





# Clinical Characteristics of *Acalypha indica* Poisoning

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**Background:** *Acalypha indica* is a tropical plant used as a herbal medicine in various parts of the world, including Thailand. In glucose-6-phosphate dehydrogenase (G6PD)-deficient patients, acute hemolysis has been reported following the ingestion of this plant. Methemoglobinemia was reported in the present study.

**Patients and Methods:** Descriptive data of patients who suffered from *Acalypha indica* toxicity reported from different hospitals to the Ramathibodi Poison Center were retrieved from 2011 to 2019.

**Results:** Eight patients were included, mostly male with a median age of 61.5 years. The plant was ground for fresh juice or boiled before consuming as herbal medicine. All patients presented with dark urine. Most had jaundice and fever, and all reported hemolysis. Seven out of eight patients were diagnosed as methemoglobinemia. Methemoglobin level was confirmed in five patients with the highest level of 23.9%. Early symptoms occurred within 24 hours of the last ingested dose.

**Discussion:** In previous case reports of *Acalypha indica* ingestion, acute hemolysis was mostly observed in G6PD-deficient patients, consistent with the current findings. However, our patients also demonstrated methemoglobinemia, with some constituents in this plant (quinine, 2-methyl anthraquinone and tectoquinone) implicated as the cause in previous studies. Further studies are crucial to validate these findings.

**Conclusion:** We report a case series in which acute hemolysis and methemoglobinemia after *Acalypha indica* ingestion were observed. This study presents methemoglobinemia as the other toxicity caused by this plant.

**Keywords:** acute hemolysis, methemoglobinemia, G6PD deficiency, plant-induced methemoglobinemia

## Introduction

Herbal medicine plays an important role as alternative medicine among Asian countries. *Acalypha indica*, a tropical plant that grows in various parts of the world including Thailand,<sup>1</sup> is used in herbal medicines and as local food. Although toxicity has not been documented in animal studies even at high doses,<sup>2,3</sup> intravascular hemolysis has been reported in humans with glucose-6-phosphate dehydrogenase enzyme (G6PD) deficiency after ingesting this plant.<sup>4-6</sup> One case report also described methemoglobinemia.<sup>7</sup> Studies of *Acalypha indica* poisoning in Southeast Asia that include Thailand are limited. Therefore, the objective of this study was to characterize the clinical manifestations and the clinical outcomes of *Acalypha indica* poisoning in Thailand.

## Patients and Methods

We conducted a cross-sectional retrospective study of all human exposures to *Acalypha indica* reported to the Ramathibodi Poison Center (RPC), Bangkok,

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Thailand from January 2011 to December 2019. The RPC is a poison center based in a tertiary teaching hospital, serves the whole country, both healthcare professionals and the general public 24 hours a day, 7 days a week. Most calls to the RPC are from medical personnel. There are approximately 20,000 calls annually. Follow-up calls are periodically made to collect and monitor case progress, to provide ongoing treatment recommendations, and to determine the medical outcomes of cases. All cases are recorded in the RPC Toxic Surveillance System database.

*Acalypha indica* was determined by 1) description of plant or plant name given by the patient or relative, 2) pictures of plant that were sent to the RPC's application Line or an email, 3) identification using botany textbooks, and 4) identification by a botanist at the Medicinal Plant Information Center, Faculty of Pharmacy, Mahidol University. This verification process was conducted by a team of information scientists and medical toxicologists.

All circumstances of human exposures to *Acalypha indica* were retrieved. We collected each patient's demographic data, reason for exposure, amount of exposure, plant preparation for consumption, duration from exposure to arrival at a healthcare facility, medical history, laboratory findings, treatment modalities, follow-up details, final diagnosis, and outcome. A case with the history of co-exposures to other drugs, chemicals, herbs, or pesticides which cause hemolysis or methemoglobinemia were excluded. In this study, a heart rate greater than 100 beats per minute was defined as tachycardia, and a heart rate less than 60 beats per minute was defined as bradycardia.<sup>8</sup> Fever was defined as an oral temperature at the morning reading above 37.2°C or an afternoon temperature of above 37.7°C.<sup>9</sup> Jaundice is often used interchangeably with hyperbilirubinemia when serum bilirubin is greater than 2 mg/dL, twice the normal upper limit.<sup>10</sup> Hemolysis was defined by the presence of dark urine, decreased hematocrit from the baseline results and increased indirect bilirubin. Methemoglobinemia was an abnormal elevation of the methemoglobin level above 1%,<sup>11</sup> or defined by the presence of oxygen saturation gap (between pulse oximetry and arterial blood gas) and desaturation not well responded to oxygen therapy or cyanosis. Acute kidney injury was diagnosed based on the patient's clinical history and laboratory data using the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines.<sup>12</sup>

The RPC data were obtained and managed using Microsoft Excel, and then analyzed with IBM SPSS Statistics for Windows, version 18 (IBM Corp., Armonk, NY, USA). Descriptive statistics were performed to

characterize the data. The median, minimum, maximum, and interquartile range (IQR) were analyzed for continuous data, while the frequency and percentage were assessed for categorical data.

