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Induced cytotoxicity caused the mitochondrial damages and oxidative stress by Aluminum phosphide; an overview of the mechanism to the clinic

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Abstract

Aluminum phosphide (AlP) is a significant fumigant and a notable, highly effective pesticide for both indoor and outdoor use. Analytical tests like the gas chromatographic method in post-mortem specimens and survivors have been developed to assess the quantity of phosphine and to differentiate between ZnP and AlP poisoning, even if clinical history can usually aid in making the final diagnosis. In this way, it is demonstrated that mitochondrial failure caused ALP to create reactive oxygen species (ROS). As a result of red blood cell hemolysis, decreased ATP synthesis, and the activation of apoptosis in cardiomyocytes brought on by ROS generation, different problems eventually develop. Since cardiomyocytes are the cells that are most significantly affected by ALP, using the right therapeutic methods to get the cells working again will prolong patient survival. Correspondingly, Phosphine's ability to inhibit cytochrome c oxidase has been demonstrated in vitro. It seems improbable that this interaction is the main driver of its toxicity, though. ALP poisoning may cause the most damage to the mitochondria, which might lead to poor ATP synthesis, metabolic shutdown, and multiorgan dysfunction (MOD). Additionally, due to an impairment in electron flow, there may be free radical formation and damage, which could also result in MOD. Rats and insects have shown signs of ALP-induced toxicity brought on by reactive oxygen species. A similar mechanism might potentially be present in people and help fill in the gap in the pathophysiology of ALP poisoning. Cellular poisoning, oxidative stress, cholinesterase inhibition, circulatory failure, cardiotoxicity, gastrointestinal and pulmonary toxicity, hepatic damage, neurological toxicity, electrolyte imbalance, and general metabolic disturbances are just a few of the many effects caused by metal phosphides. In this review article, we discuss the association of cytotoxicity, mitochondrial damage, and oxidative stress by Aluminum phosphide.

Keywords: Aluminum phosphide, Cytotoxicity, Mitochondrial damage, Oxidative stress

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Introduction

Aluminum phosphide (AlP) is an essential fumigant, a commendable and very superb outside and indoor insecticide and rodenticide, extensively bought and used because the 1940s. AlP is effortlessly reachable as pellets or a pill formulated and offered in porous baggage in a stable form, underneath change names such as Phostoxin, Quickphos Phosphume Phostek, Bhostoxin, Quickphos, Alphos, and Celphos (can launch 1 g PH3). It is utilized in growing international locations in suicide tries. AlP is handy in pesticide demands as an affordable grain rodenticide (1).

High viable houses are the purpose for the significance of its availability. The residences are close to perfect toxicity species, no longer concerning the viability of the seeds, leaving little remains on meal grains, being lower-priced and notably formulation. Moisture in the air mixed with aluminum phosphide, makes phosphine gas, the direct lively poison.

AlP is a frequent substance used in some Asian and European locations as a frequent approach to suicide. AlP, domestically known as the "rice pill", is extensively used to defend rice. In factories, most publicity entails swallowing suicide or unintended exposure, especially thru meals by using farmers and pores and skin exposure, which hardly ever reasons extreme systemic toxicity (2).

The Chemistry of AlP

AlP is normally accessible in stable structure positioned in blister packs, commonly synthesized as darkish brown/gray or yellow crystals that include 44% aluminum carbonate and 56% AlP. Absorption of phosphine gas, with odorless and colorless properties, is speedy thru mucosal and pores and skin contact, inhalation and ingestion due to the formation of diphosphines. After ingestion, which is the most frequent way of exposure, a small volume of zinc phosphide attains to the kidneys and liver and is hydrolyzed stilly in the tissues. Zinc phosphide is synthesized by way of a mixture of phosphorus and zinc.

Due to the production of diphosphines, the odorless and colorless phosphine gas is quickly absorbed by mucosal and skin contact, breathing, and ingestion (3, 4). A little amount of zinc phosphide enters the liver and kidneys after ingestion, which is the most common exposure method and is hydrolyzed slowly in the tissues. Zinc and phosphorus are combined to create zinc phosphide (5).

Practical action

It has been established that the fatal dose of AlP is approximately 0.5 g. The simplest method of absorbing is through oral consumption. ALP gas is released when various phosphide salts, particularly hydrochloric acid, react with stomach contents. The cytochrome C oxidase enzyme and mitochondrial electron transport chain are stopped after tissue absorption (6).

Phosphine mostly binds to cytochrome oxidase, changing the hemoglobin's valences and eventually causing protein aggregation, organ-specific cell membrane damage, and lipid peroxidation. According to some research, a significant phosphine level is associated with a decrease in serum cholinesterase (7). Ionic barrier disruption, and protein degradation, induce apoptosis, nucleic acid disruption, and ultimately cell death take place. AlP furthermore significantly lowers glutathione, a powerful antioxidant defense molecule. Malondialdehyde (MDA), superoxide dismutase (SOD), and catalase levels have been linked to AlP mortality. Phosphine has a significant part in the conformational changes of oxyhemoglobin, which can cause oxidative injury to cellular life, notably in the brain, lung, and liver, correspondent to research on both humans and animals (8).

Clinical indicators and diagnosis

Phosphine vaporizes immediately after ingesting a very small quantity of an AlP tablet due to air contact, and it disrupts several organs. The heart, digestive tract, respiratory system, and kidneys are the primary organs impacted by the initial exposure. Other symptoms include pulmonary edema, nausea, cyanosis, epigastric discomfort abdominal pain, and palpitations. Other symptoms include cardiac arrhythmias, shock, and metabolic acidosis, which are connected to myocardium injury that has been mentioned in some cases. Preliminary signs of AlP poisoning, such as nausea, agitation, epigastric discomfort and vomiting, and leucopenia, are important indicators (9).

Clinical symptoms and lab evaluation guide the use of clinical diagnostics. According to the findings, hepatocytes were damaged and severe AlP toxicity was indicated by increasing levels of serum glutamic pyruvic transaminase (SGPT) and glutamic oxaloacetic transaminase (SGOT) produced metabolic acidosis (10) (Table 1).

Table 1. Clinical symptoms of ALP poisoning.

System poisoning	Clinical characteristics
Respiratory	Obstructive pulmonary disease, pleural effusion, pulmonary edema, adult respiratory distress syndrome, lung inflammation
Neurological	Headache, acute dysfunction of the brain, weakness, ataxia, neuropathy tremor, paraesthesias
Hematological	Disseminated intravascular coagulation, intravascular hemolysis, methemoglobinemia
Gastrointestinal	Esophagitis, tracheoesophageal fistula, ascites, hepatic disorders, esophageal strictures
Cardiovascular	Dysrhythmias, pericardial effusion, low blood pressure, progressive cardiac conduction defect, ventricular dysfunction, pericarditis, shock, myocarditis
Metabolic	Low potassium, metabolic acidosis, low blood sugar level, hypermagnesemia, low level of serum magnesium
Renal	Regeneration of tubular epithelium, acute renal disorder, congestion within glomerules

Common symptoms include tachypnea, dyspnea, crepitations, and rhonchi. Although pulmonary edema is frequently present, its cause may be either cardiogenic or noncardiogenic. PH3 appears to interact with moisture in the lungs after inhalation to create phosphoric acid, which in turn damages the alveolar membrane. Adult respiratory distress syndrome (ARDS) cases associated with ALP poisoning have been documented, corroborating this assertion. Those who survive PH3 exposure also appear to experience long-term side effects such as obstructive airway disease (11).

