**Review Article**


Clinical & pathological features of acute toxicity due to *Cassia occidentalis* in vertebrates

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_Cassia occidentalis_ is an annual shrub found in many countries including India. Although bovines and ovines do not eat it, parts of the plant are used in some traditional herbal medicines. Several animal studies have documented that fresh or dried beans are toxic. Ingestion of large amounts by grazing animals has caused serious illness and death. The toxic effects in large animals, rodents and chicken are on skeletal muscles, liver, kidney and heart. The predominant systems involved depend upon the animal species and the dose of the beans consumed. Brain functions are often affected. Gross lesions at necropsy consist of necrosis of skeletal muscle fibres and hepatic centrilobular necrosis; renal tubular necrosis is less frequent. Muscle and liver cell necrosis is reflected in biochemical abnormalities. The median lethal dose (LD₅₀) is 1 g/kg for mice and rats. Toxicity is attributed to various anthraquinones and their derivatives and alkaloids, but the specific toxins have not been identified. Data on human toxicity are extremely scarce. This review summarizes information available on _Cassia_ toxicity in animals and compares it with toxic features reported in children. The clinical spectrum and histopathology of _C. occidentalis_ poisoning in children resemble those of animal toxicity, affecting mainly hepatic, skeletal muscle and brain tissues. The case-fatality rate in acute severe poisoning is 75-80 per cent in children.

Key words Animal toxicity - *Cassia occidentalis* - poisoning

**Introduction**

An acute illness of young children, with brain involvement and high case-fatality, has been plaguing Saharanpur and several neighbouring districts in western Uttar Pradesh (UP) over the past two decades or more. It occurs in annual seasonal outbreaks and was earlier diagnosed presumptively as acute encephalitis of unknown viral aetiology. Recent studies have shown the illness to be an acute hepatomyoencephalopathy (HME) syndrome, caused by toxicity from a common weed, _Cassia occidentalis_. The illness develops in children within several hours after eating the beans of _C. occidentalis_. The exact toxin(s) involved are not known.

For definitive diagnosis of a toxic disease the toxin has to be identified. Unfortunately, toxicological investigations in children with this syndrome have not been possible. We have so far not been able to identify laboratories capable of and willing to investigate for detection and characterization of unspecified toxins. Although several toxicology laboratories were approached, none felt interested or confident to
identify specific toxins causing HME syndrome. Plants are notorious to contain multiple toxins and it will be quite arduous and expensive to attempt to identify the specific toxin(s) causing a specific syndrome.

In the absence of identified toxin(s) involved in HME, the aetiological association is based only on epidemiological and observational studies\(^4\)\(^8\). In order to enhance the strength of evidence for causally associating *C. occidentalis* with HME, biological plausibility of such association will be helpful. Fortunately a large body of information is available on clinical features and on tissue pathology of *Cassia* poisoning in animals, due to accidental poisoning as well as experimental studies.

**The weed: *Cassia occidentalis***

*General features:* The *Cassia* spp. (family: Fabaceaeae) are erect, lightly branched leguminous trees and shrubs. Cassia shrubs are usually 6 to 8 feet tall and are mostly annual, but some species are perennial. All *Cassia* spp. are toxic or poisonous, but *C. occidentalis* and *C. obtusifolia* are considered to be more toxic than others\(^9\),\(^10\).

*C. occidentalis* is found as a weed among various crops (Fig.). In Europe it is found in corn and soybean fields\(^9\). In India it is widely prevalent as an opportunist that grows along roadsides, fence lines and over heaps of waste material, in addition to agricultural fields\(^9\)-\(^11\). In Hindi, the weed is known as *Pamaad* (*Panwaad*) and *Kasondi*. *Pamaad* is actually the name of another similar-looking weed, *C. obtusifolia*, found less frequently than *Kasondi*. *C. obtusifolia* is less prolific in growth, flowering and podding\(^10\).

The leaves of *C. occidentalis* are alternate, compound and pinnate, consisting of four to five pairs of leaflets widely spaced along a common stalk. The leaflets are pointed at the tips, in contrast to the rounded leaflets of *C. obtusifolia*. The flowers are yellow and produced in loose clusters in the terminal leaf axils\(^9\)-\(^11\). In India the flowering time is after the heavy monsoon rains (after July)\(^10\). The fruits of the plant are in form of 'pods' - thin, flat, 3-4 inches long and pale green when tender, thick and dark green when mature. The podding time is from September to November\(^10\)-\(^11\). The pods are slightly curved and with paler longitudinal stripes along the edges. Each pod contains around 50-60 small beans (seeds) together weighing 1.9 to 2.25 g. Each bean is about the size of a cumin seed, but shorter. The tender beans are green, soft and juicy and taste like peas. From December onwards the pods start drying up, turn brown and the beans turn dark brown\(^10\).