This study was approved by the Institutional Ethics Committee Board of the Faculty of Medicine Ramathibodi Hospital, Mahidol University (Reference Number: 10–61-30) and performed in accordance with the principles of the Declaration of Helsinki. Patient consent was not required by the ethics committee board because this study was retrospective in nature and used the preexisting confidential database from RPC. All results were reported anonymously.

## Results

A total of nine patients with a definite history of *Acalypha indica* ingestion reported from different hospitals between 2011–2019 were retrieved from the database system of the Ramathibodi Poison Center (RPC), Thailand. One case was excluded due to incomplete information; eight patients were included. Table 1 summarizes the demographic and exposure characteristics of patients with *Acalypha indica* ingestion. Most patients (7/8) were male, with a median age of 61.5 years (range 38–70 years). Leaves (75%) were commonly used, followed by the whole plant (25%). For ingestion, the plant was ground for fresh juice or boiled as a decoction. Four individuals drank this herbal decoction one time. The median time from ingestion to arrival at healthcare facility was 2.5 days

**Table 1** Demographic and Exposure Characteristics of Patients with *Acalypha indica* Ingestion

Characteristics	Frequency (%)
Age (years), median (min-max)	61.5 (38–70)
Gender: Male	7 (87.5)
Used parts of plant: Leaves	6 (75)
Whole: leaves, stem, roots	2 (25)
Preparation for consumption:	
Boiled	4 (50)
Fresh juice	3 (37.5)
Both	1 (12.5)
Frequency of ingestion (times)	2 (1–6)
Onset of symptoms after the 1st dose ingestion:	
1-time ingestion (hours), median (min-max)	1.5 (0.2–4)
≥2-time ingestion (days), median (min-max)	3 (2–4)
Time presenting to hospital (days)	2.5 (2–4)
Hospital stay (days), median (min-max)	10 (2–21)

(range, 2–4 days). After ingestion of the first dose, the median onset of symptoms was 18 hours (range, 4–24 hours) for single ingestion and 3 days (range, 2–4 days) for multiple ingestions. In the latter group, the symptom onset occurred within 24 hours after a last dose of ingestion. All patients presented with dark urine, most had jaundice and fever (Figure 1). Hemolysis was diagnosed in all patients. Details of each patient are shown in Table 2. The lowest hematocrit (Hct) was 10.5%; the highest indirect bilirubin level was 14.5 mg/dL. G6PD deficiency was confirmed in 2 patients; remaining patients demonstrated normal G6PD activity at presentation but were lost to follow-up G6PD activity at 3 months after discharge. Seven patients had desaturation and oxygen saturation gaps, failing to adequately respond to oxygen therapy. Some had cyanosis. Methemoglobin levels were confirmed in 5 patients, with a median level of 5.6% (range, 1–23%). All patients presented no prior personal or family history of unexplained cyanosis or low oxygen saturation. Prior to discharge, oxygen saturation returned to normal. The median duration from symptom initiation to the disappearance of dark urine, hemolysis, and methemoglobinemia was 4.5, 5, and 5 days for single, and 3.5, 5.5, and 4.5 days for multiple ingestions, respectively. Four patients developed acute kidney injury, with three requiring hemodialysis. Treatment was mainly supportive (Table 2). One patient died due to cardiovascular disease (Patient 3). He was a 70-year-old man with underlying asthma, chronic obstructive pulmonary disease, and coronary artery disease and had ingested a glass of fresh juice daily for 3 days. He

developed dyspnea, central cyanosis, dark urine, tachycardia (HR 122 bpm), fever (38.5°C), low oxygen saturation by pulse oximetry (SpO<sub>2</sub> 49–52%), and anemia (Hct 32%, his baseline Hct was 40%) on the 3<sup>rd</sup> day. He was mechanically ventilated with 100% oxygen but his SpO<sub>2</sub> was 60–62%. Laboratory tests indicated methemoglobinemia (his methemoglobin level of 23.9%) with normal G6PD. Treatment included blood transfusion, two doses of methylene blue 1% (1, 0.5 mg/kg) and supportive treatment. His condition improved until he was weaned off the ventilator. Later, he suddenly had tachypnea, SpO<sub>2</sub> levels decreased to 65%, and acute myocardial infarction was suspected; death occurred on the 2<sup>nd</sup> day of admission.