According to a current, contentious study, chronic liver destruction brought on by AlP poisoning can result in hepatotoxicity. The primary results in this regard included centrilobular necrosis, hepatocyte nuclei being destroyed, fatty liver alterations, and central venous congestion. Hepatocellular toxicity and acute fulminant hepatic failure, which have been observed in some acute intoxication cases in various studies, have also been identified to be potential causes of death. Numerous investigations have also notified common ECG changes and cardiovascular complications like PR and QRS interval prolongation, ST-segment elevation that causes severe hypotension by lowering systemic venous pressure, complete heart block due to ectopic pacemaking, and irreversible myocardial injury, and atrial fibrillation. There are ST-T alterations and sinus tachycardia in the first 3 to 6 hours following poisoning, which are followed by conduction abnormalities and persistent arrhythmias in the following 6 to 12 hours (12).

The exact cause of why liver disease frequently manifests in less severe ways is unknown. After consuming metal phosphide, transient increases of serum alanine aminotransferase and aspartate aminotransferase have been observed, however, liver damage-related jaundice is far less frequent. The most common autopsy findings include portal edema, congestion of the portal tract and central veins, and vacuolization of hepatocytes (13).

Different examples of myocardial damage have been documented that involve anterior wall ischemia with RBBB (right bundle branch block), wave flattening suggesting myocardial ischemia, and total RBBB (14).

Hematemesis, vomiting, fistula, esophageal strictures, and epigastric discomfort are the most prominent gastrointestinal symptoms of AlP consumption and result in upper gastrointestinal bleeding. Various endoscopic reports have described slugged mucosa and the destruction of the stomach and esophageal tissues (15).

Previous research has shown that dysphagia may develop later on as a result of the mucosa's increased slugging during ALP poisoning. There are some signs of a necrotic and thinner stomach wall, as well as mucosa, in the stomach's fundus wall. During oral AlP

poisoning, there have been cases of spontaneous inflammation and stomach wall burns (16). Water and electrolyte imbalances can produce hypokalemia either as a causative factor of vomiting or as a subsequent effect. Acute renal failure, metabolic acidosis, respiratory alkalosis, and significant variations in calcium, phosphate, magnesium, cortisol, and citrate levels have all been noted. Various variations in blood glucose levels are also observed (17).

To investigate rice tablet poisoning, the silver nitrate test is utilized since it is a significant, straightforward, and sensitive spot examination. To detect inhaled PH3 gas, use fresh silver nitrate solution paper. The sample color turns black with this technique. Some sophisticated biochemical assays employ blood or gastric aspiration samples to find phosphine. the detection of phosphine gas in samples is the most reliable method for ALP poisoning diagnosis. The phosphine in the bio-samples is characterized using ion chromatographic techniques. Analytical assays were utilized to measure the quantity of phosphine and to differentiate between ZnP and AlP poisoning in post-mortem specimens and survivors (18).

Tissue morphology after exposure to AlP

Numerous studies have looked into how tissues alter morphologically after being exposed to or poisoned with AlP. Target organs for AlP poisoning include the liver, brain, kidneys, heart, and lungs. Additionally, microscopic examination reveals various degrees of edema, inflammation, and congestion in bodily organs. Analysis identified congestion, interstitial edema, hemorrhage, varying degrees of alveolar collapse, alveolar thickening, and emphysema as the primary histological abnormalities in the lung tissue (19).

ALP poisoning caused significant necrosis in the liver due to the morphological examination of the liver sample revealing vacuolar degeneration in hepatocytes cells, central venous congestion, mononuclear infiltration, sinusoidal dilatation, and centrilobular hemorrhagic necrosis. Portal edema, centrilobular necrosis, nuclear fragmentation, clusters of polymorph nuclear leukocytes in sinusoids, subcapsular hemorrhage, and macrovesicular steatosis are nonetheless prevalent histopathologic diagnoses. In the aforementioned investigation, sinusoidal clusters of polymorph nuclear leukocytes, nuclear hepatocytes, and sinusoidal congestion were reported. In severe AlP poisoning, the plasma level of renin increases after liver injury while cortisol levels fall at the upper level. When the kidneys were examined under a microscope, abnormalities included swelling of the epithelial cells of the proximal convoluted tubules, glomeruli and intraparenchymal congestion, and the renal medulla (20).

Control of poisoning

Control of AlP poisoning should begin right away. Initially, a thorough history must be obtained, followed as quickly as feasible by a clinical assessment. The majority of intoxication management involves supportive measures such as mechanical breathing, inotropic support, and fluid resuscitation. The majority of therapy attempts, nevertheless, have not been wholly effective and appropriate, and no definitive therapeutic has yet been presented; various therapeutic approaches are included below (21).

Digestive system decontamination

After consuming AlP, various gastrointestinal symptoms including diarrhea, vomiting, abdominal soreness, and eventually epigastric and abdominal pain, were described.

Vomiting is a common complaint among patients, however gastric lavage with a 1/5000 potassium permanganate solution removes and/or oxidizes unabsorbed toxins. However, during gastric lavage, caution must be exercised to avoid aspiration. A 2 percent solution of bicarbonate can also be used to neutralize hydrochloric acid and then stop the release of phosphine. When the bicarbonate level is below 15 mEq/L, sodium bicarbonate must be administered intravenously at minimum doses of 50–100 mEq every 8 hours until the bicarbonate level reaches 18–20 mEq/L (21, 22).

Administration of sorbitol solution as a cathartic and liquid paraffin and vegetable oils as blockers of phosphine produced from the AlP are two more therapies that have been suggested. According to a study conducted on ALP poisoning, coconut oil can help treat acute phosphine poisoning in people up to six hours after exposure. It is uncertain how coconut oil

and other lipids work in the digestive system. Through the formation of a protective barrier surrounding the stomach mucosa, dilution of stomach HCl, and decreased phosphide breakdown, coconut oil reduces the absorption of PH3 gas. Rats poisoned with AlP had a substantial reduction in mortality after gastric lavage with sweet almond oil, which also decreased plasma cholinesterase levels. It has been advised to do a wide stomach lavage while also mixing coconut oil and sodium bicarbonate solution (23, 24).

Due to ALP's corrosive nature and the fact that oral ingestion is the most typical method of poisoning, GI tract symptoms are frequently the first and most prevalent. Retrosternal burning, epigastric discomfort, and vomiting are the early signs and symptoms following consumption. Excessive thirst, stomach pain, and tenderness in the epigastric region are gastrointestinal symptoms that appear with moderate to severe poisoning. Hematemesis, perhaps even large hematemesis, is one way that ALP's esophageal corrosive action might appear. Dysphagia in survivors may become apparent as early as 3 or 4 days after ingesting aluminum phosphide. Esophageal strictures have afterward developed in several cases. Trachea-esophageal fistulae have been documented in a few cases (25).