In some poor countries the dried mature beans of *C. occidentalis* may be roasted and a “coffee” made out of it, hence the synonym *coffee senna*. Leaves are not toxic and in some places people cook and eat leaves\(^10\).

*Geographic distribution in India:* Though *C. occidentalis* is widely distributed all over the country, its density varies in different regions\(^10\). Apparently every Indian language has its own vernacular name for this plant – for example, in Kerala and Tamil Nadu it is known as *thakara* or *ponthakarai*. Since cattle, sheep or goats do not eat this plant people recognize it as an unwanted weed and regularly de-weed when it grows in agricultural fields. The weed’s density is particularly high in and around western UP, Uttarakhand, Haryana, and Punjab, where it grows luxuriantly in all available space, such as neglected gardens, roadsides and unused grounds of public buildings including hospitals\(^8\).

*Traditional medicinal uses:* The leaves and roots of *C. occidentalis* are used in some traditional herbal medicines, but its pods or beans are avoided, or used sparingly\(^10\),\(^12\). Such medicines are considered as
remedy for bacterial and fungal infections and are also shown to boost ‘immune function’\textsuperscript{12}. The leaves/roots are an ingredient of many popular herbal liver tonics and medicines for liver disorders. People use it also for the treatment of abscesses, insect bites, scorpion sting, constipation, diabetes, oedema, fever, inflammation, itch, rheumatism, ringworm, scabies, skin diseases, snakebite, and wounds\textsuperscript{12}.

**Animal toxicity**

**General features:** Several animal studies have demonstrated the toxicity of the fresh and / or dried / roasted beans (seeds)\textsuperscript{9,11,23}. Ingestion of large amounts of the seed pods by grazing animals has caused serious illness and death\textsuperscript{11,15,16}. Cattle, sheep, goats, horses, pigs, rabbits, and chickens have been shown to be susceptible to poisoning by *Cassia* spp.\textsuperscript{13,21}. Although all parts of the plant are toxic, most poisoning occurs when animals eat the pods and beans, or are fed green-chop containing *Cassia* plants\textsuperscript{22,23}.

The toxic effects are seen on skeletal muscles, liver, kidney and heart in animals\textsuperscript{11}. The acute toxic degeneration of liver and muscles can be rapidly fatal in most animals\textsuperscript{11}. Although clinical evidence of brain disease is often present, not much studies has been done on brain pathology.

One interesting attribute of *C. occidentalis* poisoning in animals is its propensity to cause different manifestations of toxicity in different animal species. However, the physiologic systems involved in toxicity depend also upon the dose of the beans consumed\textsuperscript{11}. When the dose is low, the animal develops features of mild liver damage and myodegeneration. At higher doses, hepatic degeneration may be rapidly fatal before myodegeneration has time to develop\textsuperscript{14,16,23,24}. Ground beans of *C. occidentalis* fed to cattle at a dose of 5.0 g/kg of their body weight induce severe muscle degeneration\textsuperscript{25}. Roasting of the beans partially reduces their toxicity such that goats fed 2.5 g/kg body weight of roasted beans were unaffected, whereas unroasted beans at this dosage were fatal\textsuperscript{18,19,22}.

*Cassia* poisoning in cattle may occur when 4.0 to 120.0 g/kg (0.4-12\%) of body weight of the green plant is eaten\textsuperscript{21,25,26}. At lower doses, it can cause diarrhoea and decreased weight gain\textsuperscript{22}. The plant is not very palatable and tends to reduce feed intake. As the amount of *Cassia* in the animal’s diet increases muscle degeneration becomes a predominant characteristic of the poisoning and cause of the clinical signs. Experimentally, high doses of the plant (10 g/kg body weight daily for 3 days) induce acute liver degeneration and death before myodegeneration has time to develop\textsuperscript{11,13}.

Apparently all toxic effects are acute and it is believed that the toxins do not accumulate in body tissues. However, when consumed repeatedly over time, the ill effects would be seen as chronic, but in fact it is the result of repeated acute poisoning due to the inclusion of *Cassia* vegetation in fresh green feed in stall fed animals.

