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Research article

# Repurposing of sevelamer as a novel antidote against aluminum phosphide poisoning: An *in vivo* evaluation

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ABSTRACT

Aluminum phosphide (AlP) is widely used for protecting grains from pests. AlP releases toxic phosphine gas ($PH_3$) while exposed to humidity. Poisoning with these tablets is dangerous and can cause death or serious injuries. Up to now, no definite antidote has been introduced for specific treatment of this poisoning. Sevelamer carbonate or sevelamer hydrochloride (Renagel) is a polymeric pharmaceutical prescribed for treating hyperphosphatemia in patients with chronic kidney disease. Sevelamer can bind with phosphate groups and act as an anion exchanger. Herein, sevelamer is repurposed as a potent antidote agent in phosphine gas poisoning. *In vivo* evaluation was conducted on male Sprague Dawley rats. The evaluation was conducted on three groups of animals: control, AlP-poisoned, and AlP-poisoned treated with sevelamer. Survival percentage, serum biomarkers level of organ injury, and ATP level were recorded. The results indicate a high survival rate in sevelamer-treated animals compared with the AlP-poisoned group (75% *vs.* 0% respectively, 48 h after poisoning). The analysis of serum markers of organ injury also showed that sevelamer could reduce toxicity and organ injury in poisoned animals. ATP level of separate organs showed that sevelamer treated groups were recovered. The results showed that sevelamer could be a potent antidote for managing aluminum phosphide poisoning. Moreover, a mechanism is suggested for the interaction of sevelamer with phosphine gas.

## 1. Introduction

Phosphine poisoning caused by aluminum phosphide (AlP), or metal phosphide in general, is one of the most common causes of mortality, especially in India [1]. This chemical formulation is sold in Iran under the name of "rice tablet" and is known as a very effective pesticide for commercial and industrial use [2]. It is also sold under brand names such as Celphos, Fostox, Phostoxin, Phostek, Quick Phos, Fumitoxin, Fieldphos, Talunex, and Weevil-Cide [3]. The high lethality of metal phosphides is due to phosphine gas ($PH_3$) released by its reaction with water. The resulting gas is colorless and has a specific odor of garlic or rotten fish [4]. In most parts of the world, especially developed countries, this pesticide is used only by reputable companies and trained individuals, and there is almost no public access [5]. One of the most important properties of aluminum phosphide, which despite its significant lethality to almost all living organisms, still makes it one of the most widely used pesticides, is its ease of use and absence of residues in the products. The

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release of the deadly phosphine gas and its diffusion due to the reaction of tablets with the humidity of the air and the environment provide its pesticidal activity [6]. The important thing in using these tablets is to take enough time to remove phosphine gas from the environment. Negligence at this stage can lead to severe accidental poisoning and even death. In Iran, the reports by Forensic Medicine Facility show that most statics of mortality from poisoning were related to rice tablets, and most cases were committed suicide [7]. Routine treatment of such toxicities is the administration of sodium bicarbonate, magnesium sulfate, trimetazidine, *N*-acetyl cysteine, vitamin C and E, dihydroxyacetone, thiamine, and hydrocortisone which are effective treatments in lowering the fatal rate [8,9]. Through phosphine gas release in the body, cellular respiration failure is happened due to the effect of phosphine on mitochondria level by a disturbance in the respiratory chain, inhibiting cytochrome *c* function and production of hydroxyl radicals [10]. To date, no definite antidote has been introduced to treat this poisoning. However, several strategies were conducted by researchers to reduce the mortality rate. Coconut oil has been shown to have a role in rapidly preventing phosphine gas absorption [11]. Dihydroxyacetone was introduced as a definite treatment for phosphide poisoning [9,11–13]. The mechanism of action of dihydroxyacetone is to restore cytochrome *c* of mitochondria activity while phosphine inhibits its activity [13]. The heart is one of the main organs affected by AlP toxicity. Melatonin has been shown to be an effective therapeutic agent in alleviating cardiotoxicity, improving mitochondria activities, and oxidative stress biomarkers [14]. *N*-acetylcysteine as an antioxidant and dietary supplement improved to be an effective agent in AlP toxicity by preventing hepatic necrosis. Vitamin C administration was suggested after *N*-acetylcysteine treatment [15].