Treatment of heart symptoms

AlP poisoning begins with severe metabolic acidosis and refractory hypotension. These symptoms first cause shock and tissue perfusion failure due to cardiogenic shock and peripheral circulatory failure two hours after consumption, which marks the beginning of poisoning. Cardiovascular problems such as acute myocardial infarctions and different cardiac arrhythmias are significant and should be taken into consideration. According to post-mortem accounts, hemodynamic instability, heart problems, and AlP poisoning causes severe heart failure, non-specific localized necrosis, edema-induced separation of myocardial fibers, eosinophil or neutrophil infiltration, and vacuolation of myocytes (26).

ALP poisoning frequently results in circulatory failure and severe hypotension, both of which are major symptoms and causes of mortality. Due to the continued absorption of PH3, hypotension, which is frequently severe and refractory, can occur quickly and last for a long time. Arrhythmia, conduction issues, myocardial injury, and myocardial depression can all contribute to intractable shock. The extensive small vessel injury that causes peripheral circulatory failure can also cause peripheral vasodilatation, which can result in shock. Due to fluid loss, excessive vomiting may cause shock. Shock and a high mortality rate can also result from the direct toxic effects of PH3 on the adrenal cortex, which are accompanied by decreasing cortisol levels (27).

To treat hypotension and refractory shock, medications like norepinephrine, dopamine, phenylephrine, and dobutamine can be used. To manage cardiac arrhythmias, anti-arrhythmic medications should be given. As an anti-ischemic medication, trimetazidine has demonstrated outstanding results in stopping ventricular ectopic beats and lowering oxygen consumption by converting myocytes' metabolism from fatty acids to glucose. Recent research indicates that the intra-aortic balloon pump (IABP) is an effective way to treat AlP poisoning by mechanically maintaining the heart, particularly in cases of refractory shock brought on by toxic myocarditis. The latest data support the idea that digoxin administration can be employed to stabilize left ventricular heart problems in AlP-poisoned cardiogenic shock by increasing myocardial contractility and blood pressure (28).

Nervous system

Headache, fatigue, vertigo, weakness, paraesthesias, and drowsiness were some of the neurological complaints. Long-term victims of PH3 poisoning may experience severe headaches that don't go away and even peripheral neuropathy. Neuronal degeneration, the removal of processes and Nissl granules, an eccentric position of the degenerated nucleus, and the nucleolus are all examples of neuropathological abnormalities. The production of PH3 gas, which interferes with cellular oxygen use and causes neurocellular damage, may be the cause of these hypoxic alterations (29).

The primary target of ALP is the mitochondrial complex

More than 90% of the total ATP needed by eukaryotic cells is supplied by mitochondria. Phosphine interacts

with the mitochondrial respiratory chain, which is the primary source of free radical formation, by altering the electron transfer chain. This interaction prevents oxidative phosphorylation, which results in the high production of ROS and reduced ATP levels. A cell energy crisis results from this. As a result, it is well recognized that mitochondria are phosphine's primary target (30).

Cellular oxidative stress functions similarly to reactive nitrogen species (RNS), which are mostly comprised of NO and peroxynitrite as by-products of a group of enzymes involved in electron transfer, in that it produces ROS such as superoxide (O20) and H2O2. Cell death may result from ROS/RNS damaging biological macromolecules. After entering the system, phosphorus interferes with the creation of enzymes and proteins at the mitochondrial level. Additionally, the generation of extremely reactive hydroxyl radicals plays a role in its toxicology. The principal cause of ROS formation in the mitochondrial respiratory chain is the reaction between the extremely reactive radical phosphonate and this chain, which enters the intracellular space and disturbs mitochondrial function (31) (Figure 1).

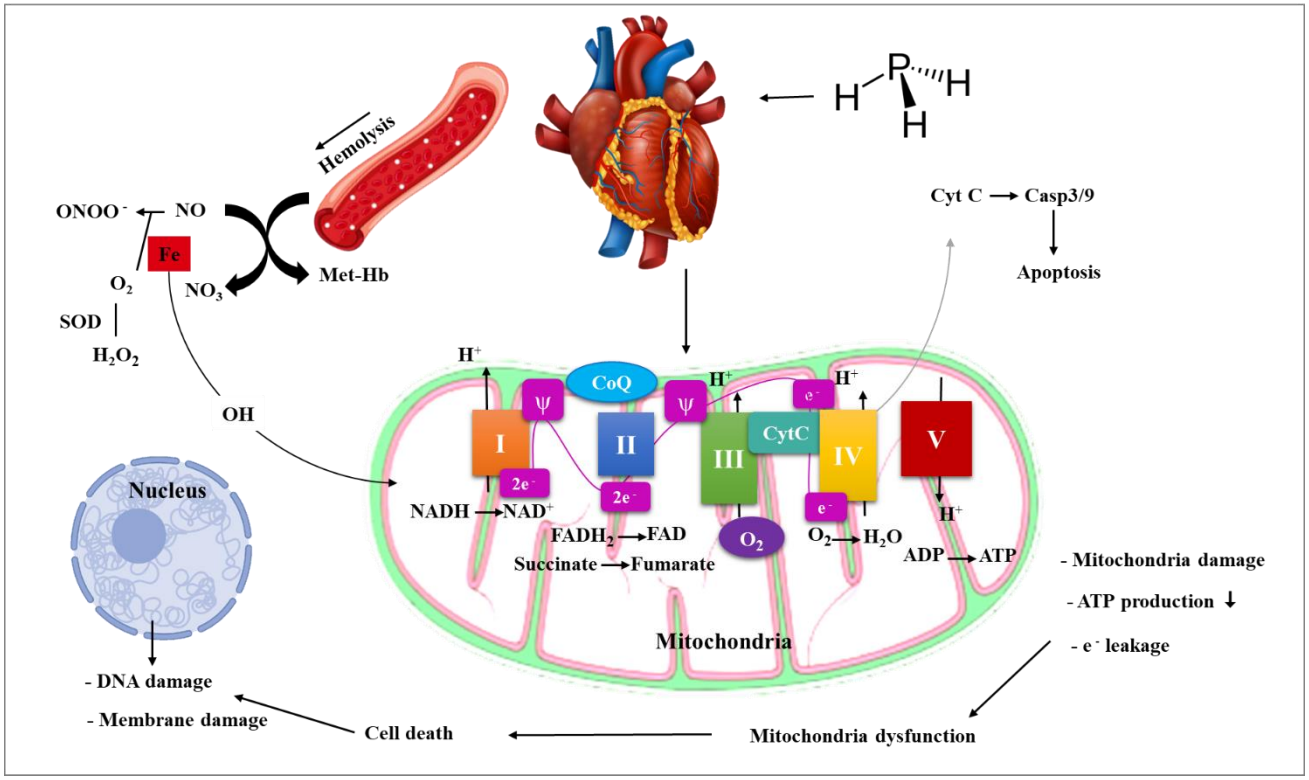

Figure 1. Phosphine functions by interfering with the mitochondrial respiratory chain at the level of the mitochondria.

