

# A review of the protective role of melatonin during phosphine-induced cardiotoxicity: focus on mitochondrial dysfunction, oxidative stress and apoptosis

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## Keywords

aluminium phosphide; apoptosis; cardiotoxicity; melatonin; mitochondrial dysfunction

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## Abstract

**Objectives** Acute poisoning with aluminium phosphide (AIP) is a major cause of mortality in developing countries. AIP mortality is due to cardiac dysfunction leading to cardiomyocyte death. The main mechanism is an inhibition of cytochrome c oxidase in the cardiomyocyte mitochondria, resulting in a decreased ATP production and oxidative stress. Unfortunately, the administration of exogenous drugs does not meet the desired requirements of an effective therapy. Melatonin is an amphiphilic molecule and can easily pass through all cellular compartments with the highest concentration recorded in mitochondria. It is known as a vigorous antioxidant, acting as a potent reactive oxygen species (ROS) scavenger. Our aim is to summarize the mechanisms by which melatonin may modulate the deteriorating effects of AIP poisoning on cardiac mitochondria. **Key findings** Melatonin not only mitigates the inhibition of respiratory chain complexes, but also increases ATP generation. Moreover, it can directly inhibit the mitochondrial permeability transition pore (mPTP) opening, thus preventing apoptosis. In addition, melatonin inhibits the release of cytochrome c from mitochondria to hinder caspase activation leading to cell survival.

**Summary** Based on the promising effects of melatonin on mitochondria, melatonin may mitigate AIP-induced cardiotoxicity and might be potentially suggested as cardioprotective in AIP-intoxicated patients.

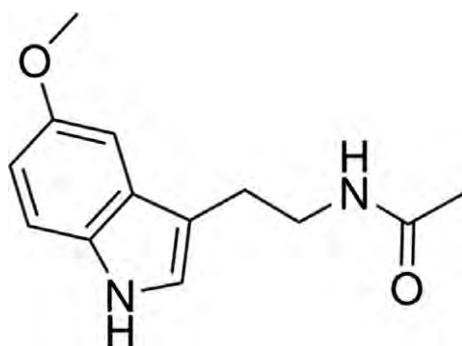
## Introduction

Aluminium phosphide (AIP) is a solid fumigant and a toxic pesticide used widely in the agriculture<sup>[1]</sup> as an efficient insecticide for grain preservation. Being inexpensive without generating any residues is among its prominent merits.<sup>[2]</sup> It affects all stages of insect development with no alteration in seed quality and viability. Interaction of AIP with atmospheric moisture or hydrochloric acid in stomach results in the liberation of phosphine which is the active form.<sup>[3]</sup> It is also known as a suicide poison that is readily available in some markets. Based on the reports, AIP poisoning is the most common suicidal poison in India<sup>[4]</sup> and the number of self-poisonings is increasing with a high mortality rate in Iran.<sup>[1]</sup> Poisoning

symptoms develop quickly after ingestion of AIP. Nausea and vomiting occur within few minutes that followed by respiratory, cardiovascular and neurologic problems. Hepatic and renal failure is also seen later. The most prominent cardiovascular features of AIP poisoning include refractory hypotension, dysrhythmias and congestive heart failure. Although these presentations are unspecific, diagnosis can be done on the basis of patient history and getting information from the relatives. Silver nitrate paper test can be done on gastric content.<sup>[1]</sup> AIP mortality is due to cardiac dysfunction caused by cardiomyocyte death. The main mechanism is believed to be an inhibition of cytochrome c oxidase in the cardiomyocyte mitochondria leading to decreased ATP production and inducing oxidative stress.<sup>[5]</sup>