## Discussion

Acute hemolysis has been primarily reported in G6PD-deficient patients after ingesting *Acalypha indica*,<sup>4–6</sup> with only one case in normal G6PD status.<sup>13</sup> In this study, all patients had acute hemolysis. At presentation, most patients had normal G6PD status except two patients had G6PD deficiency. The measurement of G6PD activity can be normal during hemolysis. Phenotypic test for G6PD deficiency is best done 2–3 months after hemolytic crisis.<sup>14</sup> Therefore, we cannot elucidate the G6PD status in six patients who lost to follow-up after discharge.

Seven patients (88%) in our study presented symptoms suggesting methemoglobinemia, with five confirmed by methemoglobin levels ranging from 1–23.9%. The level of 1% was low because it was monitored on the 10<sup>th</sup> day

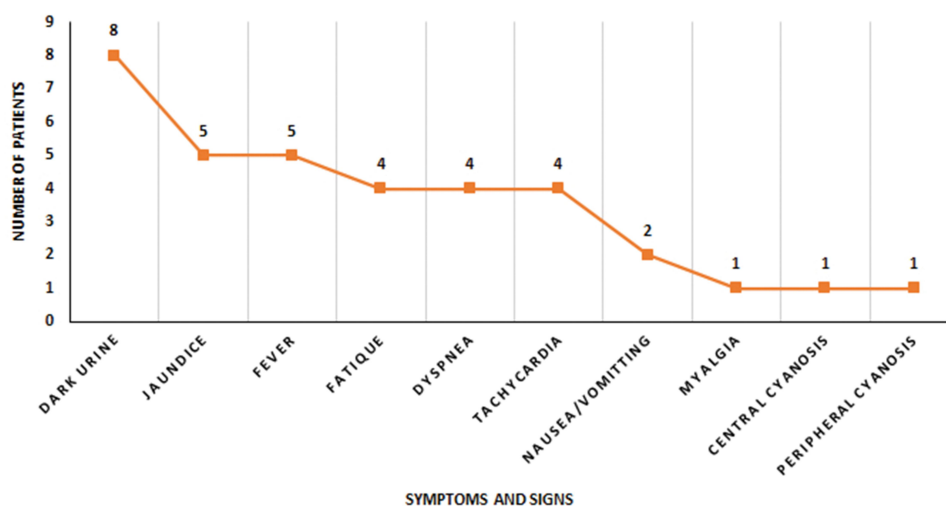


Figure 1 Clinical signs and symptoms at first presentation.

**Table 2** Demographic Data, Clinical Manifestations, Laboratory Results and Treatment in Each Patient Who Exposed to *Acalyha Indica*