The major sites of contact between phosphine and the electron transport chain are Complex IV and cytochrome C oxidase. By suppressing this enzyme at the site of Complex IV, phosphine decreases the chances of the mitochondrial membrane. In addition, phosphine decreases the activity of complexes I and II, which in turn decreases the activity of mitochondrial complexes and inhibits aerobic respiration, causing a significant increase in ROS generation, reduced ATP synthesis, and a loss of energy. A reduction in Ros generation and a reduction in energy metabolism can enhance resistance to phosphine, while ROS generation caused by phosphine poisoning is a deadly cause of energy deficit (18).

As a result of phosphine's suppression of cytochrome oxidase, catalase and peroxidase activity are reduced, hydrogen peroxide (H2O2) builds up, and hydroxyl radicals (OH) are produced. While this is happening, ROS can harm or change mitochondrial DNA, impairing respiration and overriding genes that protect against phosphine poisoning. Increased phosphine resistance results from the suppression of mitochondrial respiration chain genes, and its persistence may be brought on by the activation of the

genes that code for the respiratory chain's constituents, Complexes I (NADH/ubiquinone) and III (cytochrome c reductase). Gene complex III has a more significant function in phosphine resistance as evidenced by the fact that resistance is increased when this complex is reduced (32).

Phosphine efficiency is linked to enhanced lipid peroxidation (LPO) after glutathione (GSH) decreases in addition to boosting H2O2 generation. Since GSH catalyzes H2O2 to O2 and H2O, which is a strategy to guard against oxidation, a decreased concentration of GSH in many tissues in ALP poisoning can also explain cellular damage (33). The elevation in free radicals created by blocking respiratory chain complexes has been linked to cardiac damage. These free radicals target the apoptotic process in cardiomyocytes by causing LPO, DNA damage, and eventually oxidative stress . Furthermore, in the event of PH3 poisoning, measuring cardiac damage markers like troponin can help determine how quickly the heart is being damaged (34).

There is proof that PH3 inhibits cytochrome c oxidase in vitro (complex IV). Since PH3 inhibits cytochrome c oxidase activity less severely in vivo than in vitro, this inhibition does not appear to be the main cause of toxicity. In contrast to other cytochrome c oxidase inhibitors like cyanide, which significantly reduces cytochrome c oxidase activity in vivo, PH3 does not do so. A decrease in cytochrome c oxidase activity has also been observed in cyanide poisoning, hemorrhagic shock, and sepsis (35). Hence, inhibition of cytochrome c oxidase might not be the primary mechanism of its toxicity. Research on the spectrum and dichroism have shown a connection to the heme moiety of cytochrome oxidase. Additionally, it has been noted that PH3 interacts with hemoglobin's heme to generate Heinz bodies. It is unknown if PH3 interacts with iron from FeS centers, Cu cytochromes, and metal centers of enzymes in addition to iron from heme. Studies that have also demonstrated a decline in the activity of complexes I and II in rats lend weight to the idea that PH3 may affect the function of other cytochromes and metalloproteins. Therefore, inhibiting the electron transport chain (ETC) could lead to an increase in the formation of reactive oxygen species (ROS) (36).

Applicability of ALP and Intravascular Hemolysis

Organ damage results from vascular wall degradation, hemolysis, and methemoglobinemia (Met-Hb), which follow the intake of phosphine through the stomach mucosa. ALP can damage blood vessels and the RBC membrane, or it can cause hemoglobinemia and intravascular hemolysis via producing free radicals, where oxidative stress significantly contributes to the development of these lesions (37).

Met-Hb can be produced as a result of interaction with substances that oxidize ferrous hemoglobin to ferric form. Multiple organ failure after exposure to ALP may also be caused by decreased Met-ability Hb's to adequately oxygenate tissues. According to recent studies, there is a strong and significant correlation between blood levels of Met-Hb and death in poisoned persons. These manifestations depend on blood concentration. The delivery of oxygen to the target tissues may be significantly impacted by intravascular hemolysis. Patients with Glucose-6-phosphate dehydrogenase (G6PD) deficiency frequently have intravascular hemolysis, and when G6PD levels are low, erythrocytes' capacity to generate NADPH is decreased and cells are more vulnerable to hemolysis (38).

Metabolic acidosis, a typical symptom of ALP poisoning, may also contribute to hemolysis. Despite the frequent G6PD insufficiency that results from this poisoning, which is caused by cardiogenic shock and mortality before hemolysis, hemolysis is infrequently documented. Reduced G6PD also affects NO synthesis and heightens vascular oxidative stress, which promotes the course of cardiovascular disease (CVD) (39).

It was discovered that PH3 inhibited insect catalase in three kinds of beetles that were kept. Another study on insects found that superoxide dismutase (SOD), a metalloenzyme, increased in activity in response to PH3 treatment whereas catalase and peroxidase activity decreased. Superoxide anion (O2•) is dismutated into hydrogen peroxide (H2O2), which is more stable and invasive, as SOD activity is increased by PH3. The ability of catalase and peroxidase to scavenge peroxide radicals is inhibited. The highly reactive hydroxyl radical can then be created by hydrogen peroxide. This is in line with an elevation in hydroxyl radical-related damage that has been seen in vitro, like lipid

peroxidation. The activity of antioxidant enzymes in humans may be impacted by PH3, but this is unknown, as is whether the rise in SOD levels is controlled at the transcriptional level (40, 41).

ALP's impact on cardiomyocytes

The major organ that is harmed by ALP poisoning is cardiac. During 12 to 24 hours of exposure, cardiovascular problems brought on by ALP poisoning, such as refractory hypotension, dysrhythmia, and heart problems, manifest. The main causes of death in ALP poisoning have been recognized as cardiac toxicity, cardiac dysfunction, and circulatory collapse that result in cardiomyocyte death. Seventy-five percent of the heart's tissue is made up of cardiomyocytes, which are crucial to the heart's blood flow. Cardiomyocytes include many mitochondria, which are essential organelles. By making ATP through the process of oxidative phosphorylation, mitochondria help cardiomyocytes contract and generate 90% of their energy (42).

Impaired hemostasis of cardiac energy is one of the most significant and obvious symptoms of ALP poisoning, with ALP primarily damaging cardiac myocytes. ALP also interferes with the electron transport chain, which interferes with cell energy demand, inhibits the function of cytochrome c oxidase, an enzyme in the ETC, lowers ATP levels, and eventually lowers myocardial energy. ALP-induced cardiac toxicity is caused by lowering energy as well as the generation of free radicals, particularly ROS, and oxidative stress, which results in LPO. Because of its high oxygen intake, little amount of antioxidant system, and high metabolic activity, the heart is generally particularly sensitive to oxidative damage. Additionally, superoxide radical production and enzyme inhibition decrease NO bioavailability (43, 44).