In this work, for the management of AlP-induced toxicity, the administration of Sevelamer (SVLM) was suggested. SVLM is also sold under the brand name of Renagel or Renevela, which have US Food and Drug Administration approval for treating hyperphosphatemia in patients with chronic kidney disease or end-stage renal diseases. SVLM is among polymeric drug made of polyallylamine hydrochloride cross-linked with epichlorohydrin [16]. SVLM has amine and ammonium-free groups, which can interact with phosphate groups through ion exchange and hydrogen binding [17].

We believe phosphine gas could react with ammonium groups in SVLM and change to phosphonium salt, which loses its high reactivity toward other organs and could be excreted through feces. By this means, an *in vivo* evaluation is conducted on rat models. Four groups were selected: control, AlP-poisoned, and AlP-phosphide-poisoned treated with SVLM (5 and 10 mg/kg). The third group was divided into two groups receiving two different doses of SVLM. Serum biomarkers of organ injuries were determined. Recording survival percentage, analysis of serum biomarkers level of organ injury, and measuring the amount of adenosine triphosphate (ATP) showed that SVLM could act as a potent antidote agent in AlP poisoning.

In continuous of our previous studies in the field of toxicology by introducing novel antidote agents made of mesoporous silica with high capacity in adsorption of paracetamol and phenobarbital [18], iron [19], and copper [20], and management of hepatic encephalopathy [17], herein, SVLM is repurposed as a distinguishing antidote of AlP.

## 2. Materials and methods

### 2.1. Chemicals and reagents

AlP was provided by Detia DEGESH GmbH-Germany. Each bag contains 34 g of powder, capable of releasing 11.34 g of phosphine gas. Sevelamer hydro carbonate (Renevela) was provided from SVLM carbonate was provided from Genton. All solvents were available from Merck Chemical Company. The kit for evaluation of tissue ATP content was obtained from ENLITEN®, Promega.

### 2.2. Animals

Male Sprague Dawley rats (250–300 g, total number of 80 animals) were used and provided by Shiraz University of Medical Sciences (SUMS). Animals were handled and housed according to SUMS guidelines approved by the ethics committee of SUMS for this project and registered by this ethical code IR.SUMS.REC.1398.1348. Animals were maintained in a standard environment (12 h photo schedule, 40% relative humidity, and temperature 24±1 °C) with free access to tap water and rodents' diet (Behparvar®, Iran).

### 2.3. Experimental setup

In *in vivo* study, we tried to induce AlP toxicity in rats and make a treatment with SVLM. The assessment was conducted among four groups of animals that were divided according to the following protocol (10 animals/group). Control animals were treated with olive oil (2.5 ml/kg, gavage). The second group was treated with an acute toxic dose of AlP (40 mg/kg, suspended in olive oil, gavage). The third group received AlP (40 mg/kg in olive oil, gavage) and was treated with SVLM (5 mg/kg, suspended in olive oil, gavage) 2 h after AlP treatment. The fourth group was treated with AlP (40 mg/kg in olive oil, gavage), and then SVLM (10 mg/kg, suspended in olive oil, gavage) was administered 2 h after AlP treatment. Animals were anesthetized (80 mg/kg, *i.p*), and blood samples were collected from the abdominal aorta and centrifuged (3000 g, 20 min, 4 °C). Serum was used to assess organ injury biomarkers [21]. Moreover, a series of animals (n = 10/group) were monitored for seven consecutive days to investigate the survival rate. It should be noted that the data collected in each group depended on the surviving animals in each group (data are represented as individual values in Figures). Hence, the data shown in the Figures in this study are reported for survived animals which are variable between groups. The dose of AlP was selected based on previous studies in this field. It has been found that 40 mg/kg of AlP is a fatal dose of this toxicant (about 4-fold of the aluminum phosphide LD50) [22–25]. A wide range of SVLM doses (from low doses to 1500 mg/kg) has been investigated in animal models [26,27]. In the current study, we used a minimum low dose of this drug to emphasize the potency of SVLM against AlP poisoning. SLVM was administered 2 h after AlP to allow the interaction of poison with moisture and acid and the release of

phosphine gas. Moreover, there is a time frame from poisoning to patients' hospitalization. Hence, the results are more reliable to translate to the clinical situation when SLVM is administered post-AlP poisoning.