Characteristics	Patient 1	Patient 2	Patient 3 <sup>a</sup>	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
<b>Patient characteristics</b>								
Gender/Age (years)	F/47	M/38	M/70	M/68	M/61	M/64	M/62	M/56
Underlying disease	NA	None	Asthma/ COPD/CAD	HT/BPH/ Hyperthyroid	Renal calculi, HT, Old CVA	HT, BPH	HT	NA
Time presenting to hospital since exposure (days)	3	2	3	2	3	4	2	2
<b>Uses of plant</b>								
Purpose	Asthma	Health supp.	Health supp.	Muscle pain	Health supp.	Allergy	Rash/Pruritus	Constipation
Used part	Whole	Leaves	Leaves	Leaves	Leaves	Leaves	Whole	Leaves
Preparation for consumption	Fresh juice	Both	Fresh juice	Boiled	Boiled	Boiled	Fresh juice	Boiled
Frequency of drinking (times)	1	1	3 (1x3 days)	1	3 (1x3 days)	4 (1x4 days)	1	4-6 (2x2-3 days)
<b>Laboratory results</b>								
Initial Hct/Lowest Hct (%)	19.0/19.0	11.0/10.5	32.0/32.0	30.0/13.0	32.0/27.0	30.4/23.1	26.0/19.0	31.0/19.7
Initial TBIL/Initial InBIL (mg/dL)	5.5/4.9	5.4/2.0	2.2/1.9	5.2/3.3	4.0/3.1	8.2/7.3	15.3/14.5	6.3/5.5
Max InBIL/TBIL same day (mg/dL)	4.9/5.5	5.8/6.9	1.9/2.2	6.1/7.1	7.3/4.0	7.3/8.2	14.5/15.3	8.5/9.5
G6PD at presentation/3 months after discharge	Normal/Def	Normal/NA	Normal/NA	Normal/NA	Normal/NA	Def/NA	Normal/NA	Normal/NA
Initial SpO2/Lowest SpO2 (%)	60/40	83/83	49/49	98/98	70/70	85/85	98/60	88/82
MetHb level (%) / Day after exposure	NA	NA	23.9/3	-	1.0/10	4.5/5	8.8/2	5.6/3
Initial SCr/Max SCr (mg/dL)	1.8/10.2	1/NA	0.9/2.1	6.8/12.3	1.6/18.5	0.8/0.8	0.7/0.7	1.2/1.2
AKI (yes/no)	Yes	NA	Yes	Yes	Yes	No	No	No
<b>Methemoglobinemia diagnosis by (yes/no)</b>								
MetHb level	No	No	Yes	No	Yes	Yes	Yes	Yes
Oxygen saturation gap	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Desaturation not well responded to oxygen	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Cyanosis	Yes	No	Yes	No	No	No	No	No
<b>Onset of symptoms after 1<sup>st</sup> exposure (days) / Duration until symptoms subsided (days)</b>								
Dark urine	0.16/12	1/4	3/3	1/NA	3/NA	4/5	0.5/5	2/4
Hemolysis	3/5	2/5	3/4	2/10	3/12	4/7	2/5	2/4
Methemoglobinemia	3/5	2/3	3/5	-	3/6	4/4	2/5	2/5
<b>Treatment (yes/no)</b>								
Oxygen therapy/ Endotracheal intubation	Yes/No	Yes/No	Yes/Yes	Yes/No	Yes/Yes	Yes/No	Yes/No	Yes/No
Blood transfusion	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Methylene blue 1% intravenous	Yes	No	Yes	No	No	No	No	No
Hemodialysis	Yes	No	No	Yes	Yes	No	No	No
<b>Hospital stay (days)</b>	12	5	2	19	21	7	10	10

**Note:** <sup>a</sup>Dead case.

**Abbreviations:** COPD, chronic obstructive disease; CAD, coronary artery disease; HT, hypertension; BPH, benign prostatic hyperplasia; CVA, cerebrovascular accident; NA, not applicable; Health suppl, health supplements; Def, deficiency; Hct, hematocrit; Max, maximum; TBIL, total bilirubin; InBIL, indirect bilirubin; mg/dL, milligram/deciliter; G6PD, glucose-6-phosphate dehydrogenase; SpO2, oxygen saturation by pulse oximetry; MetHb, methemoglobin; SCr, serum creatinine; AKI, acute kidney injury.

after ingestion when methemoglobinemia symptom recovered. Methemoglobinemia is commonly an acquired condition, although it can rarely be hereditary. Our patients were not screened for hereditary methemoglobinemia but the presence of normal oxygen saturation on pulse oximetry at discharge could demonstrate the improbability of an altered hemoglobin form, such as Hemoglobin M, or the absence of an essential enzyme, such as homozygotes of NADH-cytochrome b5 reductase deficiencies. Owing to a lack of in-depth investigation, some limitations include the heterozygosity in the patients, necessitating future validation studies.

To date, methemoglobinemia due to *Acalypha indica* has been previously presented in one case report.<sup>7</sup> This report describes “acute hemolysis and methemoglobinemia in G6PD deficiency” in a 59-year-old patient, with no additional information of plant part used or implementation, laboratory results, methemoglobin level and treatment. *Acalypha indica* is composed of various phytochemicals (Table 3) and nutrients which most of

them play a role in human therapeutic property.<sup>1</sup> On the other hand, previous studies have implicated three constituents found in leaf and the whole parts of this plant; quinine,<sup>15</sup> 2-methyl anthraquinone and tectoquinone<sup>16</sup> resulting in methemoglobinemia (Table 3). These constituents might have oxidative potentials. Oxidative chemicals may cause both acute hemolysis and methemoglobinemia.<sup>15–17</sup> Although this plant contains cyanogenic glycosides and hydrogen cyanide, no patient developed or demonstrated any signs/symptoms of cyanide poisoning.

