

***NERIUM OLEANDER*: PHYTOCHEMISTRY, POISONING AND CASE STUDIES**

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ABSTRACT

Nerium oleander is one of the plant, which is traditionally used for treatment of some ailments like bleeding of nose, tonsillitis, influenza, cardiac insufficiency, cold, headache, toothache, diabetes, irritable bowel syndrome, jaundice etc. Even though, the plant, possess medicinal properties, it equally exhibits its toxic nature. The toxicity associated with the plant is due to presence of glycosides as chemical constituents like oleandrin, odoroside and adigoside in different parts of the plant. In this review, two case reports were presented. Among them, the 1st case a, female subject had used the leaf extract as traditional medicine for conception and lost life. In the 2nd case, the subject was female and she had consumed herbal tea prepared from *N. oleander* leaves also had lost her life. ECG of the 1st case was presented in the study and this study revealed, that mortality has resulted in bradycardia and heart block, due to inhibition of Na⁺K⁺ATPase, which resulted in hyperkalmia. Data was collected from 11 patients, who had been exposed to *N. oleander* poisoning. The results were presented in tabular form and it revealed that 4 patients had not survived and 7 patients had survived after successful treatment. Hence, any plant which is

exploited for its medicinal values had to be used very cautiously in the required therapeutic dose only, if used beyond the therapeutic dose, may act as poison.

Keywords: *Nerium oleander*, oleandrin, poisoning, case studies, leaf extract

INTRODUCTION

Nature is the wellspring of 87% of medications obtained to treat majority of human diseases. 25% of the drugs originated from plants. Uddin *et al.* [1] expressed that till now about 80% individuals in the developing countries depend on conventional plant based medicines for their primary health care. Plant poisoning has overwhelmed living beings throughout their history. Now-a-days poisonous plants have been part of our daily life either indoors or outdoors. Some of the plants are so common, that we do not even expect their level of toxicity. In our environment, there are number of plants, among them relatively few of them, when ingested, cause acute life-threatening illnesses [2]. Nearly 5000 taxa have been studied in detail of the world's estimated 400,000 plant species for their medical uses and only 1 % of indigenous cultures surveyed for their identification and accumulating knowledge of medicinal plants and natural products [3, 4, 5]. The plant world helps animal as well as human beings to sustain their life because of larger consumption of numerous plants [6]. Most of these are useful for the treatment of various

diseases and others can be produce sudden unfavorable health effects. The diversity of phytochemicals in plants is quite incredible that, they play a vital role in the normal growth and ecology of the plant. There are quite a lot of toxicologically significant plant constituents which include alkaloids, amino acids, peptides and proteins, glycosides, minerals, acids, oxalates, terpenes, phenolics and tannins, phytotoxins, photosensitizing compounds, resins and essential oils. Some of the above phytochemicals may cause allergic reactions, dermatitis, internal poisoning or irritation, blood, nerve or cardiac poisoning, and are commonly known as secondary metabolites. The impression of secondary metabolite was first defined by Albrecht Kossel in 1910 [7]. Thirty years later, Czapek described them as end-products [8]. However, with regard to the species, the sensitivity to the toxic effects of plants were differs [9]. On basis of the plant species, the poisonous parts of the plants may be leaf, flower, bulb, fruit, seed, stem, branch, root, rhizome, nectar or sap, pollen. They basically poison on contact, by absorption or ingestion or inhalation causing different reactions in

humans or animals [10]. After choosing plants for ethnopharmacological contemplates, analysts are urged to scan accessible writing for known poisonous properties of plants of interest, preceding leading to biological activity studies. In this review article, the authors have selected a toxic plant i.e. *Nerium oleander* because, it was usually easily accessible within reach. The toxic part of the plant, constituents, chemical structure of constituents, symptoms and case studies were reviewed and presented.