### 2.4. Plasma biochemistry

Several biomarkers were analyzed, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), Bilirubin, gamma-glutamyl transpeptidase (γ-GT), Alkaline phosphatase (ALP), and creatine kinase-myocardial band (CMKB) [28]. A MindrayBS-200® chemistry analyzer (Guangzhou, China) and standard kits (Pars Azmun®, Tehran, Iran) were utilized to measure organ injury plasma biomarkers. These markers are routinely evaluated in clinical settings to assess the severity of AlP poisoning and monitor patients' recovery process [29].

### 2.5. Tissue ATP level

Tissue ATP content was evaluated using a luciferase-luciferin-based kit (ENLITEN®, Promega) [30,31]. For this purpose, samples (500 mg) of the brain, heart, liver, and kidney were homogenized in ice-cooled Tris-HCl buffer (5 ml of 40 mM solution). 100 μl of trichloroacetic acid (0.3% w: v) were added to homogenized samples, and samples were centrifuged at 16,000 *g* for 20 min at 4 °C. The supernatant was collected to determine tissue ATP level. Buffers were prepared according to the kit instructions. The luminescence intensity was determined at $\lambda = 560$ nm. Plates were read by a multi-functional fluorimeter (FLUOstar Omega®, Germany) [30,32].

### 2.6. Statistical analysis

Data are given as the mean ± SD. Data sets were compared using the one-way analysis of variance (ANOVA) and Tukey's multiple comparisons test. The differences were considered statistically significant when $P < 0.05$.

## 3. Results

Management of toxicity in human beings requires prompt action from health care services and the administration of proper therapeutic agents. For AlP toxicity, no definite antidote was introduced. Herein, we introduce SVLM as a potent antidote to AlP toxicity. Assessment of its efficiency was performed through *in vivo* analysis. The results are presented here.

The survival rate study was conducted by comparing four groups of animals (*i.e.,* Control, AlP poisoned, and two groups of AlP poisoned were treated with SVLM). Survival percent was calculated in 7 consecutive days from starting studies. The animals in the control groups were all alive. The AlP-poisoned animals died on the first day. Two groups of poisoned animals treated with SVLM received two doses of the drug (*i.e.*, 5 mg/kg and 10 mg/kg). The survival rate in treated groups with 5 mg/kg of SVLM after seven days was 75%, while the other group treated with a higher dose of SVLM (10 mg/kg) encountered a lower rate of death, with a survival percent of 90 (Fig. 1). The result shows that SVLM acts as a suitable treatment for AlP poisoning.

The same group division was conducted in another series of animals, and rats were sacrificed to analyze serum biomarkers of organ

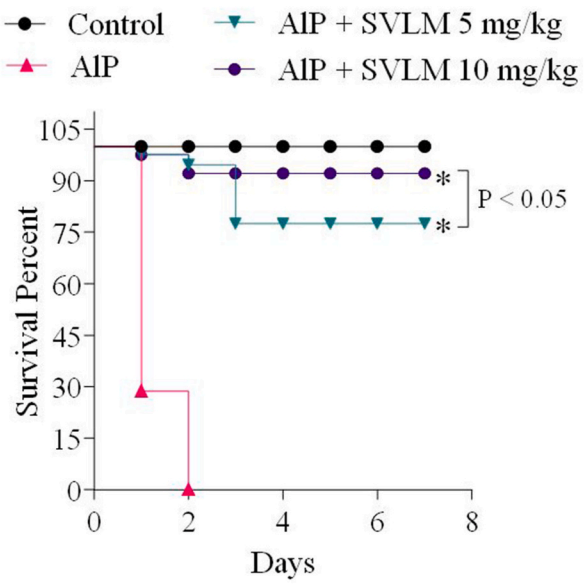


**Fig. 1.** Effect of sevelamer (SVLM) administration on the survival rate of aluminum phosphide (AlP)-treated animals. *Indicates significantly different than AlP-treated rats ($P < 0.05$).

injuries. Several biomarkers of liver, kidney, and heart injuries were assessed by collecting aorta blood samples. The biomarkers of different organ injuries, including ALT, AST, LDH, bilirubin, and ALP for the liver, GT for the kidney, and CKMB for the heart, were analyzed for all groups of animals (Fig. 2). For the control group, all biomarkers were at an average level. However, for the AlP-poisoned group, the enzymes were in the high range with a significant difference from the control group. In AlP-poisoned groups treated with SVLM, the biomarkers of organ injuries were prevented. However, no significant differences were observed among the two doses of SVLM, 5 or 10 mg/kg, unless for AST (Fig. 2).