Unfortunately, administration of exogenous drugs, such as triiodothyronine,<sup>[6]</sup> vasopressin,<sup>[7]</sup> iron sucrose,<sup>[8]</sup> sodium bicarbonate,<sup>[9]</sup> digoxin,<sup>[10]</sup> Mg nanoparticle,<sup>[11]</sup> pralidoxime<sup>[12]</sup> and N-acetylcysteine,<sup>[13,14]</sup> has not been complete effective therapeutic agents in the case of ALP-induced cardiotoxicity. The lack of specific antidote and effective supportive care results in high mortality of this poison.<sup>[5]</sup> The reason underlying the suboptimal efficacy of these therapeutics is possibly the fact that these interventions are mostly symptomatic and do not alter the pathogenic mechanisms of ALP toxicity, with the exception of those possessing antioxidant properties, which, even then, are inferior to melatonin because of the extensive interactions of melatonin with mitochondrial components such as the complexes discussed further. Therefore, endogenous substances have become of interest in the recent investigations. Melatonin is an amphiphilic molecule (Figure 1) and can easily pass through all cellular compartments with the highest concentration recorded in mitochondria, potentially protecting it against oxidative stress.<sup>[15]</sup> It is shown that melatonin has protective effects in various organs including the heart,<sup>[16]</sup> liver,<sup>[17,18]</sup> brain,<sup>[19]</sup> kidney,<sup>[20]</sup> lung<sup>[21]</sup> and testis.<sup>[22]</sup> This endogenous molecule is known as a potent antioxidant,<sup>[23]</sup> anti-apoptosis<sup>[24]</sup> and anti-inflammatory<sup>[25]</sup> agent. In this paper, the authors focused on the ALP-induced cardiotoxicity and introduced how melatonin may protect the cardiomyocytes, especially regarding to mitochondrial complexes. The probable effects of melatonin on respiratory transport chain, apoptosis and oxidative stress against ALP-induced cardiotoxicity are illustrated in Figure 2. Moreover, recent findings on ALP-induced cardiotoxicity involving mitochondrial function are summarized in Table 1.

As mentioned above, the mechanism of phosphine toxicity is not yet clear and more studies are required to elucidate the exact mechanisms in order to be able to design specific antidotes. Despite all the previous reviews, this is the first study that evaluates the mechanistic pathways of ALP-induced cardiotoxicity in association with



**Figure 1** Formula of melatonin.

mitochondrial dysfunction and probable protective effects of melatonin as an effective therapeutic agent.

## Approach to systematic review

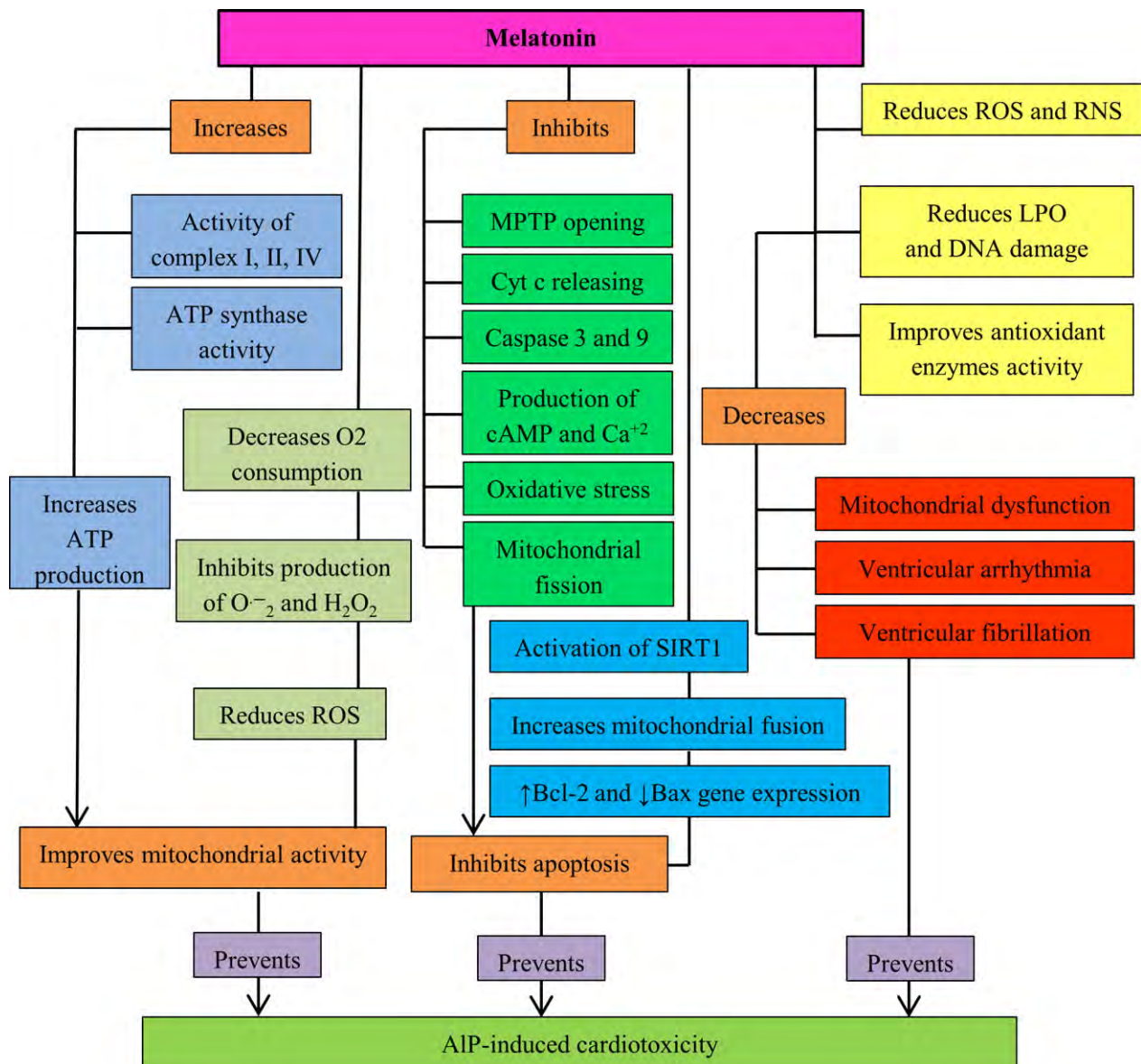
An online literature search was performed on PubMed, Scopus and Web of Science databases for the key words of 'Aluminium phosphide' and 'cardiotoxicity' without time limit up to August 2015. The search strategy was illustrated in the following flow diagram (Scheme 1).