Plant description-

Botanical name - *Nerium oleander*

Family - Apocynaceae (Oleander family)

Synonyms - *Nerium indicum*, *Nerium odorum*

Common name – English: Oleander

Hindi: Kaner

Manipuri: Kabirei

Mizo: Kananpar,

Tamil: Arali

Telugu: Olinḍar puvvu

Bengali: Raktakarabi

Assamese: Korobi

Biogeography and Botanical Study - A beautiful blossom, of fragrant pink flowers in bunches, at the tip of branchlets rendering an eye-catching sight that is 'Oleander'. It is a plant native of Europe and Africa and also is

commonly found in the tropical and subtropical regions of the [11]. India and China are popular for its hue and fragrance. This plant is grown more in northern regions. It grows spontaneously on the rocky banks of rivers, sometimes even in coastal areas, usually devolve to halophilic species. It adapts to drought and is very decorative [12]. It rises up to 3 meters erect with its short branches and dark dusty green leathery narrow leaves, which grow in whorls. They are narrow lance like, 5-21 cm long and 1-3.5 cm broad, with an entire margin. The flowers grow in clusters at the end of each branch; they are white, pink or yellow, 2.5-5 cm diameter, with 5 petals fringed at the base. They are often, but not always, sweetly scented. The fruit is a long narrow capsule 5-23 cm long, which splits open at maturity to release numerous downy seeds. These plants are almost free from pests and diseases and untouched by cattle and goats, due to its toxicity. In India they are thus, the most favored plants used for the road dividers, where a plant can withstand heat and dust, and requires little water. There are single and double forms in white, pink and red. Several other cultivars have been developed. One example is a popular variety called 'Petit Salmon' which is a dwarf that grows to only 4 ft (1.2 m).

Poisonous Part - All parts of the plant (leaves, stems, blossoms, seeds, sap, honey, and berries) are toxic to humans, animals, and some insects [13]. This shrub is highly poisonous, which should not be confused with bay leaf, which is used as a seasoning [14]. Boiling or drying the plant does not inactivate the toxins [15]. The plant also irritates mucus membranes, causing buccal erythema, bitter taste, dysesthesias, and a burning sensation in the mouth. Gastrointestinal effects include nausea, vomiting, increased salivation, abdominal pain, and diarrhea. Headache is reported occasionally. CNS reactions include altered mental status, visual disturbances (including yellow vision), mydriasis, peripheral neuritis, and weakness [16-20].

Traditional uses - Although, *oleandrin* is very bitter in taste, but has some traditional uses like stops nose bleeds, tonsillitis, cardiac insufficiency, swollen gums, cold, headache, teeth, rheumatism, sedative, mumps, influenza, jaundice, ear infections, mouth-ulcers, diabetes, torticollis, irritable bowel syndrome, skin problems.

Toxic signs - Death due to oral consumption, irregularly increased heart rate, eye toxicity, abdominal pain, stomachache, digestive system disorders [21].

Treatment - The seeds of *oleander* are highly toxic although, all parts of the plant are poisonous. The toxins are in the form of glycosides are oleandrin, oleandrogenin and oleandroside. Cardiac arrhythmias and hyperkalemia are lethal complications. Toxicity is treated by activated charcoal, N-acetyl cysteine [22, 23]. Calcium chloride is contraindicated during hyperkalemia because it leads to an increase Calcium ions in the myocardium leading to hypercalcemia. Digoxin specific Fab fragment is specific antidote for digoxin overdose.

PHYTOCHEMISTRY

Active Ingredients - The toxic principles are digitalis glycosides, present in all parts of the plant, as, cardenolides, which account for about 1.5% of the weight of the leaves. Oleandrin, a major, constituent is heteroside of oleandrose and oleandrogenin. The seeds contain oleandrin and related compounds like odoroside, adigoside and glucostruposide.

Chemical Structure - Oleandrin is a cardiotonic glycoside derived from aglycone, portion and oleandrogenin (16-acetylgitoxigenin), and a sugar oleandrose (2-deoxy-3-Omethylrhamnose), has empirical formula $C_{32}H_{48}O_9$. It is a pure crystalline solid and completely soluble in organic solvents like chloroform and ethanol but, insoluble in water (**Figure 1**).