Tissue ATP levels were also monitored as a marker of mitochondrial functionality in AlP-treated animals (Fig. 3). A significant decrease in the brain, heart, liver, and kidney ATP levels was detected in AlP-treated animals compared to the control group (Fig. 3). On the other hand, tissue ATP content was at a higher level when AlP-treated animals received SVLM (5 and 10 mg/kg) (Fig. 3).

## 4. Discussion

AlP or rice tablet poisoning is one of the most hazardous conditions resulting in a high mortality rate. Hence, emergency management of such cases is vital. However, several types of such poisoning have occurred in urban areas, and most cases suffer from unrepaired injuries while transferring to related toxicological centers. The lack of a definite antidote in treating this poisoning is another limitation in the immediate treatment of such cases. The high mortality rate in Asia from this poisoning is regretful. Researchers are trying to introduce and check different treatments for such cases to reduce mortality.

In the current study, we found a robust antidotal effect of SVLM against a fatal dose of AlP *in vivo*. The effects of SVLM on the mortality rate of AlP poisoning is the boldest achievement of the current study. It was demonstrated that the AlP-induced toxicity has a fatal dose (40 mg/kg), and all poisoned animals died on the first day. The groups that received treatment in two doses of SVLM (5 and 10 mg/kg) survived at the rate of 75 and 95%, respectively. It has been found that AlP at fatal doses (*e.g.*, 40 mg/kg) caused animals' death within the first hours of poisoning [25]. As reported in our study, this dose caused 70% lethality within 24 h and 100% lethality within 48 h in rats (Fig. 1). This lethal dose of AlP also caused significant changes in rat serum biomarkers of organ injury (Fig. 2). Our data show a significant decrease in AlP mortality by SLVM, even at a high fatal dose of this toxicant. These data mention the robust antidotal effects of SLVM.

This point also should be emphasized here that the AlP dose used in this study (40 mg/kg) is ideal for investigating the complications of acute poisoning (especially the mortality rate as the endpoint highlighted in the current investigation). Hence, it is expected that changes such as tissue histopathological changes may not be revealed in the time frame evaluated in the current study. We detected significant changes in serum biomarkers in the current study, but no significant histopathological changes were evident. In line with these findings, previous studies on AlP toxicity used lower doses of this toxicant and evaluated tissue histopathological

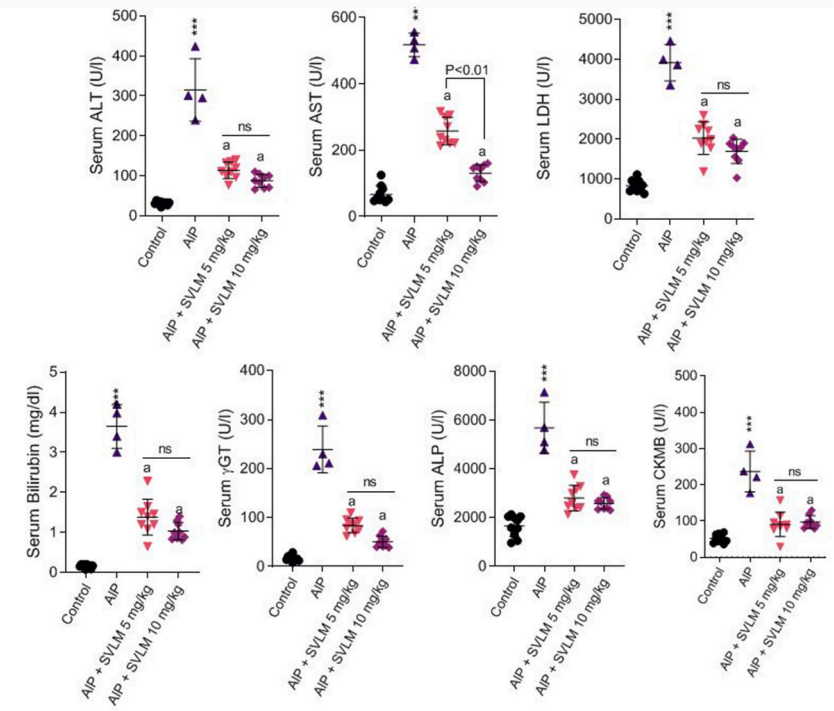


**Fig. 2.** Serum biomarkers of organ injury in aluminum phosphide (AlP)-treated rats. SVLM: Sevelamer. Data are presented as mean ± SD. ***Indicates significantly different from the control group ($P < 0.001$). [a] Indicates significantly different as compared with the control group ($P < 0.01$). ns: not significant.