In rare instances, alterations in biochemical indicators such as creatine phosphokinase (CPK), creatine kinase myocardial band (CK-MB), and troponin-T are also linked to ALP-induced myocardial injury. Some publications claim that these biomarkers alter after ALP poisoning, while research conducted by Soltaninejad and her team claims that these markers are inaccurate. Additionally, despite ECG changes in acute poisoning, there are conflicting reports of normal and abnormal levels of CPKMB. Despite the average level of these enzymes, myocardial damage could still exist. As a result, it can be concluded that in the future, with more research establishing the value of CPK and CK-MB indicators as diagnostic markers, it will be feasible to forecast ALP damage to cardiomyocytes and to stop the progression of the disease utilizing the most effective treatment options (14).

The majority of electrocardiographic (ECG) changes are nonspecific, including ST and T-wave alterations that are likely caused by localized myocardial necrosis and modifications to a membrane action potential. 80 percent of patients with hypokinesia of the left ventricle and septum, 3 percent with akinesia, and significantly lower ejection fractions were found in echocardiographic investigations. Heart congestion, myocardial fiber separation and fragmentation, nonspecific myocyte vacuolation, localized necrosis, and neutrophil and eosinophil infiltration are common autopsy results. It makes sense that the myocardial damage caused by PH3 is the cause of cardiac dysfunction. Arrhythmias and abnormal conduction routes could occur as a result of focal myocardial damage, whereas contractile dysfunction and hypotension could ensue from broad myocardial damage (45).

The exposure's biochemistry

Numerous research has sought to concentrate on the specific mechanisms of metal phosphide toxicity, notably on the direct impacts of PH3 gas, due to the accessibility, common utilization, and terrible health consequences of exposure. These research results can be divided into two areas that are loosely correlated to one another, mitochondrial dysfunction and oxidative stress (36).

The oxidative stress function

lipid peroxidation and ROS—

Regarding the impact of metal phosphides and their off-gas product PH3 on oxidative stress, basic toxicological abnormalities have been documented. The effects of phosphine gas have been linked to the production of reactive oxygen species (ROS) and the suppression of detoxifying enzyme systems, according

to chemical models. Studies conducted in vitro have demonstrated that PH3 can convert Fe3+ to Fe2+ in cytochrome oxidase and cytochrome c. In the presence of hydrogen peroxide (H2O2), 30 Fe2+ produces the ROS hydroxyl free radical (•OH), which is essential for the creation of the highly unstable superoxide anions, •O2, as well as a significant reactant and initiator of lipid peroxidation in Fenton processes. Decreased glutathione (GSH) levels were shown to drop as a result of phosphonate-induced oxidative damage in rats, while lipid peroxidation levels in the liver, lungs, and brain rose. Studies on rats exposed to AlP provide evidence for the presence of lipid peroxidation products in the brain. The rat cerebellum, brain stem, and cerebrum all had decreased levels of total and nonprotein sulfhydryls, according to Dua and Gill. Malondialdehyde (MDA), a measure of lipid peroxidation, has increased significantly in rat cardiac tissue after intragastric delivery of AlP. Additionally, after being exposed to PH3 intraperitoneally, mouse liver MDA elevated. In a different investigation, intraperitoneal injection of PH3 gas resulted in considerably increased MDA concentrations in the rat brain, liver, and lung (36).

Rats exposed to metal phosphide had a reduction in GSH as well as other aspects of the GSH redox cycle, such as GSH reductase activity. Nevertheless, neither catalase nor glutathione peroxidase changed in a different rat investigation conducted by these same teams. Following exposure to AlP, patients' serum enzyme activities of catalase and superoxide dismutase (SOD), which detoxify O2 to create H2O2, were both lowered and increased (46).

8-hydroxydeoxyguanosine (8-OH-dGuo), an oxidation byproduct of DNA guanine, was raised by around 70% in the brain and by 39% in the liver, which is an intriguing impact of PH3 poisoning. Increased levels of 8-OH-dGuo indicate that metal phosphide toxicity affects nuclear and mitochondrial DNA (mtDNA) in addition to the simple target organ, tissue, or cellular damage since it is a sensitive measure of ROS and a key mutagen in DNA replication. Following their metabolic conversion to reactive nucleophiles, electrophilic substances might develop inherent mutagenesis properties. The long-term implications on the downstream gene expression in the instance of metal phosphide-induced mutagenesis have not been experimentally investigated or epidemiologically (47).

Mitochondria function

The functions of mitochondria in producing energy, controlling redox, maintaining calcium homeostasis, and intermediate metabolism are well established. Exposure to metal phosphide can have extremely hazardous effects, and some of those symptoms may be brought on by impaired metabolic processes. For instance, numerous studies have demonstrated that the disruption or inhibition of mitochondrial function, namely the suppression of cytochrome c oxidase activity, may result in toxicity (48).

In contrast to their function in energy metabolism, mitochondria also contribute significantly to the generation of ROS and the activation of cell death-related pathways. The intrinsic pathway of programmed cell death, as opposed to the extrinsic pathway, which is primarily driven by extracellular inputs, involves mitochondrial signaling. Numerous studies that have been published recently suggest that ROS are crucial to pathophysiological processes, particularly when considering the function of mitochondrial cell signaling and biological consequence. The majority of intrinsic detoxification enzymatic activities, including manganese SOD, remove or render harmless ROS, which are by-products of cellular respiratory activity (MnSOD) (49).

In reality, undamaged mitochondria are necessary for the matrix enzyme MnSOD to convert O2 to H2O2. In MnSOD mutant mice, loss of control over O2 and H2O2 generation has been demonstrated to be lethal. Increased ROS generation has the potential to swiftly overwhelm the detoxifying mechanism if active electron transport through the respiratory chain is interrupted. In comparison to the cytosol and nuclear regions, steady-state oxygen levels in the mitochondria can be up to 10-fold greater, according to Cadenas and Davies. This is a significant source of ROS that is ready to be released in the event of an improper signal (50).

In addition to being a significant generator of H2O2 and •O2, mitochondria also act as targets. By altering mitochondrial proteins, lipids, and DNA, the resulting oxidative damage can cause bioenergetic abnormalities and the start of cell death. 43 Complexes I, II, and III-

embedded Rieske Fe-S clusters, which are oxidatively damaged areas of the respiratory chain, can sometimes enhance the generation of oxygen by a factor of four. MnSOD quickly converts mitochondrial matrix O2 into H2O2, which can diffuse past membranes and into the cytoplasm, where it can function as a second messenger in the control of NF-B. The proinflammatory cascade, which consists of TNF, MIP-2, and IL-8, has been demonstrated to depend on NF-B. In humans, significant metabolic diseases that ultimately endanger survival can be caused by flaws in oxidation, phosphorylation, and/or anomalies along any part of the aforementioned respiratory chain complex. An excellent and thorough review of mitochondria and ROS production (51).