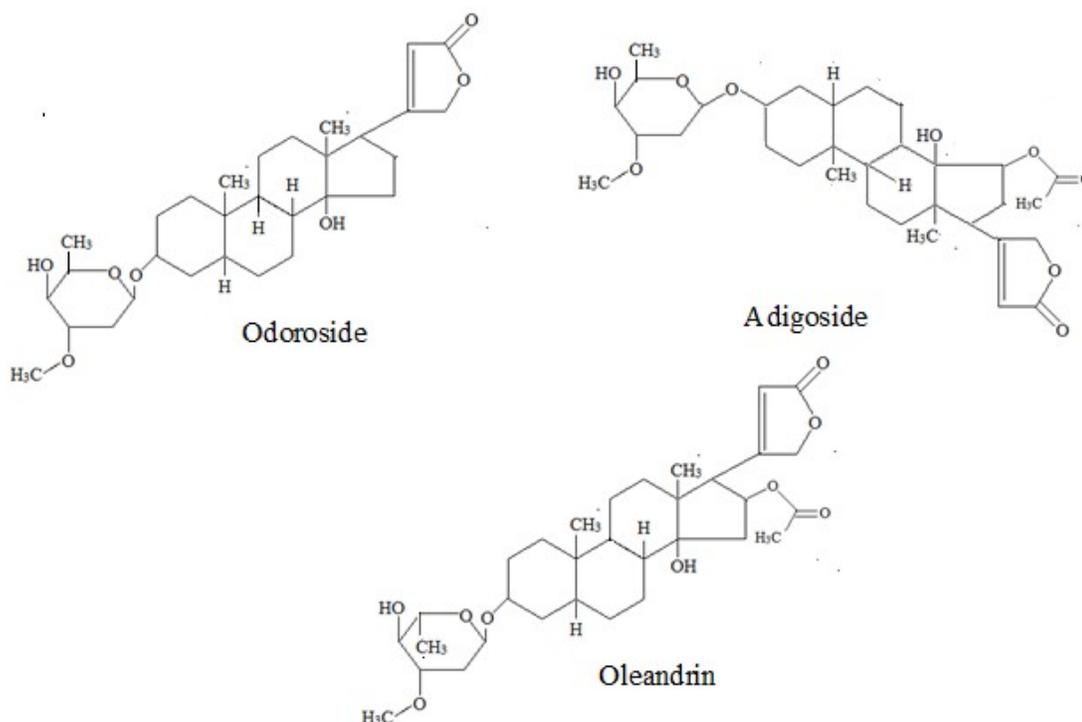


Figure 1: Chemical structure of chemical constituents of *N. oleander*

TOXICITY IN HUMANS

Human exposure to *N. oleander* may result from accidental ingestion, intentional ingestion, as ingestion in medicinal preparations, and criminal poisoning. Oleander poisonings were reported widely from locations such as Europe, United States (including Hawaii), Australia, Southern Africa, India, Sri Lanka, East Asia and the Solomon Islands [24, 25]. Other species of oleander like *T. peruviana* poisonings were rare but its occurrence in Sri Lanka was not known until local news papers reported the story of two girls who committed suicide using *T. peruviana* seeds in 1980. Since then, this method of self-harm

has become very popular and several thousands of cases have been reported each year with more cases fatality rate between 4 and 10% [25, 26, 27].

CASE REPORT

Report 1 - The poisonous nature of any part of the plant is due to production of toxic substances. *Oleander*, consists of cardio toxic glycosides. Poisonous plants encountered in India include [28] *Oleander*. The extract of the leaves was advised to be consumed by a, 21-years female, as medication to get her conceived. 15 hours after consumption, she was admitted in the emergency ward with symptoms of vomiting and lightheadedness. Previous history of the patient was non-

smoker, non-alcoholic, non allergic to drugs as well mentally strong.

Initial vitals performed indicated B.P 122/80 mmHg, pulse was 46 beats/minutes, chest and lungs were clear, cardiovascular examination indicated irregular rhythm of S1 and S2 nodes. Electrocardiogram (ECG) indicated inverted P and prolonged PR (0.28 seconds), with different degrees of AV blocks and normal QRS duration (**Figures 2a and 2b**). Treatment was initialized using

intravenous (I.V) atropine sulfate 6mg, but no improvement, in the symptoms were observed. Follow up treatment involved atropine sulfate 6mg, I.V twice a day (B.D), along with orciprenaline 10 mg thrice a day (T.I.D). After 3 days of continuous treatment, the patient was discharged for the symptoms, due to which she was admitted but, later she had suffered from severe dysfunctioning of sinus node and AV blocks (**Figure 2b**).