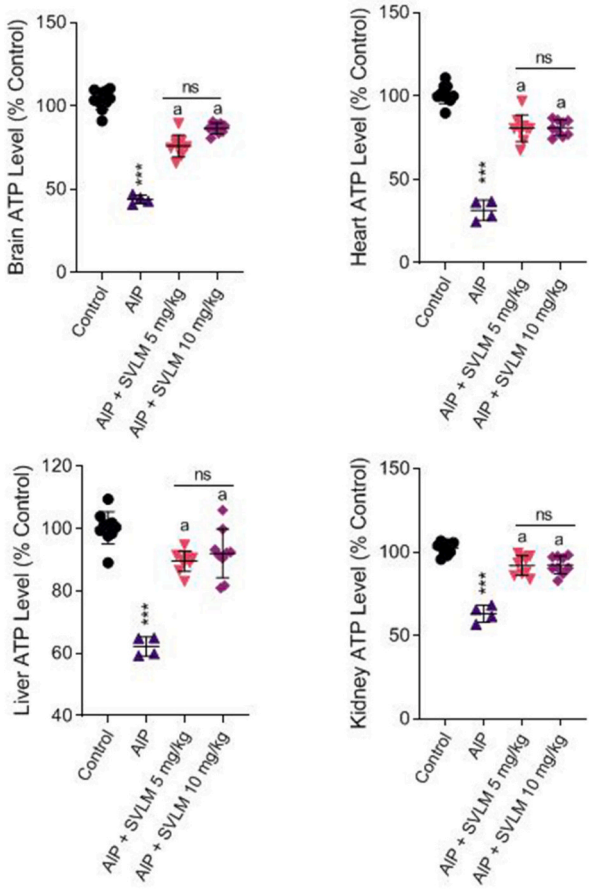


**Fig. 3.** Effect of sevelamer (SVLM) treatment on tissue ATP levels in aluminum phosphide (AlP)-treated rats. Data are presented as mean ± SD. ***Indicates significantly different from the control group ($P < 0.001$). [a] Indicates significantly different as compared with the control group ($P < 0.01$). ns: not significant.

changes at longer times post-poison administration [33]. Moreover, in the current study, evaluation of ATP levels revealed a significant decrease in this marker in acutely-poisoned mice (Fig. 3). These data indicate that serum indicators and markers such as tissue ATP are more sensitive biomarkers rather than histopathological alterations for evaluating the effect of high lethal doses of AlP.

The amount of ingested AlP among poisoned patients varies widely in different countries. Hence, a major factor for this variability could depend on the dosage of AlP in various formulations available in various regions [25]. Hence, patients are referred to hospitals with a wide range of symptoms and poisoning severity. The lethal dose of AlP for a 70 kg subject is reported to be between 150 and 500

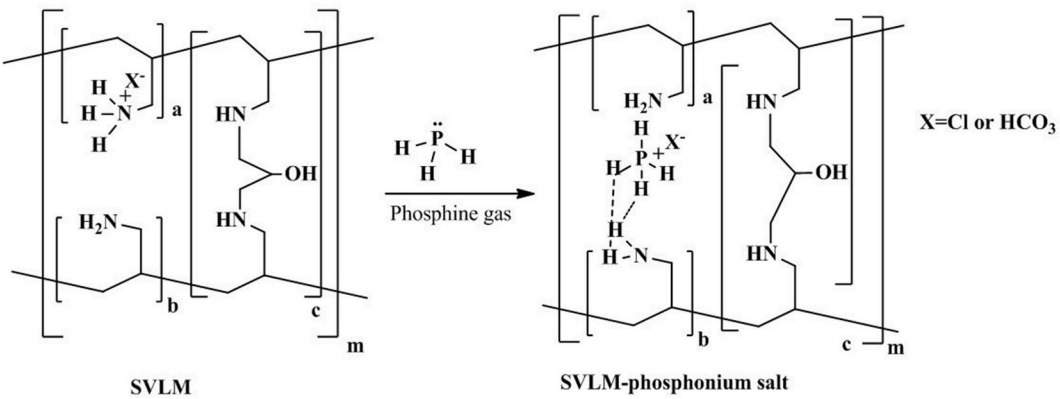


**Fig. 4.** Schematic representation of the potential mechanism of interaction between phosphine gas and the amine groups of sevelamer (SVLM).

mg [29]. Moreover, the availability of clinical care as well as patient hospitalization time after AlP ingestion, affect the outcome of clinical interventions. In the current study, we used a fatal dose of AlP and administered SVLM 2 h post-AlP poisoning to consider all mentioned variables possibly. As our results revealed, SVLM could surprisingly abate the lethality of a very high fatal dose of AlP. These data represent SVLM as a potent novel antidote for AlP poisoning.