## Mitochondria as a target organelle of melatonin and aluminium phosphide

The mitochondrion is a key organelle present in virtually all mammalian cells (with exception to red blood cells) with a high abundance in cardiomyocyte, which produces energy through the mitochondrial electron transport chain (ETC), leading to ATP synthesis through the oxidative phosphorylation (OXPHOS) process. Mitochondria constitute about 45% of the myocardial volume, thus providing the energy requirements of cardiomyocytes.<sup>[26,27]</sup> Mitochondria are the major intracellular source of reactive oxygen species (ROS), as well as the main target for free radicals.<sup>[28]</sup> It is believed that mitochondria are the main target for ALP, which is able to inhibit complexes I and II and cytochrome c oxidase activity, causing a reduction in the production of ATP.<sup>[5]</sup> The affinity of ALP to mitochondrial complexes and the propensity to disrupt them could be explained by the difference in the low electrochemical potential of phosphine and high electrochemical potential of electron chain complexes, especially complex IV and the ability of phosphine to bind with iron in complex IV.<sup>[2,29]</sup> Interestingly, melatonin has a high affinity to mitochondria and accumulates in these organelles at abundant concentrations reversing mitochondrial dysfunction by reducing oxidative stress and preventing mitochondrial transition pore opening (mPTP), which mediates cell death through the release of pro-apoptotic agents to the cytosol, such as cytochrome c.<sup>[30]</sup> Recently, it has been hypothesized that mitochondria were the primary sites of melatonin synthesis during the early stages of endosymbiosis.<sup>[31]</sup> In the light of such a scenario, mitochondria can be also a principle target for melatonin.

## Mitochondrial complexes: role of melatonin and aluminium phosphide

The respiratory chain located in the inner mitochondrial membrane is responsible for generating 90% of ATP. This system encompasses four enzyme complexes: complexes I, II, III and IV (cytochrome c oxidase). ATP synthesis is formed through two coupled processes involving ETC and OXPHOS.<sup>[32]</sup> The most important feature of ALP poisoning



**Figure 2** Proposed mechanisms for cardioprotective effect of melatonin in aluminum phosphide-induced cardiotoxicity. [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