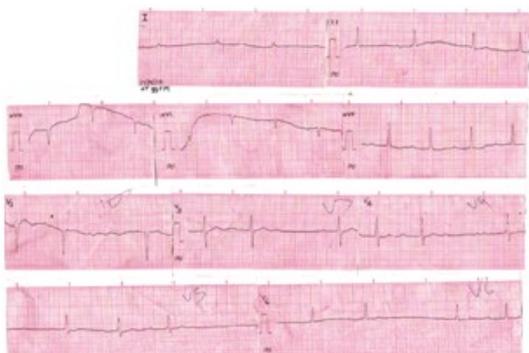


Figure 2a

Figure 2a: ECG recorded after 15 hours consumption of extract [29] and Figure 2b: ECG indicating dysfunctioning of sinus node and AV blocks [29]

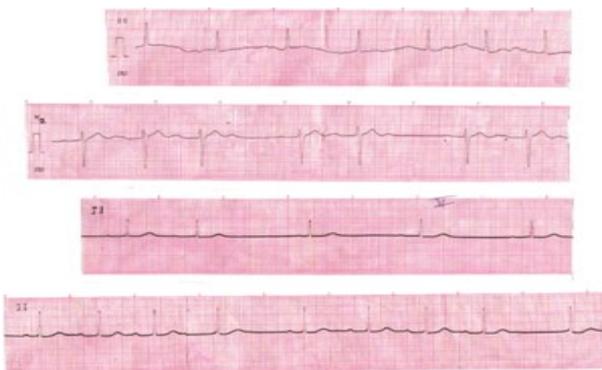


Figure 2b

The active constituents present in *N. oleander* are oleandrin and neriine of caused poisoning by inhibiting pasmalemmal Na^+ , K^+ -ATPase [30]. Akhtar et al, 2014 [31], showed that alterations of hematological and histopathological parameters was observed after administration of *N. oleander* leaves extract in wistar rats (**Figure 3 and 4**).

In the experimental animals, it has been found that alteration of hematological parameter indicated an elevated level of red

blood cells (RBCs), Hemoglobin (Hb), hematocrit (Hct) and Mean corpuscular volume (MCV). Elevation of RBC's was directly related to an increase in Hb level [32] and an indication of polycythemia and erythropoiesis occurred in the bone marrow. Additionally increased RBC's may enhance the chance of clot formation, which may cause heart attack or stroke. It is also a fact that as Hct level increased, many variations in physiological conditions was observed

such as Dengue, Shock Syndrome, myeloproliferative disorders, polycythemia, hypoxia and COPD chronic obstructive pulmonary diseases [33, 34]. An increase in

erythropoietin produced from the kidneys also had direct effect on increasing the Hct contents of the blood [35].