**Clinical presentations in animals:** Lethargy, jerky respiration, tremor, ataxia, hyperpnea, diarrhoea, incoordination and recumbency are the usual manifestations of *cassia* toxicity in most animal species\textsuperscript{11}. In cattle a moderate to severe diarrhoea develops shortly after consumption of the plant\textsuperscript{22}. Abdominal pain, straining (tenesmus), and diarrhoea are thought to be due to the irritant effects of anthraquinones in *Cassia* spp. Depending on the amount of plant or seeds consumed, muscle degeneration begins after several days, causing weakness and recumbency\textsuperscript{15,16,28,29}. The urine may be coffee coloured due myoglobinuria from acute muscle degeneration\textsuperscript{13,27,30}. The levels of serum enzymes creatine kinase and aspartate transaminase are usually markedly elevated, reflecting acute muscle degeneration. Renal failure may develop secondarily to the myoglobinuria. In severe cases hepatic failure may be the predominant organ failure leading to death of the animal\textsuperscript{10}. Respiratory difficulty develops as a result of the degeneration of the intercostal and diaphragm muscles\textsuperscript{17}. Death may occur within 24-48 h after signs of acute illness and is almost inevitable in animals that become recumbent\textsuperscript{11}. In more prolonged sickness, cardiomyopathy and hyperkalemia from muscle degeneration cause cardiac irregularities and contribute to the death of the animal\textsuperscript{21,22,25}.

Horses may not exhibit the digestive and muscle degenerative signs of poisoning seen in cattle\textsuperscript{11,14}. Myoglobinuria may not develop in horses because they apparently succumb to liver degeneration sooner than to the degeneration of the musculature\textsuperscript{11}. Poisoned horses are severely ataxic and may die early without showing other clinical signs\textsuperscript{14}. Serum liver enzymes may be elevated reflecting acute liver degeneration\textsuperscript{11,14}.

**Postmortem lesions:** Gross lesions at postmortem examination consist primarily of pale skeletal muscles necrotic foci similar to those seen in ‘white muscle disease’ associated with selenium and vitamin E deficiency. Skeletal muscle necrosis and renal tubular
and hepatic centrilobular necrosis are characteristic histologic findings that differentiate *Cassia* poisoning from vitamin E and selenium deficiency.\textsuperscript{13,21,25} Confirmation of the diagnosis should be based on access to and consumption of *Cassia* spp. along with the presence of degenerative lesions in the muscles, heart, and liver.\textsuperscript{21,22,31}

**Experimental studies on animals:** Studies on rats\textsuperscript{32} and chickens\textsuperscript{33,34} fed a ration contaminated with *C. occidentalis* seeds at different doses had shown histopathological and biochemical changes in muscles, liver, and central nervous system. Barbosa-Ferreira et al.\textsuperscript{32} divided 40 male Wistar rats into four groups of 10 animals each, three of them respectively fed rations containing 1, 2 and 4 per cent *C. occidentalis* seeds, and the last one (control) fed commercial ration for a period of 2 wk. The rats of the experimental groups showed lethargy, weakness, recumbency, depression and emaciation. Histopathological study showed fiber degenerations in the skeletal (tibial, pectoral and diaphragm) and cardiac muscles. In the liver parenchyma, was observed vacuolar degeneration and, in the kidney, mild necrosis in the proximal convoluted tubules. All of these alterations occurred in a dose-dependent fashion. Moderate to severe degeneration and spongiosis was seen in the central nervous system, especially in cerebellum. Electron microscopy revealed mitochondrial lesions in all analyzed tissues.\textsuperscript{32}

Haraguchi et al.\textsuperscript{33} studied the effects of 0.5, 0.3 and 0.1 per cent w/w concentrations of *C. occidentalis* seeds mixed with commercial rations of 32 broiler chicks each, from 1 day to 49 days of age. All birds were killed at 49 days of age, and blood was collected from 10 birds in each group for biochemical studies. A complete necropsy was performed on 3 birds from each group. No significant differences in the biochemical parameters in the serum were found between the control and experimental chicks given 0.1 per cent of the beans. Birds treated with 0.5 per cent Cassia beans gained less weight than controls. Chicks that received 0.3 or 0.5 per cent *Cassia* beans developed degenerative changes in striated skeletal muscles, particularly pectoral, as well as in the myocardium and liver.\textsuperscript{33}

Flory et al.\textsuperscript{34} evaluated feed grains suspected of causing death in a group of pigs for toxic potential in chickens. The contaminated grain (sorghum mixture) was examined visually and was found to contain 3.7 per cent *C. occidentalis* and 1.6 per cent *C. obtusifolia* seeds, by weight. Chickens receiving the contaminated grain lost weight rapidly, exhibited clinical signs typical of intoxication with *Cassia* spp., and by day 16 were severely debilitated. Necropsy and histologic and electron microscopic examinations demonstrated a skeletal and cardiac degenerative myopathy consistent with toxic effects of *C. occidentalis*.\textsuperscript{34}