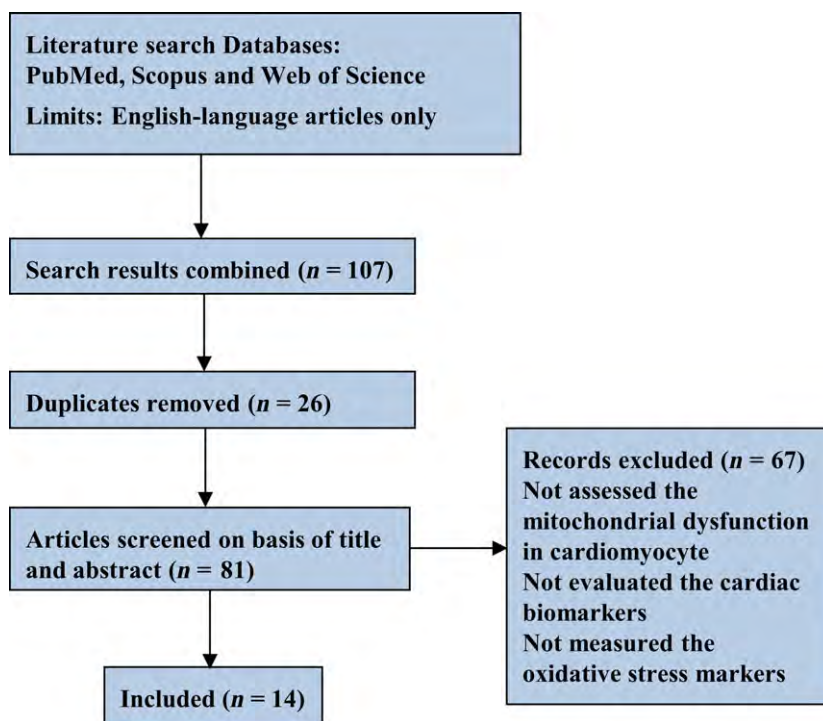
is disruption of cardiac energy homeostasis. Recent findings have demonstrated that AIP induces mitochondrial dysfunction by disrupting mitochondrial respiratory chain through the inhibition of respiratory chain complexes and phosphorylation.<sup>[7,33]</sup> In particular, animal studies indicated that AIP decreases the activity of complexes II and IV. It was also shown that administration of AIP can reduce cellular ATP levels.<sup>[6–8]</sup> Moreover complexes I, II and IV activity were mitigated in patients with AIP ingestion.<sup>[34]</sup> Based on the evidence, AIP inhibits the mentioned complexes especially cytochrome c oxidase and could consequently lead to elevated ROS production.<sup>[34]</sup>

Various studies demonstrated that high-dose exogenous melatonin can influence mitochondrial energy homeostasis. It was shown that melatonin is able to neutralize the reduced activity of complexes I and IV in ruthenium red toxicity.<sup>[21,35]</sup> Furthermore, melatonin can prevent the inhibition of complex IV and may increase ATP production in cyanide-treated groups.<sup>[36]</sup> In the context of the heart, melatonin alleviated the inhibitory effect of isoproterenol on complexes I and IV. It also increased the ATPase activity.<sup>[15,37]</sup> Taking together, it seems that melatonin is a useful alternative to exogenous drugs which can counteract the inhibition of respiratory chain complexes and may also

**Table 1** Effects of protective agents on cardiomyocyte mitochondrial function in aluminium phosphide (AIP) poisoning

Toxicant/dose	Model	Effective dose of protective agent	Mitochondrial alterations	Ref.
AIP (12.5 mg/kg)	Rat	Vasopressin (2.0 U/kg) + Milrinone (0.25 mg/kg)	↑Complex IV activity; ↓ADP/ATP ratio; ↑CAT activity; ↓Caspase 3 and 9 activity	[7]
AIP (12 mg/kg)	Rat	Triiodothyronine (T3) (3 µg/kg)	↑Complex II and IV activity; ↓ADP/ATP ratio; ↓Caspase 3 and 9 activity ↑FRAP and thiol level; ↓LPO; ↓SOD activity	[6]
AIP (6 mg/kg)	Rat	Iron sucrose (10 mg/kg)	↓TBARS level; ↑FRAP level; ↑Complex II, IV and V activity	[8]

CAT, catalase; FRAP, ferric reducing/antioxidant power; LPO, lipid peroxidation; SOD, superoxide dismutase; TBARS, thiobarbituric acid-reactive substances.



**Scheme 1** Search strategy. [Colour figure can be viewed at wileyonlinelibrary.com]

have the potential to increase ATP production in AIP-induced cardiotoxicity.