Several mechanisms could be presented for the antidotal role of SVLM against AlP poisoning. SVLM, with a polymeric structure, is a hydrogel formula used to treat hyperphosphatemia. The binding interaction between amine hydrochloride-containing polymers and phosphate anions has been reported in previous investigations [34–36]. In this regard, it has been reported that SVLM could significantly capture phosphate ions *in vitro* [35]. In the SVLM structure, the ammonium salt is available, which can be prepared by encountering chloride or hydrogen carbonate ion. A hypothesis regarding the potential of SVLM in adsorbing AlP was proposed in our group. The following route of action is proposed for the mechanism of SVLM action in controlling phosphine poisoning (Fig. 4). SVLM has ammonium salt and amine groups. After releasing phosphine gas, the administration of SVLM can inhibit phosphine gas distribution in other organs. Phosphine can react with SVLM by reacting with ammonium groups. In this reaction, phosphonium salt is produced, which is ionic salt and can be trapped in the polymeric network of SVLM by hydrogen binding (Fig. 4). In this case, the highly toxic poison is changed to ionic salt of phosphonium, which lost its toxicity and adsorbed in the polymeric network of SVLM. If SVLM chloride was administrated, the phosphonium chloride salt would be produced.

In this work, sevelamer carbonate was administrated. SVLM carbonate is another formula that can be suggested for this application. The mechanism of action of SVLM carbonate might be the same as the suggested mechanism for SVLM (Fig. 4), while the product is an ionic salt of phosphonium carbonate.

SVLM excretion is through feces [37,38]. In another part of this work, we had planned to perform a clinical trial on poisoned patients of AlP. The project was approved in SUMS and gained an ethical code (IR.SUMS.REC.1400.575). Along with other routine management of phosphine-poisoned patients, SVLM can act as a definite antidote agent and be applied as prompt treatment in local clinics, even in urban areas in the future.

Obviously, there are some limitations in evaluating the effects of SLVM on some parameters, such as the capacity of this drug to capture $PH_3$ in the *in vitro* conditions due to high toxicity induced by this gas, as well as limited control on the amount of $PH_3$ gas release. Hence, we had to evaluate the effects of this potential antidote against phosphine poisoning in an *in vivo* setup. Fortunately, SVLM showed promising antidotal activity against AlP poisoning in this study.

## 5. Conclusion

SVLM is categorized as a nanomedicine used in the treatment of phosphatemia. Herein, this polymeric drug is administrated to treat AlP-induced toxicity *in vivo*. The results of two evaluations among Sprague Dawley rats were reported. In the current study, the survival percent of four groups of animals was recorded. It was found that in the AlP-poisoned group treated with SVLM, a low mortality rate was observed. The analysis of serum markers of organ injury also showed that SVLM can reduce toxicity and organ injury. ATP levels in various organs showed that SVLM treatment prevented ATP depletion. Moreover, a high level of ATP was detected in different tissue of animals that received SVLM compared to the AlP-treated animals. The possible mechanism of SVLM action is through phosphine gas reaction with ammonium chloride or ammonium carbonate groups available in SVLM by producing phosphonium salt, which is harmless and trapped in the SVLM network. SVLM could be excreted through feces. This strategy could be considered an immediate treatment for phosphine toxicity. As mentioned, we have planned to use Renagel or SLVM in AlP-poisoned patients. As SLVM is clinically administered in the management of hyperphosphatemia worldwide, it's repurposing for the management of AlP could be a significant clinical achievement.

## Author contribution statement

Reza Heidari: Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Hamid Reza Mohammadi: Performed the experiments; Contributed reagents, materials, analysis tools or data.

Fazel Goudarzi: Conceived and designed the experiments; Wrote the paper.

Fatemeh Farjadian: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

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## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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