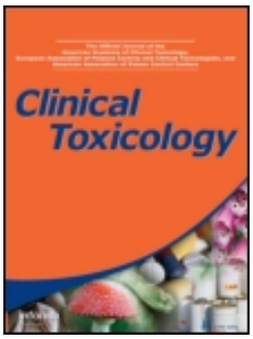

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CASE REPORT

# Human *Melia azedarach* poisoning

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*Introduction*. In traditional Chinese medicine, *Melia azedarach* (Ku-lian) is used orally and topically as an antiparasitic and antifungal agent. Although toxicity of this plant has been widely described in veterinary literature, human poisoning is rarely reported. We describe five patients with *M. azedarach* poisoning who recovered with supportive care. *Case series.* Five patients were identified retrospectively from the database of the Taiwan National Poison Center at the Taipei Veterans General Hospital. Three cases were on-site patients, and two were telephone consultations from outside hospitals. Neurological symptoms were the major manifestation in four cases: weakness, myalgia, numbness, and ptosis. Treatment was symptomatic and supportive; all patients recovered without sequelae. *Discussion*. It is not known which limonoids are responsible for human toxicity. In the Chinese medical literature, human *M. azedarach* poisoning is said to occur if six to nine fruits, 30 to 40 seeds, or 400 g of the bark is consumed. Onset of symptoms typically occurs within 4–6 h, but as short as 0.5 h had been documented. In our patients, the onset of *M. azedarach* poisoning was variable, ranging from a few hours to up to 3 weeks after consumption of the herb. *Conclusions*. *M. azedarach* poisoning may result in gastrointestinal, cardiovascular, respiratory, or neurological effects, and death in severe cases.

**Keywords** Acute poisoning; Chinese herb; *Melia azedarach*; Meliatoxin; Toosendanin

## Introduction

*Melia azedarach* (Ku-lian) is also known as China tree, China berry tree, bitter China berry tree, or Chinese neem tree. It is native to Asia but is now found in parts of Northern Australia, Africa, North America, tropical South America, and Southern Europe. In traditional Chinese medicine, it is used as an antiparasitic and antifungal agent, both orally and topically (1). Toxicity of this plant has been widely reported in veterinary literature (2–5). Human poisonings have been reported in an out-of-print botanical text (6), the Chinese medical literature (7), and once previously in the English medical literature (8).

## Methods

To better understand the toxicity of *M. azedarach* in humans, we searched the database of the Taiwan National Poison Center at the Taipei Veterans General Hospital (VGH) to find any case of *M. azedarach* poisoning. Between 1998 and 2007, we found nine cases of possible *M. azedarach* toxicity (Ku-lian, Ku-lian oil, or Ku-lian seed). After carefully reviewing the case records, we excluded a patient who developed mild gastrointestinal discomfort after exposure to Ku-lian seed (Ku-lian-zi, chuan-lian-zi, fruit of *Melia toosendan*). Although the Chinese nomenclature is very similar between *M. azedarach* and *M. toosendan*, and in some parts of China these two herbs are even used interchangeably, *M. toosendan* is much less toxic than *M. azedarach* (1,9). We also excluded three patients who manifested gastrointestinal symptoms after exposure to Ku-lian oil (Ku-lian-yu, neem oil). Neem oil is made from the fruits and seeds of *Azedarach indica*, which is known in Chinese as Ku-lian-shu (Ku-lian tree) and is very similar in appearance to *M. azedarach*. It is therefore possible to confuse between *Azedarach indica* and *M. azedarach* ingestion. The three patients, however, were exposed to neem oil, not *M. azedarach*. We describe the clinical features of the remaining five patients with *M. azedarach* ingestion.

## Case series

### *Case one*

A 51-year-old man with history of diabetes mellitus took an herbal concoction containing leaves of *M. azedarach*, *Ficus microcarpa*, *Acacia confusia*, and rice wine. It is not clear

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why he took these Chinese herbs. After two doses on day 1, he started to experience generalized weakness and tiredness. After a third dose on day 2, he experienced headache with blurred vision, nausea, palpitations, and frontal numbness over his head. He had an episode of fever with chills that evening, but he did not record the temperature. On the next day, the frontal numbness over his head progressed to mouth numbness. He was sent to Taipei Veterans General Hospital (VGH) for treatment.

On arrival, he complained of generalized weakness and dizziness. Vital signs were normal and physical examinations were all unremarkable. Laboratory investigations revealed elevated blood level of aspartate transaminase (AST) at 70 U/L (reference 5–45 U/L), alanine transaminase (ALT) at 55 U/L (reference <40 U/L), alkaline phosphatase at 153 U/L (reference 10–100 U/L), and creatinine kinase (CK) at 334 U/L (reference 27–168 U/L). Other investigations including electrocardiography (EKG), chest X-ray, blood counts, renal function, and serum electrolytes were normal. He was hospitalized and managed supportively. All abnormal laboratory values returned to normal range the next day and he was discharged after a day of hospitalization.