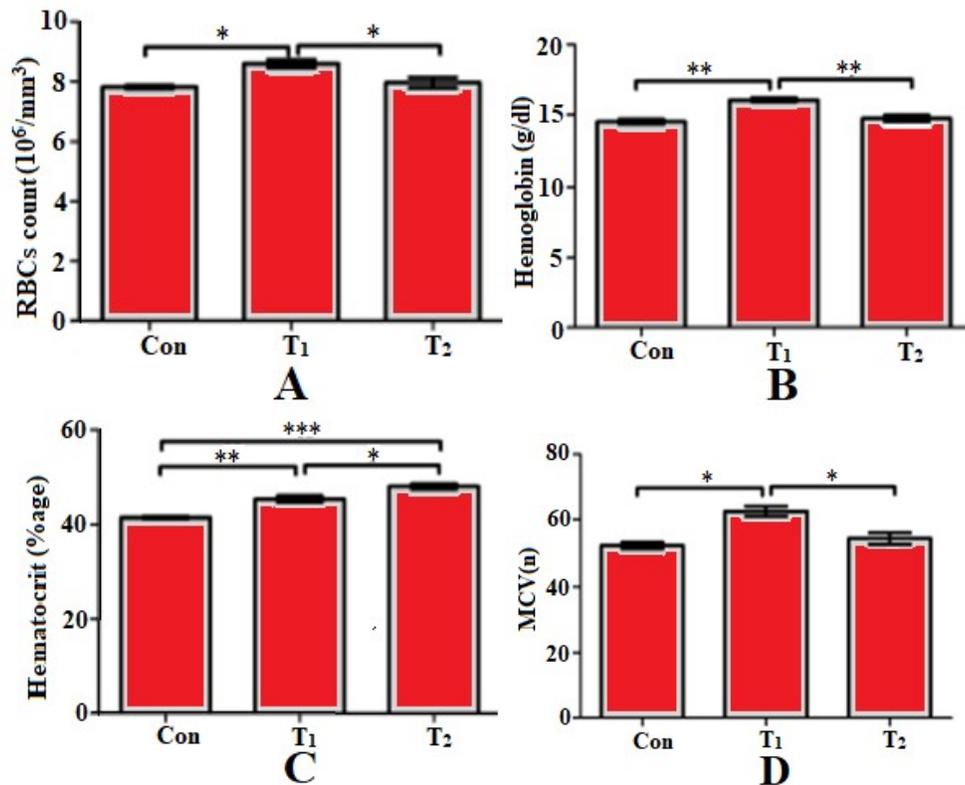


Figure 3: Effect of *N. oleander* leaves extract on hematological parameter in the control and experimental animals. a: On RBCs count; b: On hemoglobin level; c: On hematocrit level; d: on MCV; Con (control group); T1 (leaves extract oral intake for 3 days) and T2 (leaves extract oral intake for 7 days). Values are mean \pm SEM, Error bar indicating the standard deviation. * = $P \leq 0.05$, ** = $P \leq 0.01$, *** = $P \leq 0.001$

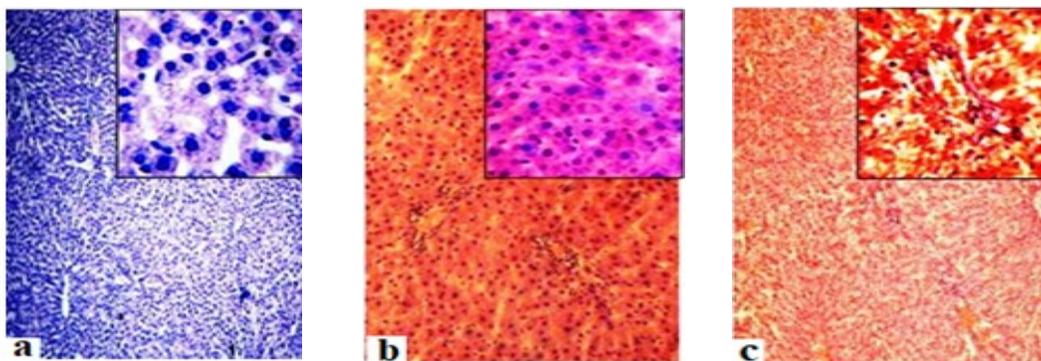


Figure 4: Hematoxylin and Eosin(H &E) staining on liver tissue a:Control group (normal drinking water); b: T1 group(3 days oral intake of extract); c: T2 group(7 days oral intake of extract).

Report 2 - On one fine day, about 10 hours before getting admitted in hospital, 30-year-old woman had prepared herbal tea from oleander (*Nerium oleander*) leaves and after she had tea, had complained the symptoms of nausea, numb tongue, later began vomiting [36].

When patient had arrived hospital, paramedics found that the patient was exhibiting slurred speech and complaining of skin becoming pale, moist, and cool, pulse 30 per minute, and irregular, blood pressure was not palpable. Lungs were clear, but respiration was 36/min, an ECG rhythm strip transmitted by telemetry revealed an idioventricular rhythm of 32/rain.

Oxygen was administered by nasal cannula at 6 L/rain and an intravenous (IV) infusion with lactated Ringer's solution was started at 100 cc per hour. Naloxone 0.8 mg and dextrose 50% 50 mL was administered IV without change in the patient's condition. Atropine sulfate 0.5 mg was given sequentially IV in, a dose of 2 mg. Pneumatic antishock trousers were applied and inflated, followed by infusion of a 300 ml fluid challenge. These maneuvers transiently accelerated the patient's heart rate, which quickly returned to 30/min; blood pressure remained impalpable. Isoproterenol was administered at 2 µg/min; ventricular

tachycardia of 140/min ensued, and degenerated into ventricular fibrillation on arrival at the hospital. Time taken on-scene treatment and transport to the hospital was approximately 45 minutes because of difficulty in shifting the patient due to loss of radio contact with the hospital.

In the emergency department (ED) the patient was orotracheally intubated, defibrillated at 200 W/sec, and a right infraclavicular subclavian central venous catheter was placed. Additional doses of lactated Ringer's solution, 50 mEq sodium bicarbonate, 0.8 mg naloxone, and 1 mg atropine sulfate were administered, along with 1 mg epinephrine and 250 mg calcium chloride. Emergency personnel identified that leaves of oleander, was the reason for poison and contacted poison control center.