### Oxidative stress: effect of melatonin and aluminium phosphide

It is demonstrated that AIP-induced cardiotoxicity is due to the generation of free radicals.<sup>[38]</sup> On the other hand, the heart is highly susceptible to oxidative damage. Two prominent features of the heart including a high rate of oxygen consumption and limited antioxidant defence systems make it more vulnerable.<sup>[39,40]</sup> Superoxide anion radical  $O_2^{\cdot-}$  is a by-product of mitochondria respiration. All respiratory complexes can transfer single electrons to  $O_2$

molecules, reducing them to  $O_2^{\cdot-}$ ; and the extent of contribution of each complex in this process varies depending on the organ. Complex III seems to be the major culprit in the heart. Other determinants increasing  $O_2^{\cdot-}$  generation are presence of high  $O_2$  concentrations and exogenous blockade of electron transport chain.  $O_2^{\cdot-}$  is subsequently quenched by mitochondrial SOD present in the matrix, although some leakage may occur.<sup>[41]</sup> The inhibition of respiratory chain complexes by AIP seems to initiate disastrous events resulting in ROS production. Consequently, these free radicals induce lipid peroxidation and DNA damage ending in blemished cycle which eventually leads to more oxidative stress and triggers apoptosis cascade in the cardiomyocytes.<sup>[42–44]</sup> In a previous study, AIP caused



huge alterations in the levels of antioxidant enzymes.<sup>[13]</sup> In other studies, severe reduction in antioxidant capacity was observed.<sup>[44]</sup> A significant decrease was also shown in thiol group levels.<sup>[6]</sup> Furthermore, AIP diminished catalase (CAT) activity; however, no change in superoxide dismutase (SOD) activity was noted.<sup>[7]</sup> Results regarding SOD activity are controversial. Some investigators believe that AIP mitigates antioxidant defence through the reduction of SOD activity causing cellular toxicity.<sup>[4,45,46]</sup> In contrast, others suppose that AIP increases H<sub>2</sub>O<sub>2</sub> levels via stimulating SOD activity, which is more stable and diffusible than O<sub>2</sub><sup>-</sup>, resulting in lipid peroxidation and consequent ROS generation.<sup>[47,48]</sup>

Melatonin can efficiently oppose these events by increasing the activity and expression of ETC complexes leading to ATP production.<sup>[49]</sup> It is demonstrated that melatonin is a vigorous antioxidant acting as a potent ROS scavenger.<sup>[50]</sup> Fortunately, the metabolites of melatonin also possess antioxidant properties.<sup>[51]</sup> Concerning antioxidant enzymes, melatonin can promote gene expression and activity of various antioxidant enzymes including glutathione peroxidase (GPx), SOD, glutathione reductase (GR) and CAT.<sup>[49,52,53]</sup> Several studies have uncovered the upregulation of antioxidant enzymes by melatonin via activation of Nrf2/ARE signalling in various models, and it could also be the case here.<sup>[54,55]</sup> Furthermore, melatonin increases glutathione (GSH) synthesis by stimulating  $\gamma$ -glutamylcysteine synthetase ( $\gamma$ -GCS).<sup>[56]</sup> Additionally, melatonin behaves as a selective iNOS/i-mtNOS (inducible nitric oxide synthase/mitochondrial iNOS) inhibitor preventing high production of nitric oxide (NO) in cardiac mitochondria which blocks its detrimental roles in mitochondrial respiratory chain, thereby mending cardiac mitochondrial function during sepsis.<sup>[57]</sup>

Briefly, we can classify melatonin antioxidant activity into three subdivisions including: (1) direct free radical scavenging activity, (2) increasing antioxidant enzymes activity and (3) improving mitochondrial OXPHOS process and decreasing electron leakage and consequently reducing free radicals. As mentioned above, melatonin is a valuable agent which can perfectly prevent AIP-induced cardiotoxicity associated with oxidative stress by scavenging ROS and improving antioxidant enzyme activity.