### *Case two*

A 77-year-old previously healthy man took a drink prepared from the boiled bark of *M. azedarach* to improve his urination. He started taking this preparation 3 weeks before presentation. A day before admission he consumed two bowls of the drink (500 mL) and soon noticed drooling of saliva. The same evening he developed muscle soreness and generalized weakness. He was sent to a local hospital.

On presentation, he was noted to have ptosis of his right eye, with generalized muscle weakness and muscle power of 3. He was transferred to VGH for further management 3 days later. At the VGH, he complained of generalized muscle weakness, but stated that his symptoms had improved a lot. He also complained of soreness over his shoulder and lumbar region. His vital signs were normal and physical examinations were unremarkable. Laboratory investigations revealed elevated ALT (101 U/L), AST (69 U/L), and CK (434 U/L) levels. Blood counts, renal function, plasma and red blood cell cholinesterase levels, and serum electrolytes were normal. EKG and chest X-ray were unremarkable. After receiving supportive management, he recovered fully and was discharged after 4 days of hospitalization. Electromyography performed on day 5 was normal.

### *Case three*

Case three was a 66-year-old woman, the wife of case two. She took the same drink prepared from the boiled bark of *M. azedarach* to improve her urination. Like her husband, she had started taking the preparation 3 weeks previously. She noticed slight drooling of saliva on one side of her face after each time of consumption, but ignored that because the symptom was not severe and always recovered within a day.

On the day of admission, she took four bowls (about 1,000 mL) of the drink and soon developed numbness over her lips and drooling. Her symptoms got worse in the night with generalized weakness and malaise. She was sent to a local hospital where she complained of dry mouth and dysphagia. She was noted to have unstable gait, ptosis, and her muscle power was 3. Laboratory investigations showed hypokalemia 2.7 mmol/L (reference 3.4–4.7 mmol/L) and hypomagnesemia 1.3 mmol/L (reference 1.8–2.5 mmol/L). After 3 days of supportive treatment and correction of electrolyte imbalance, she was sent to the VGH for further management. At the VGH, she complained of generalized weakness, malaise, and numbness. Vital signs were normal and physical examinations showed right eye ptosis and muscle weakness with muscle power of 4. Laboratory investigations revealed elevated ALT (92 U/L), AST (145 U/L), and CK (226 U/L) levels. Blood counts, renal function, and serum electrolytes were unremarkable. She was hospitalized and managed supportively. She recovered well and was discharged after 4 days of hospitalization.

### *Case four*

Case four was a telephone inquiry case reported from another hospital. A 40-year-old man with a history of alcohol abuse took soup cooked with the bark of *M. azedarach* to treat his alcoholism. He started consuming the soup 3 days before presentation, he noted weakness in his jaw muscle and eyelids resulting in ptosis. The patient was hospitalized and recovered within 2 days.

### *Case five*

Case five was a telephone inquiry case from another hospital regarding a 48-year-old man who consumed a brew containing alcohol and the bark of *M. azedarach*. It was not clear why he had taken the herb. He took the brew three times in a day, and after that started to experience multiple episodes of diarrhea, together with dyspnea and hoarseness of voice. Laboratory tests revealed mild elevation of liver transaminases; the patient recovered after 2 days of hospitalization.

## Discussion

The bark of *M. azedarach* is used in Chinese material medica and is listed as Ku-lian-pi (i.e., Ku-lian bark). It is also known as Ku-ling or Ku-mu-shu (Ku-mu tree) and Ku-pi. The leaves, flowers, and fruits of *M. azedarach* have been reported to result in toxic effects in animals, mainly in rat studies, and in dogs and pigs that had consumed fallen fruits (2–5,10). Table 1 summarizes the toxicity that had been reported in animals. Although only the bark of *M. azedarach*

**Table 1.** Animal toxicities of *Melia azedarach* reported in the English literature

| Author and year | Animal tested | Parts of plant | Symptoms |
|---|---|---|---|
| Kwatra 1974 | Pigs | Fruits and leaves | Death |
| Zakir-ur-Rahman 1991 | Mice and rats | Flowers and berries | Central nervous system sedation<br>Death |
| Hare 1997 | Dogs | Fruits | Gastrointestinal disturbance<br>Hepatic congestion<br>Neurological disturbance |
| del Mendez 2002 | Cattle | Fruits | Ataxia<br>Diarrhea<br>Dyspnea<br>Hepatocyte necrosis<br>Hypothermia<br>Raised aspartate transaminase<br>Creatinine kinase |
| Cooper 2007 | Ostriches | Fruits | Kicking movement<br>Muscle tremors<br>Respiratory distress |

is listed as the medicinal part, in some reports as well as in our first patient, leaves or other parts may be used and cause toxicity. It seems possible that the entire plant is toxic. Prior investigations had further suggested that the toxicity of this plant can vary depending on the growing conditions (3).