Complex I is thought to be the main source of electron leaks, resulting in the release of O2.47 Increased ROS and/or intracellular Ca2+ concentrations can negatively affect the regulation of MPTP if their neutralizing systems are unable to keep up with them. Apoptotic proteins are enhanced as a result of Δψm opening, and cytochrome c triggers more caspases into the cellular environment. In cultured hepatocytes, trichlorfon led to the release of cytochrome c from the mitochondria, activating caspase 3. When oxidative damage to cells or tissues occurs, harmful chemicals other than caspases are also released. The cytokine TNF can promote either cell death or life by acting on particular receptors. An increase in mitochondrial ROS activity in a human embryonic kidney cell line after TNF treatment suggests that impaired mitochondrial metabolism may result from the extramitochondrial production of inflammatory cytokines. The buildup of electrons from highly reactive carriers and the loading of the cell with extra ROS can both be caused by inhibition along specific segments of the respiratory chain. Cardiolipin, a mitochondrial lipid produced in response to TNF-induced caspase 8 activation, can be oxidized by additional ROS (52).

To maintain certain cytosolic Ca2+ gradients, mitochondria typically build up and release Ca2+ over time. This process is essential for cell survival. However, highly high intramitochondrial Ca2+ can overwhelm the remaining undamaged mitochondria when discharged into the cytosol as a result of damage, leading to the collapse of the electrochemical gradient across the inner membrane and the inability to make ATP. It is believed that endothelial cells' ryanodine receptors on the endoplasmic reticulum cause Ca2+ release in response to mitochondria-derived ROS (52).

Numerous studies demonstrate that metal phosphides/PH3 attack affects mitochondrial metabolic balance and detoxifying mechanisms. In isolated mouse liver mitochondria, PH3 has been demonstrated to inhibit complex IV (cytochrome c oxidase) of the respiratory chain and reduce the potency of Δψm. There is evidence that metal phosphide exposure affects the brain and liver's balance of glucose. High metabolic rates are needed by the brain, which also depends on glucose to maintain neuronal activity. The rats exposed to acute levels of AlP have enhanced lactate dehydrogenase (LDH) activity in the brain (53).

This strongly suggests that aerobic metabolism has changed to anaerobic metabolism and denotes serious mitochondrial malfunction. Elevation in LDH activity, according to research, leads to the reversible conversion of pyruvate to lactate and the reoxidation of NADH (nicotinamide adenine dinucleotide reduced form) to NAD+ (NAD oxidized form), both of which are independent of mitochondrial electron transport. When this happens, lactate builds up in the brain, which puts animals at risk for problems with CNS-related activities. Both rodents' and insects' liver mitochondria activity is significantly influenced by PH3. Both create H2O2 after being challenged with PH3. Insect mitochondrial myxothiazol and antimycin inhibition of respiratory chain activity revealed that glycerophosphate dehydrogenase auto-oxidation is the source of H2O2 generation after PH3 exposure. PH3 inhibits the cytochrome c cascade's electron transport, but cyanide—another well-known metabolic toxin and a well-known example of a respiratory chain toxicant—blocks the passage of electrons from cytochrome a and a3 to oxygen. However, further research revealed that, in some circumstances, PH3 predominantly inhibits one component of the cytochrome aa3 complex (complex IV), such as cytochrome a. This inhibition may be caused by PH3 altering the valence state of heme iron (54).

The availability and metabolic absorption of oxygen have been directly connected to the toxicity of PH3. In the presence of oxygen, toxicity rises, whereas, in

anoxic conditions, it falls. In contrast to anaerobic settings, the toxicity of PH3 rises in more aerobic environments (36) (Figure 2).

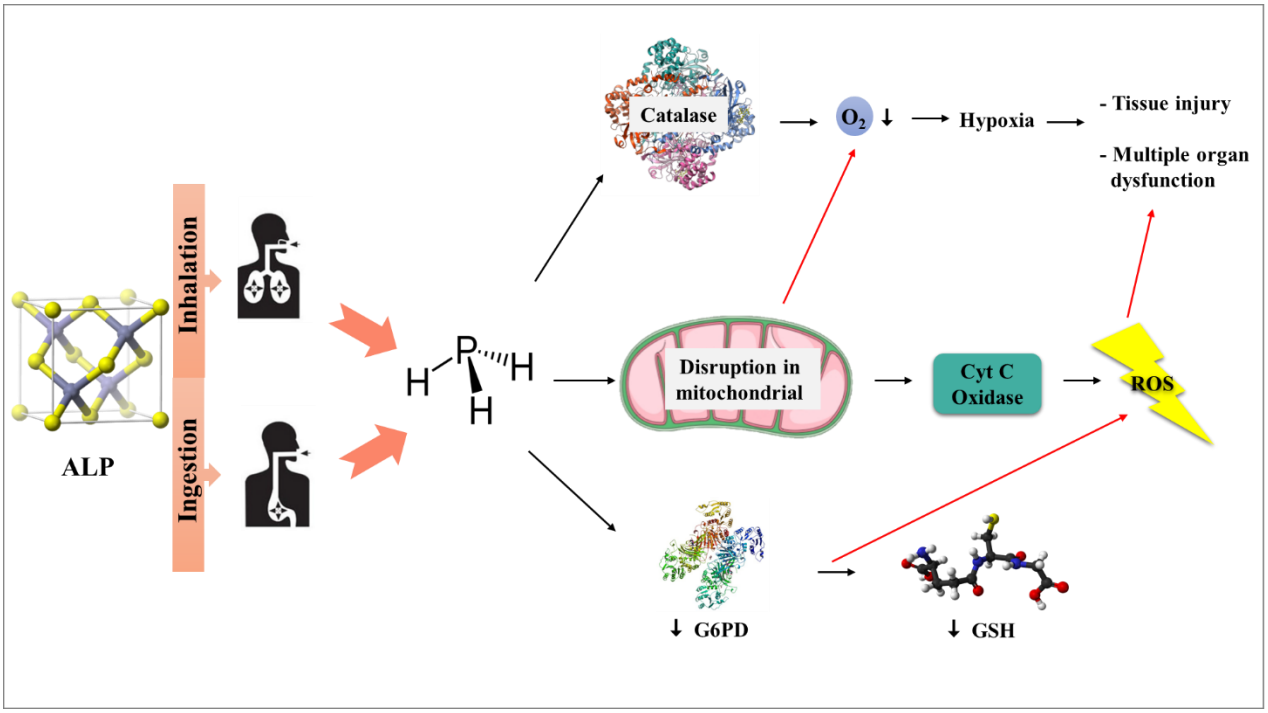

Figure 2. Aluminum phosphide releases phosphine gas when exposed to moisture and/or stomach acid due to oxidative damage.