This case demonstrates that a cross-reactivity between the cardiac glycosides in *oleander* and the digoxin by radioimmunoassay. Digoxin specific fab antibody fragments were not used in oleander poisoning, but it may prove to be lifesaving. Treatment of *oleander* toxicity was aimed at controlling arrhythmias and hyperkalemia, inactivation of the Na-K ATPase pump.

Consumption of >3 seeds of Oleander resulted in significant mortality. It has been found that in the above 2 case reports the

subjects expired due to ventricular arrhythmias. The cardiac glycosides have vagotonic effects, resulting in bradycardia and heart block. Inhibition of Na^+K^+ ATPase in skeletal muscle resulted in hyperkalemia [37].

Kumari *et al*, 2019 [38], reported that, plant poisoning was the second common poisoning next only to pesticides (77.9%). Oleander

contributes to the most common poisoning (66.6%) than other plants poisoning. Vomiting and abdominal pain are the common symptoms observed in patients who consumed the plant. From the data of 11 patients collected, who were exposed to *oleander* poisoning, 4 cases were fatal and 7 cases were survived (Table 1, Figure 5).

Table 1: Summary of case reports and studies of oleander poisoning

Case History	Plant part Ingested	Country name	Treatment
20 yr, female [39]	Leaf extract oral and rectal administration	Florida, USA	Digoxin specific Fab antibody fragments
30 yr, female [36]	Leaves	California USA	Supportive
96 yr, female [19]	Leaves 4gms of extract	California, USA	Supportive
49 yr, male [40]	Leaf extract	United Arab Emirates	Fentanyl, propofol, morphine, midazolam, Digoxin specific Fab antibody fragments
Middle aged, female [41]	Tea made with oleander	Italy	Supportive
83 yr, female [42]	Leaves	USA	Atropine sulfate, activated charcoal, supportive
47 yr, female [43]	Flowers	Germany	Activated charcoal, supportive, temporary cardiac pacemaker
37 yr, male [44]	Leaves	California, USA	Ipecac, Activated charcoal, Digoxin specific Fab antibody fragments
45 yr, female [45]	Leaves	France	Gastric lavage, activated charcoal, supportive
52 yr, male [46]	Root extract	Australia	Supportive
17 yr, female [47]	Leaves	Croatia	Haemodialysis, haemoperfusion

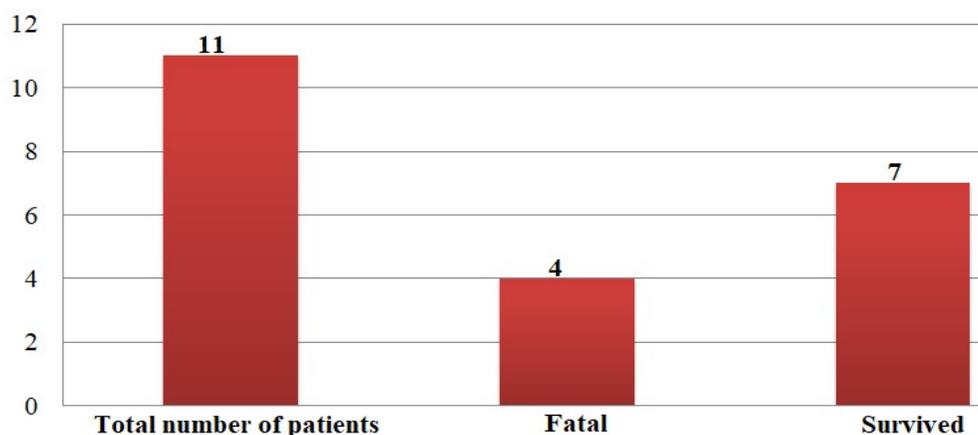


Figure 5: Statistical data of oleander poisoning cases

CONCLUSION

N. oleander consists of oleandrin, odoroside and adigoside as chemical constituents, which are glycosides, toxic in nature. ECG of one case was presented, which clearly exhibits the role of constituents on heart. Based on the two case reports, it can be concluded, that any chemical constituent of the plant, when used for its medicinal purposes in the required and therapeutic range may serve the purpose, but beyond its therapeutic dose may act as poison leading to fatality.

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CONFLICTS OF INTEREST

The authors declare that, there are no conflicts of interest for publication of this paper.

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