Reportedly, most patients ingested cooked leaves,<sup>4–6</sup> except for one patient who ingested uncooked leaves.<sup>13</sup> In this study, patients consumed either a decoction or fresh juice. Hence, these phytochemicals might be heat stable. Moreover, ingestion patterns among countries, preparation methods, phytochemical contents, and concentrations in the *Acalypha indica* cultivars might contribute to the distinct findings. As doses were inadequately documented, no distinction was observed between the onset and duration of

**Table 3** Phytochemical Compounds in *Acalypha Indica*.<sup>1</sup>

Lists of Phytochemical Compound				
• Acaindinin	• Ellagic acid	• Phenol, 24 BIS (1,1-Dimethylethyl)	• Tannin	• 1H-Pyrrole-2,5-dione, 1-ethenyl
• Acalyphamide	• Flavonoid such as chrysin, hesperetin	• Potassium Brevifolin carboxylate	• Tectoquinone*	• 16 $\alpha$ , 17-dihydroxy-ent-kauran 19-oic acid
• Acetylgeraniin	• Flindersin	• Proline,3,4-didehydro-	• Triacetanamine	• 2-methyl anthraquinone*
• Aurantiamide	• Ferulic acid	• Quebrachitol	• Trimethyl[4-(1,1,3,3, Tetramethylbutyl) phenoxy] Silane	• 3,3'Methylene bis (4-hydroxyl coumarin)
• Caffeic acid	• Gallic acid	• Propanenitrile,3- (5-diethylamino-1-methyl-3-pentynyloxy)	• Tri-O-methylellagic acid	• 3,8-Nonadien-2-one, E
• Catechol	• Geranin	• Quinine*	• $\beta$ -sitosterol acetate	• -4,4',5,5',6,6' hexahydroxy diphenic acid
• Chebulagic acid	• Glucogallin	• Repandusinic acid	• $\beta$ -Sitosterol $\beta$ -D-glucoside	• 4-Amino-3-methoxy-pyrazolo[3,4-d] pyrimidine
• Clotrisiloxane, Hexamethyl-	• Hydrogen cyanide	• Resin	• $\gamma$ -Sitosterol	
• Corilagin	• Inositol methyl ether	• Stigmasterol	• $\gamma$ -Sitosterol acetate	
• Cyanogenic glucoside such as acalyphine, acalyphin amide	• Kaur-en-18-oic acid	• Succinimide	• 1,2,3,6-tetra-O-galloyl- $\beta$ -D-glucose	
• Cysteine	• N-methyl-3-cyanopyridones	• Syringic acid	• 1,3-Dioxolane,4-Ethyl-5-Octyl-2,2-Bis (Trifluoromethyl)-, Trans	

**Note:** \*These compounds are reported to cause methemoglobinemia in previous studies.<sup>15,16</sup>



symptoms between single and multiple ingestions, failing to support a dose–response relationship. Symptoms usually occurred within 24 hours of the last ingested dose.

Here, one out of eight patients died. The cause of death might be contributed by hemolysis, severe methemoglobinemia and his preexisting diseases. Hemolysis and methemoglobinemia could be a susceptibility factor that resulted in death, especially in elderly patients with pre-existing medical conditions. The main treatment of *Acalypha indica* toxicity was supportive care, while methylene blue might be considered in the patient who developed severe methemoglobinemia. To our knowledge, this is the first case series of patients with methemoglobinemia attributed to *Acalypha indica*.

This study had some limitations which can be listed as follows. First, it is not mandatory to report potentially adverse exposures from *Acalypha indica* to our poison center. Thus, not all exposures are reported, especially the negligible and mild cases. Second, this study was retrospective in nature together with data obtained from telephone consultations, such that it might have contained some incomplete data. Third, methemoglobin level was not measured and confirmed in all patients, especially during the patient had signs of methemoglobinemia. Therefore, we needed to rely on the saturation gap, response to oxygen therapy and/or cyanosis for diagnosis in these patients. Finally, there was no laboratory test performed to confirm the exact dose of ingestion or to exclude the adulterants causing these adverse events. In addition, we did not retrieve and analyse the biological samples from these patients.

## Conclusion

*Acalypha indica* is used as a herbal medicine in several countries, including Thailand, and can induce adverse effects, such as acute hemolysis. This study presents methemoglobinemia as the other toxicity caused by this plant. The responsible oxidizer might be heat stable. Further studies are needed to elucidate the etiology. Elderly patients with preexisting medical conditions might demonstrate poor outcomes. Public education could help prevent *Acalypha indica* poisoning cases.

## Disclosure

The authors report no conflicts of interest in this work.

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