**Lethal dose in animals:** The toxicity of cassia seed-pods is dose-dependent. The time of appearance of illness and duration are inversely proportional to the dose.\textsuperscript{24} Animal experimental studies have calculated a lethal dose (LD\textsubscript{50}) of 1 g/kg for mice and rats when aqueous extract of the plant was injected intraperitoneally.\textsuperscript{15}

**Toxins and their actions:** Several compounds that bind strongly to cell membranes occur in *Cassia* spp., but the specific toxin(s) responsible for muscle degeneration have not been identified.\textsuperscript{13,36,36} While the exact toxic principles are yet to be defined, various anthraquinones and their derivatives like emodin glycosides, toxalbumins, and other alkaloids are usually blamed for *C. occidentalis* toxicity.\textsuperscript{9,12}

Originally it was thought to be due to uncoupling of oxidative phosphorylation in skeletal muscle mitochondria. However, this was disproved since mitochondrial damage was preceded by degeneration of myocardial fibers. The most recent theory indicates a high blockade of electron transport, rather than uncoupling of oxidative phosphorylation.\textsuperscript{24,36}

**Toxicity in humans**

**General features:** There is no definitive study on human toxicity of *C. occidentalis*. Only a few reports on human toxicity are available. According to one report, repetitive (prolonged) ingestion of a ‘health drink’ made from Senna extract (*C. acutifolia*—another herb of *Cassia* genus) resulted in severe hepatotoxicity in an adult.\textsuperscript{37} Another study mentions: “In humans, ingestion of *Cassia occidentalis* can cause severe purging. Whereas this may produce great discomfort and pain in adults, the result in a child can be death; hence, while consumption of few pods might not have any ill effect in an adult or older child, it can prove fatal for a young child”\textsuperscript{38} However, no further details are available on this count.

**Poisoning in children**

**Case scenario-1:** Three rural children of a join family of daily wages workers consumed beans of *C. occidentalis* weed while playing ‘kitchen game’ in the field where they cooked and consumed a ‘mock dish’. After six hours of consuming the ‘dish’, the eldest of them, 6 yr old female child started vomiting and developed...
drowsiness. Later, she became unconscious and died in the night after a brief illness without being attended by any doctor.

The second child of the group, a 4 yr old boy developed vomiting and fever next morning. The child was taken to Mangla Hospital, Bijnor, Uttar Pradesh. At the time of admission, the child was drowsy with frothing at mouth and up-rolled eyes, extremely irritable-biting, scratching cloths and body parts, protruding and moving his tongue and lips in a repetitive stereotyped manner, throwing his arms and legs in a jerky-fashion, but there was no frank seizures. The child was pale, non-icteric, B.P. was 88/33/56 mm of Hg, liver was just palpable, pupils were dilated but reacting to light, and ‘doll’s eye movements’ were preserved. On investigation, serum glucose was 15.5 mg per cent, hemoglobin-12.1 gm per cent, total leucocyte count (TLC) -3900/c.mm with 66 per cent polymorphs, platelet count-1.92 lacs/cmm, serum ALT-2030 U/L, AST-2160 U/L, serum bilirubin-2.4 mg/dl with direct-1.3 mg/dl, PT-18 sec (control-13 sec), PTT-76 sec (control-44 sec), serum CPK-246 U/L, serum LDH-245 U/L, serum creatinine-1.1 mg per cent, and CSF examination was normal. She was treated with intravenous fluids, IV vitamin K, frequent bowel washes, lactulose enema, phenobarbitone and other supportive therapy. During the course of treatment she developed high grade fever, myoclonic jerks, irregularity of respiration, decerebrate posturing, fluctuation of BP, and died after 64 h of admission.

The two other children (aged 4 and 6 yr old) who had also consumed cassia beans though in a smaller quantity, also developed symptoms of vomiting, loose stools, fever, malaise, giddiness, drowsiness, change in voice and behaviour, anorexia and signs of general weakness. Both of them were admitted for 24 h in the hospital and recovered completely after 3-4 days.

Young rural children aged 2-8 yr belonging to poor socio-economic strata seem to be particularly vulnerable to the poisoning of C. occidentalis. A history of eating beans of C. occidentalis pods is available only occasionally at the time of presentation as the actual incident is usually not witnessed by the parents and there is a considerable lag period (ranging from few hours to a day) between consumption of beans and onset of symptoms.