Conclusions

Metal phosphide poisoning, particularly aluminum phosphide (ALP), is one of the major health hazards facing modern human societies. Numerous studies have been conducted on the pathophysiology of ALP in patients, and the majority of these studies' findings highlight the fact that ALP leads to mitochondrial dysfunction.RBC intravascular hemolysis and ATP generation are both diminished by mitochondrial failure. It has been established that irreparably damaged metabolism is a component of PH3 poisoning. Mechanistically, this might happen due to a metabolic crisis or as an indirect result of increased ROS production brought on by the metabolism, which ultimately causes cellular/target organ collapse. Overall, this has had a seriously negative impact on the survival rates of those who were exposed. Myocyte performance is lowered as a consequence of these diseases, and CVD results. It might be argued that finding indicators linked to cardiac diseases in the early stages of sickness would be beneficial because cardiac ailments, particularly cardiac shock, are the major causes of death in ALP patients. A more logical approach to treatment and the identification of temporal therapeutic windows will be made possible with further research into the precise correlations between exposure, metabolic, and systemic toxicity.

Author contribution

MRT and HMK designed the project, wrote the manuscript and analyzed the data. All the authors read and confirmed the final edited version of the manuscript.

Conflict of interest

The authors declare that they have no conflicts of interest.

References

1. Gurjar M, Baronia AK, Azim A, Sharma K. Managing aluminum phosphide poisonings. J Emerg Trauma Shock. 2011;4(3):378-84.

2. Sedaghattalab M. Treatment of critical aluminum phosphide (rice tablet) poisoning with high-dose insulin: a case report. J Med Case Rep. 2022;16(1):192.

3. Singh S, Bhalla A, Verma SK, Kaur A, Gill K. Cytochrome-c oxidase inhibition in 26 aluminum phosphide poisoned patients. Clin Toxicol (Phila). 2006;44(2):155-8.
4. Goel A, Aggarwal P. Pesticide poisoning. Natl Med J India. 2007;20(4):182-91.
5. Tiwary AK, Puschner B, Charlton BR, Filigenzi MS. Diagnosis of zinc phosphide poisoning in chickens using a new analytical approach. Avian Dis. 2005;49(2):288-91.
6. Mohan B, Gupta V, Ralhan S, Gupta D, Puri S, Wander GS, et al. Role of Extracorporeal Membrane Oxygenation in Aluminum Phosphide Poisoning-Induced Reversible Myocardial Dysfunction: A Novel Therapeutic Modality. J Emerg Med. 2015;49(5):651-6.
7. Dadpour B, Mokhtarpour M, Abdollahi M, Afshari R. An outbreak of aluminium phosphide poisoning in Mashhad, Iran. Arh Hig Rada Toksikol. 2016;67(1):65-6.
8. Salimi A, Jamali Z, Shabani M. Antioxidant Potential and Inhibition of Mitochondrial Permeability Transition Pore by Myricetin Reduces Aluminium Phosphide-Induced Cytotoxicity and Mitochondrial Impairments. Front Pharmacol. 2021;12:719081.
9. Farahani MV, Soroosh D, Marashi SM. Thoughts on the current management of acute aluminum phosphide toxicity and proposals for therapy: An Evidence-based review. Indian J Crit Care Med. 2016;20(12):724-30.
10. Moghadamnia AA. An update on toxicology of aluminum phosphide. Daru. 2012;20(1):25.
11. Pannu AK. Pulmonary Management in Aluminum Phosphide Poisoning. Indian J Crit Care Med. 2017;21(1):63-4.
12. Bagheri-Moghaddam A, Abbaspour H, Tajoddini S, Mohammadzadeh V, Moinipour A, Dadpour B. Using Intra-Aortic Balloon Pump for Management of Cardiogenic Shock Following Aluminum Phosphide Poisoning; Report of 3 Cases. Emerg (Tehran). 2018;6(1):e3.
13. Gadour E, Kotb A. Systematic Review of Antifungal-Induced Acute Liver Failure. Cureus. 2021;13(10):e18940.
14. Soltaninejad K, Beyranvand MR, Momenzadeh SA, Shadnia S. Electrocardiographic findings and cardiac manifestations in acute aluminum phosphide poisoning. J Forensic Leg Med. 2012;19(5):291-3.
15. Kim BS, Li BT, Engel A, Samra JS, Clarke S, Norton ID, et al. Diagnosis of gastrointestinal bleeding: A practical guide for clinicians. World J Gastrointest Pathophysiol. 2014;5(4):467-78.
16. Dorooshi G, Mirzae M, Fard NT, Zoofaghari S, Mood NE. Investigating the Outcomes of Aluminum Phosphide Poisoning in Khorshid Referral Hospital, Isfahan, Iran: A Retrospective Study. J Res Pharm Pract. 2021;10(4):166-73.
17. Dhondup T, Qian Q. Electrolyte and Acid-Base Disorders in Chronic Kidney Disease and End-Stage Kidney Failure. Blood Purif. 2017;43(1-3):179-88.
18. Anand R, Kumari P, Kaushal A, Bal A, Wani WY, Sunkaria A, et al. Effect of acute aluminum phosphide exposure on rats: a biochemical and histological correlation. Toxicol Lett. 2012;215(1):62-9.
19. Hugar BS, Praveen S, Hosahally JS, Kainoor S, Shetty AR. Gastrointestinal hemorrhage in aluminum phosphide poisoning. J Forensic Sci. 2015;60 Suppl 1:S261-3.
20. Saleki S, Ardalan FA, Javidan-Nejad A. Liver histopathology of fatal phosphine poisoning. Forensic Sci Int. 2007;166(2-3):190-3.
21. Jafari A, Baghaei A, Solgi R, Baeeri M, Chamanara M, Hassani S, et al. An electrocardiographic, molecular and biochemical approach to explore the cardioprotective effect of vasopressin and milrinone against phosphide toxicity in rats. Food Chem Toxicol. 2015;80:182-92.
22. Tehrani H, Halvaie Z, Shadnia S, Soltaninejad K, Abdollahi M. Protective effects of N-acetylcysteine on aluminum phosphide-induced oxidative stress in acute human poisoning. Clin Toxicol (Phila). 2013;51(1):23-8.
23. Agrawal VK, Bansal A, Singh RK, Kumawat BL, Mahajan P. Aluminum phosphide poisoning: Possible role of supportive measures in the absence of specific antidote. Indian J Crit Care Med. 2015;19(2):109-12.
24. Mirakbari SM. Proposal for a new mechanism of action for aluminum phosphide (ALP) for causing local injuries in ALP poisoning: Should treatment strategies be modified? Hum Exp Toxicol. 2016;35(10):1145-6.