## Melatonin and aluminium phosphide-induced apoptosis

Previous studies demonstrated that phosphine can trigger apoptosis pathways in several tissues such as heart, kidney and liver.<sup>[58]</sup> It was shown that AIP affects mitochondrial membrane fluidity leading to mitochondrial swelling and outer membrane rupture, thus resulting in the release of pro-apoptotic factors which in turn activates caspases to induce cell death.<sup>[38,59]</sup> The recent studies also confirmed

the AIP-induced cardiomyocyte death through several pathways. AIP generates ROS leading to cell death. Free radicals cause mitochondrial dysfunction through breakdown of mitochondrial DNA (mtDNA) resulting in the activation of caspases 3 and 9.<sup>[7]</sup> Furthermore, phosphine can induce lipid peroxidation<sup>[45]</sup> and may decrease mitochondrial redox potential. Consequently, it may be able to open the mPTP, leading to the release of cytochrome c to induce the apoptotic cascade.<sup>[30]</sup> Unfortunately, due to the lack of sufficient information on the exact responsible mechanisms, the effective treatment of this fatal poison has remained to be elucidated and further investigations should be conducted to fully explore its apoptotic mechanisms.

Otherwise, numerous studies have demonstrated that melatonin has pronounced anti-apoptotic effects.<sup>[30,60]</sup> It was shown that melatonin can directly inhibit the mPTP opening, thus preventing apoptosis.<sup>[61]</sup> In addition, melatonin prevents the release of cytochrome c from mitochondria to inhibit caspase activation and apoptosis. Moreover, decreased activation of caspase 3 and DNA damage has been noted.<sup>[62–64]</sup> The cardioprotective effect of melatonin was attributed to the reduction of cardiomyocyte apoptosis through the suppression of DNA fragmentation.<sup>[65]</sup> As mentioned above, melatonin can reduce oxidative stress by removing reactive oxygen and nitrogen species which in turn inhibits downstream mechanisms that trigger apoptosis. Recently, several anti-apoptotic mechanisms of melatonin have been explored. This endogenous hormone can localize Bcl-2 to mitochondria, rendering Bax in an inactive form into mitochondria to prevent apoptosis.<sup>[60]</sup> Furthermore, melatonin attenuated mitochondrial dysfunction through the activation of the silent information regulator 1 (SIRT1) signalling, a kind of histone deacetylase associated with the enhancement of Bcl-2 and a decrease of Bax expression.<sup>[57,66,67]</sup> On the other hand, the mitochondrion is a dynamic organelle which can adapt to cellular conditions.<sup>[68]</sup> This property is associated with fission and fusion mechanisms. In prosperous adaptation to a stressful environment, mitochondria have a tendency to form expanded networks by a process called mitochondrial fusion.<sup>[68]</sup> Conversely, in a stressful condition, mitochondria become small fragments through mitochondrial fission.<sup>[69,70]</sup> Mitochondrial fission stimulates cytochrome c release and caspase activation which can eventually result in apoptosis.<sup>[69]</sup> Remarkably, it has been shown that melatonin can reduce ROS-mediated mitochondrial fission and improve mitochondrial networking by inducing mitochondrial fusion resulting in cardiomyocytes protection.<sup>[71]</sup> In the light of the stated information, these beneficial effects of melatonin on mitochondria can mitigate AIP-induced apoptosis via several mechanisms and provide promising evidence to introduce it as an effective cardioprotective agent not only as treatment but also as protective.<sup>[72]</sup>

## Conclusion

Acute poisoning with ALP is a major problem in many developing countries with an increased rate of death especially in India and Iran. Despite all efforts in critical care to prevent mortality, a successful treatment still has failed. It is believed that mitochondria are the main target of ALP. This chemical inhibits the respiratory chain complexes resulting in a reduced ATP production and initiates the detrimental events leading to ROS generation. Consequently, these free radicals induce lipid peroxidation and DNA damage inducing a vicious cycle and more oxidative stress which promotes the apoptotic cascade in cardiomyocytes. It also exerts a significant decrease in thiol levels and CAT activity; however, controversial findings regarding SOD activity have been observed. The effect of phosphine on mitochondrial membrane fluidity causes mitochondrial swelling and outer membrane rupture leading to the release of pro-apoptotic factors which in turn activates caspases to induce apoptosis. The increasing number of reports regarding the effects of melatonin on mitochondrial respiratory chain, its action on apoptosis and oxidative stress, its role

in ROS scavenging and antioxidant activity will undeniably provide insights that melatonin is a perfect option which can ameliorate ALP-induced cardiotoxicity associated with mitochondrial dysfunction. However, further experimental studies are required to determine the precise effects of melatonin on all mitochondrial mechanisms including those mentioned above.

## Declarations

### Conflict of interest

Declared none.

### Authors' contribution

MHA participated in the literature search and drafted the article. MA conceived and supervised whole study. MRO and MN participated in editing the article.

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