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# Molecular and biochemical evidences on the protective effects of triiodothyronine against phosphine-induced cardiac and mitochondrial toxicity

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ABSTRACT

*Aim:* Aluminum phosphide (AlP) is a widely used fumigant and rodenticide. While AlP ingestion leads to high mortality, its exact mechanism of action is unclear. There are ample evidences suggesting cardioprotective effects of triiodothyronine (T3). In this study, we aimed to examine the potential of T3 in the protection of a rat model of AlP induced cardiotoxicity.

*Main methods:* In order to induce AlP intoxication animals were intoxicated with AlP (12 mg/kg; LD50) by gavage. In treatment groups, T3 (1, 2 and 3 μg/kg) was administered intra-peritoneally 30 min after AlP administration. Animals were connected to the electronic cardiovascular monitoring device simultaneously after T3 administration. Then, electrocardiogram (ECG), blood pressure (BP), and heart rate (HR) were monitored for 180 min. Additionally, 24 h after AlP intoxication, rats were deceased and the hearts were dissected out for evaluation of oxidative stress, cardiac mitochondrial function (complexes I, II and IV), ATP/ADP ratio, caspases 3 & 9, and apoptosis by flow cytometry.

*Key findings:* The results demonstrated that AlP intoxication causes cardiac toxicity presenting with changes in ECG patterns such as decrement of HR, BP and abnormal QRS complexes, QTc and ST height. T3 at a dose of 3 μg/kg significantly improved ECG and also oxidative stress parameters. Furthermore, T3 administration could increase mitochondrial function and ATP levels within the cardiac cells. In addition, administration of T3 showed a reduction in apoptosis through diminishing the caspase activities and improving cell viability.

*Significance:* Overall, the present data demonstrate the beneficial effects of T3 in cardiotoxicity of AlP.



## 1. Introduction

Aluminum phosphide (AlP) is a commonly used insecticide, rodenticide and fumigant. Poisoning by deliberate self-ingestion of AlP is a common cause of death and socioeconomic loss worldwide, especially in developing countries [2,13,26]. AlP is sold as pallet, tablet, porous blister pack, sachets, and as dusts [43].

While the exact mechanism of AlP toxicity is still unclear, several studies suggest that phosphine gas ($PH_3$) is a key player in AlP toxicity. $PH_3$ is a highly reactive radical, which can freely diffuse into intracellular compartments. $PH_3$ is released from AlP upon contact with water, moisture or hydrochloric acid of the stomach [43]. There are ample evidences suggesting that $PH_3$ can initiate a nucleophilic attack and reduce vital enzymes [3].

AlP intoxication is mostly fatal by causing multiorgan damage through denaturation of cell membranes [53,56,57]. While AlP can cause a wide range of clinical manifestations, circulatory failure is the most common cause of mortality and morbidity in AlP ingested patients [5,60]. Ventricular arrhythmias or dysfunction is a primary outcome of

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