25. Mehrpour O, Jafarzadeh M, Abdollahi M. A systematic review of aluminium phosphide poisoning. Arh Hig Rada Toksikol. 2012;63(1):61-73.
26. Oghabian Z, Mehrpour O. Treatment of Aluminium Phosphide Poisoning with a Combination of Intravenous Glucagon, Digoxin and Antioxidant Agents. Sultan Qaboos Univ Med J. 2016;16(3):e352-5.
27. Sahoo D, Kujur ST, Das DS, Dey A, Devi S. Aluminium Phosphide Poisoning: Early Suspicion of Cardiotoxicity Is Necessary for Improved Outcomes. Cureus. 2020;12(9):e10237.
28. Siddaiah L, Adhyapak S, Jaydev S, Shetty G, Varghese K, Patil C, et al. Intra-aortic balloon pump in toxic myocarditis due to aluminum phosphide poisoning. J Med Toxicol. 2009;5(2):80-3.
29. Shafiee Dolat Abadi S, Zamani N, Abbasi S, Shojaei M, Hassanian-Moghaddam H. Neurologic sequelae of phosphide poisoning: A case report. Front Neurol. 2022;13:888493.
30. Baghaei A, Solgi R, Jafari A, Abdolghaffari AH, Golaghaei A, Asghari MH, et al. Molecular and biochemical evidence on the protection of cardiomyocytes from phosphine-induced oxidative stress, mitochondrial dysfunction and apoptosis by acetyl-L-carnitine. Environ Toxicol Pharmacol. 2016;42:30-7.
31. Kariman H, Heydari K, Fakhri M, Shahrami A, Dolatabadi AA, Mohammadi HA, et al. Aluminium phosphide poisoning and oxidative stress: serum biomarker assessment. J Med Toxicol. 2012;8(3):281-4.
32. Nath NS, Bhattacharya I, Tuck AG, Schlipalius DI, Ebert PR. Mechanisms of phosphine toxicity. J Toxicol. 2011;2011:494168.
33. Jagadeesan R, Collins PJ, Daglish GJ, Ebert PR, Schlipalius DI. Phosphine resistance in the rust red flour beetle, Tribolium castaneum (Coleoptera: Tenebrionidae): inheritance, gene interactions and fitness costs. PLoS One. 2012;7(2):e31582.
34. Haghi Aminjan H, Abtahi SR, Hazrati E, Chamanara M, Jalili M, Paknejad B. Targeting of oxidative stress and inflammation through ROS/NF-kappaB pathway in phosphine-induced hepatotoxicity mitigation. Life Sci. 2019;232:116607.
35. Bogale DE, Ejigu BD, Muche TA. Clinical Profile and Treatment Outcome of Aluminum Phosphide Poisoning in Felege Hiwot Referral Hospital, Northwest Ethiopia: A Retrospective Study. Open Access Emerg Med. 2021;13:239-48.
36. Sciuto AM, Wong BJ, Martens ME, Hoard-Fruchey H, Perkins MW. Phosphine toxicity: a story of disrupted mitochondrial metabolism. Ann N Y Acad Sci. 2016;1374(1):41-51.
37. Vosooghi AA, Salmasi M. G6PD deficiency and aluminum phosphide poisoning. J Res Med Sci. 2018;23:83.
38. Lehoux J, Hena Z, McCabe M, Peek G. Aluminium phosphide poisoning resulting in cardiac arrest, successful treatment with Extracorporeal Cardiopulmonary resuscitation (ECPR): a case report. Perfusion. 2018;33(7):597-8.
39. Kuhn V, Diederich L, Keller TCSt, Kramer CM, Lückstädt W, Panknin C, et al. Red Blood Cell Function and Dysfunction: Redox Regulation, Nitric Oxide Metabolism, Anemia. Antioxid Redox Signal. 2017;26(13):718-42.
40. Doukyu N, Taguchi K. Involvement of catalase and superoxide dismutase in hydrophobic organic solvent tolerance of Escherichia coli. AMB Express. 2021;11(1):97.
41. Bian Y, Rong Z, Chang TM. Polyhemoglobin-superoxide dismutase-catalase-carbonic anhydrase: a novel biotechnology-based blood substitute that transports both oxygen and carbon dioxide and also acts as an antioxidant. Artif Cells Blood Substit Immobil Biotechnol. 2012;40(1-2):28-37.
42. Asghari MH, Moloudizargari M, Baeeri M, Baghaei A, Rahimifard M, Solgi R, et al. On the mechanisms of melatonin in protection of aluminum phosphide cardiotoxicity. Arch Toxicol. 2017;91(9):3109-20.
43. Goharbari MH, Taghaddosinejad F, Arefi M, Sharifzadeh M, Mojtahedzadeh M, Nikfar S, et al. Therapeutic effects of oral liothyronine on aluminum phosphide poisoning as an adjuvant therapy: A clinical trial. Hum Exp Toxicol. 2018;37(2):107-17.
44. Gouda AS, El-Nabarawy NA, Ibrahim SF. Moringa oleifera extract (Lam) attenuates Aluminium phosphide-induced acute cardiac toxicity in rats. Toxicol Rep. 2018;5:209-12.
45. Guru S, Kumar R, Behera A, Patra S, Kumar P, Jr. Aluminium Phosphide-Induced Expression of Covertly Present Brugada Pattern in Electrocardiogram: A Rare Case Report. Cureus. 2020;12(9):e10552.

46. Żebrowska E, Maciejczyk M, Żendzian-Piotrowska M, Zalewska A, Chabowski A. High Protein Diet Induces Oxidative Stress in Rat Cerebral Cortex and Hypothalamus. Int J Mol Sci. 2019;20(7).
47. Solgi R, Baghaei A, Golaghaei A, Hasani S, Baeeri M, Navaei M, et al. Electrophysiological and molecular mechanisms of protection by iron sucrose against phosphine-induced cardiotoxicity: a time course study. Toxicol Mech Methods. 2015;25(4):249-57.
48. Jiang J, Liang S, Zhang J, Du Z, Xu Q, Duan J, et al. Melatonin ameliorates PM(2.5) -induced cardiac perivascular fibrosis through regulating mitochondrial redox homeostasis. J Pineal Res. 2021;70(1):e12686.
49. Marchi S, Giorgi C, Suski JM, Agnoletto C, Bononi A, Bonora M, et al. Mitochondria-ros crosstalk in the control of cell death and aging. J Signal Transduct. 2012;2012:329635.
50. Dikalov S. Cross talk between mitochondria and NADPH oxidases. Free Radic Biol Med. 2011;51(7):1289-301.
51. Chan CM, Huang DY, Sekar P, Hsu SH, Lin WW. Reactive oxygen species-dependent mitochondrial dynamics and autophagy confer protective effects in retinal pigment epithelial cells against sodium iodate-induced cell death. J Biomed Sci. 2019;26(1):40.
52. Zorov DB, Juhaszova M, Sollott SJ. Mitochondrial reactive oxygen species (ROS) and ROS-induced ROS release. Physiol Rev. 2014;94(3):909-50.
53. Dua R, Gill KD. Effect of aluminium phosphide exposure on kinetic properties of cytochrome oxidase and mitochondrial energy metabolism in rat brain. Biochim Biophys Acta. 2004;1674(1):4-11.
54. Yaku K, Okabe K, Gulshan M, Takatsu K, Okamoto H, Nakagawa T. Metabolism and biochemical properties of nicotinamide adenine dinucleotide (NAD) analogs, nicotinamide guanine dinucleotide (NGD) and nicotinamide hypoxanthine dinucleotide (NHD). Sci Rep. 2019;9(1):13102.