage to the cellular membrane, changes in membrane action potential, altered permeability to sodium, magnesium, and calcium, and finally cardiac arrhythmias [13].

In the treatment field of AlP poisoning, there is no specific antidote to inhibit the effects of phosphine. However, the therapeutic effects of different ionic compounds, including sodium bicarbonate and magnesium sulfate, have been shown previously [44]. In addition, potassium permanganate and calcium gluconate reduce phosphine absorption or inhibit its destructive action in tissues [45]. In the phosphine compound, the non-bonding pair of electrons of the phosphorus could participate in dative covalent bonding with acceptor atoms. Since Ca+2, Na+, and K+ have empty orbitals in CaCo3, NaBr, and KNO3 molecules that the shared electrons can fill, it is hypothesized that these molecules may react with phosphine in a moist environment and neutralize it. Thus, the current study, for the first time, surveyed the effects of CaCO3, KNO3, and NaBr on histopathological changes in the lung and heart and oxidative-antioxidative markers in the serum and lung of AlP-intoxicated rats. Overall, CaCO3 and NaBr improved some markers of oxidative and antioxidative systems in the serum and lung tissue of AlP-poisoned rats.

The absence of necrosis in both NaBr- and $CaCO_3$-treated groups, along with the lack of hemorrhage in the high-dose $CaCO_3$ group, suggests a potential protective role of these compounds. This effect is likely mediated through the neutralization of acidic metabolites and restoration of ionic homeostasis. Among the treated groups, low-dose NaBr effectively reduced serum ALT levels, indicating partial hepatoprotective activity. Moreover, elevated levels of SOD and TAC in the lung tissues of $CaCO_3$- and NaBr-treated animals further support the enhancement of the antioxidant defense system against AlP-induced oxidative damage. These findings are in line with previous studies demonstrating that the administration of antioxidants, such as N-acetylcysteine (NAC), in animal models of AlP poisoning can improve oxidative stress parameters [46, 47].

Although the exact mechanisms underlying the protective effects of $CaCO_3$ and NaBr were not fully elucidated in this study, it is likely that their actions involve direct interaction with phosphine gas, thereby reducing its toxicity, and/or exerting antioxidant activity.

Considering the positive effects of CaCO3 and NaBr in the prevention of oxidative stress, it could be argued that oral administration of CaCO3 and NaBr leads to a significant reduction in the deteriorating effect of AlP in the heart and lungs of poisoned rats. Of note, one of the major limitations of this study is the lack of a detailed investigation into the molecular mechanisms by which $CaCO_3$ and NaBr neutralize AlP

toxicity. Dose–response studies are needed to determine the optimal therapeutic dosages of these compounds. Additionally, future research should explore their combined effects with well-established antioxidants such as N-acetylcysteine (NAC) to assess potential synergistic benefits.

## Conclusion

Our results revealed that administration of CaCO3 and NaBr improved serum cardiac markers and antioxidant indexes in the lung tissue of AlP-intoxicated models, as indicated by reduced ALT, MDA, and SOD levels, as well as increased TAC levels in the serum and lung tissue. So, CaCO3 and NaBr may be promising and potential options for managing and treating AlP toxicity. This study provides a foundation for the development of low-cost and accessible therapeutic strategies in regions with a high prevalence of AlP poisoning. However, translation of these results to human models requires further investigation.

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## Conflicts of Interest

The authors report there are no competing interests to declare.

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