Multiple limonoid tetranotriterpenes have been isolated from various parts of this plant (6,7,9,11–15). Well-characterized limonoids include toosendanin from the bark and meliatoxin from the fruit (6,7,9,15,16). In animal studies (2–5,10), toosendanin caused abdominal distension, anorexia, and respiratory depression in rats; severe vomiting and shock in dogs; and transaminitis and muscle weakness in monkeys. In mice, cats, dogs, and monkeys, muscle weakness, respiratory depression, and seizures were also observed. The $LD_{50}$ of toosendanin varies between animals and routes; in mice the oral $LD_{50}$ ranges between 250 and 500 mg/kg (9).

In pig studies, meliatoxin caused severe rapid muscular contraction that degenerated to spasmodic quivering, tachycardia, midrise, hypothermia, coma, and death at about 30 h, and the oral $LD_{50}$ in pigs is 6.4 mg/kg (6,9). Other limonoids isolated from the bark were shown to have cytotoxic effects (11,14). Zakir-ur-Rahman et al. (10) also reported that the alcoholic and aqueous extracts of the flowers and berries can have mild sedating effect and can be lethal to mice and rats. To date, at least 20 different limonoids have been isolated from various parts of *M. azedarach*. However, it is still not known which limonoids are responsible for human toxicities.

In the Chinese medical literature, human *M. azedarach* poisoning is said to occur if six to nine fruits, 30–40 seeds, or 400 g of bark is consumed. Onset of symptoms typically occurs within 4–6 h, but as short as 0.5 h had been documented (8,15). In China, some 2,000 cases of human poisoning have been reported since 1968 (7). The reported clinical features generally involve four organ systems – gastrointestinal (abdominal discomfort, dry mouth, nausea, and vomiting), cardiovascular (arrhythmia, tachycardia, and hypotension), respiratory (cyanosis, dyspnea, and respiratory depression), and neurological systems. Neurological features are the most numerous and may manifest blurred vision, diplopia, decreased visual field, numbness of lip, generalized numbness, giddiness, headache, inability to masticate or swallow, lethargy, weakness ataxia, agitation, or seizure. Fatal cases generally died of respiratory arrest (7,8).

In the English medical literature, Toh (8) described a woman who complained of giddiness and fainted 0.5 h after consuming a concoction prepared from grounded bark of *M. azedarach*. In the hospital, she was comatose with mild tachycardia, mydriasis, and loss of all reflexes. Her blood pressure became unrecordable later requiring inotropic agents and intubation. Laboratory investigations showed severe acidosis of pH 6.98 and hypokalemia of 2.6 mmol/L. She died 3 days later; autopsy disclosed cerebral edema, midbrain necrosis, left caudate nucleus hemorrhage, pulmonary congestion, gastrointestinal hemorrhages, yellow discoloration of the liver, and congested kidneys (8).

Neurological symptoms were the major manifestation in four of our patients. One of our patients also complained of palpitations and another complained of dyspnea and hoarseness of voice. Only one patient had prominent gastrointestinal symptoms. It may be possible that patients with only mild gastrointestinal symptoms do not present to hospital or that different toxins produce different clinical features upon poisoning. In animal studies, sublethal doses of fruits from this plant only produced gastrointestinal symptoms, whereas lethal doses of fruits or purified extract of certain toxins did not produce gastrointestinal symptoms at all (6).

One of our patients had hypokalemia and hypomagnesemia, an effect that was not observed in animal studies. We speculated that prolonged diuresis over 3 weeks might result in electrolyte imbalance seen in our second patient. Hypokalemia can cause muscle weakness, but this

would not be the only explanation as other patients without hypokalemia also manifested muscle weakness.

In some of our patients, elevation of blood transaminase and CK levels suggested hepatic and muscular injuries. This was also seen in animal studies (3). It is not known which toxin or toxins cause this, but muscular injury can lead to muscle weakness. One of our patients also complained of soreness which is in keeping with muscular injury. In animal pathology studies, necrosis of gastrointestinal cells and hepatocytes were observed; hyaline and proteinaceous cast were also seen in renal tubules (3,6). No renal function abnormality was observed in our patients.

Onset of *M. azedarach* poisoning in our patients is variable, ranging from a few hours to up to 3 weeks after consumption of the herb. The clinical course is short with complete recovery and hospital discharge after a few days. No antidote was administered and supportive management appears to be sufficient. Although the course of poisoning was relatively benign in our patients, there were reports of human mortality from *M. azedarach* poisoning (7,8). It is not known whether this difference in severity is because of the nature of the plant, the parts used, or the amount used. To provide more clues to this question, it is important to measure the blood or urine levels of limonoid tetranotriterpenes in poisoned patients. Unfortunately, we did not have such data in our patients, which is the main limitation of this report.

## Conclusions

*Melia azedarach* poisoning may result in gastrointestinal, cardiovascular, respiratory, or neurological effects, and death in severe cases.

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