The clinical spectrum of C. occidentalis poisoning in children resembles toxicity induced by the plant in animals. The beans are the most toxic part of the plant and children tend to eat only the beans and no other part. As with animals, the clinical features depend upon the amount of beans eaten by the children. While consumption of the beans in 2-3 pods by a young child may not have any deleterious impact, a large ‘binge’ can lead to serious disease and death. Since some children eat very few beans and remain asymptomatic, people have a tendency to consider the beans as non-toxic. With a larger ‘dose’, such as the beans in 6-7 pods, they develop a non-fatal illness.
with vomiting, loose stools, malaise, giddiness, drowsiness, change in voice and behavior, anorexia and signs of general weakness. The body may be warm to touch, interpreted by many as fever, but whether or not oral or rectal temperature rises is not known. They usually recover after about 3-4 days of illness. The fatal hepatomyoencephalopathy syndrome ensues with relatively larger amount of beans - such as what would be equal to a handful in the cupped hand of a child - or a cupful in a toy cup.

The hepatomyoencephalopathy (HME) syndrome

The acute severe *C. occidentalis* poisoning in children affects multiple systems. Functional and biochemical evidences to show toxic effect on the brain, liver and striated muscles. Pathologically there is acute onset massive zonal necrosis of liver and histopathology evidence of acute muscle fibre degeneration. The degenerative changes in the brain are mild, but brain oedema is severe and is believed to be the immediate cause of death. Wide fluctuations of blood pressure and rise in CK-MB fraction (creatinine kinase - isoenzyme of cardiac muscle) of creatinephosphokinase (CPK) in some children point toward probable myocardial involvement.

In children, like in many animal species, massive hepatic damage predominate the clinical presentation with concurrent brain oedema without inflammation or CSF pleocytosis, which closely resembles Reye syndrome encephalopathy. Clinically there is extreme irritability, various degree of brain function depression ranging from mere confusion to decerebrate coma. Histopathologically, only mild spongiosis and gliosis without any inflammation have been reported. Involvement of the brain appears to be secondary to massive hepatic necrosis. Although liver enzymes are markedly raised, serum bilirubin level is usually normal and most children are non-icteric. Low serum and CSF glucose levels are frequent features and serum ammonia levels are raised in two-third cases. All these point towards acute and severe liver cell necrosis.

As Reye syndrome is a well known clinical diagnosis, and since liver enzymes are elevated in that disease as well as in HME, the latter was earlier mistaken for the former. In Reye syndrome there is intracellular microvesicular fatty acid accumulation without necrosis, while in HME the pathology was quite different, with massive, dose-dependent centrilobular necrosis - a feature seen consistently in many animal species upon necropsy. Raised CPK and lactic dehydrogenase (LDH) levels are the biochemical clues of muscle degeneration. Apart from myalgia and muscular twitching, clinical signs of myodegeneration are not very pronounced in ill children.

HME due to *Cassia* poisoning is a fatal disease in the majority, in spite of intensive care and supportive therapy. The case-fatality ratio is 75-80 per cent in children who became comatose. Most of them die within a few hours to a few days (varied from 1 to 7 days) of consumption of cassia beans.

**Summary and conclusions**

On comparing clinical presentation, biochemical alterations and histopathological changes of *Cassia* poisoning in children, the very close similarity, if not identical to toxicity described in animals can be appreciated. In different animal species, hepatic and skeletal muscles systems are mainly affected in a dose-dependent manner. In some animals, the myocardium is also affected. Brain function is affected due to acute hepatic encephalopathy.

The similarity of reported clinical, laboratory and histomorphological features of *Cassia* poisoning in animals and children along with a strong epidemiological association further strengthen the causal association of *C. occidentalis* poisoning with the acute hepatomyoencephalopathy syndrome in children.

Since the specific toxin(s) remain unidentified, the disease cannot be named according to aetiology. Therefore it has been named as a syndrome. The highly toxic nature of the putative phytotoxins present in *C. occidentalis* beans underlies the urgent need to launch massive educational campaigns to make people aware of the risk of children eating them. Children should be given adequate common facilities and opportunities for playing, especially in overcrowded communities. Pica has shown strong correlation with *C. occidentalis* consumption and needs to be diagnosed and treated in time. Long term measures are essential for improving economic conditions of marginalized families in the villages. Key to successful management of ecology ultimately lies in safe coexistence of human beings and all plants including toxic weeds, such as *C. occidentalis*. As a leguminous plant it is a nitrogen fixer in the soil and it needs not be targeted for total elimination.
References


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