The Tantalizing Toxins of Tantalus, A Brief Review of Select Natural Poisons of O‘ahu

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In the book *Micro*, Michael Crichton and Richard Preston describe natural ways to die on the island of O‘ahu. In particular, the authors describe a detailed process by which the main characters devise their own “curare” from the poisons of the *Strychnos nux-vomica*, yellow oleander, and chinaberry plants to defend themselves against wild creatures. Of course, this is adventure science fiction writing - meant to stir the imagination while using enough fact to make it believable - but the book does beg the question: how toxic are the flora and fauna of O‘ahu? The authors did substantial research (as evidenced by a thorough bibliography) and highlighted some of the toxic plants - native or introduced - of the Hawaiian Islands. But how much reality lies within the science fiction of the story? Do humans need to be worried about the toxicity from these natural sources? How important is it to consider exposure to natural toxins when evaluating patients with concerning symptoms? In a brief overview, this article focuses on some of those poisons that innocuously live alongside us in the Aloha State.

One of the oldest and most classic toxins, strychnine, comes from multiple sources, particularly *S. nux-vomica* - a dense, deciduous tree with orb-like berries and characteristically flat seeds that was introduced to the Hawaiian Islands by the first physician at Queen’s Medical Center, Dr. William Hillebrand. (Figure 1). The knowledge of this plant and its toxin date back long before Dr. Hillebrand brought it to Hawai‘i, and were likely the reason he included it in the botanical specimen collection he kept while living on the islands. The plant has long been used for its natural compounds in medicinal and nefarious ways, including in traditional Chinese medicine and in famous poisonings from the Victorian era. However, it was not until 1818, that the specific alkaloid now known as strychnine was isolated by the chemists Pierre Joseph Pelletier and Joseph Bienaimé Caventou, leading to a widespread use of the compound for pest control and medicine. Due to the alkaloid’s perceived stimulant effects, the extract of the “strychnine tree” was often cited as a useful cardiac, respiratory, and digestive stimulant, an antidote to barbiturates, and a treatment for opioid overdoses. Sports figures used it to obtain competitive advantage, including the winner of the 1904 Olympic Marathon who was accused of using an elixir of brandy and strychnine. Between 1926 and 1928, an estimated three Americans per week died from strychnine toxicity, either by accident or murderous intent. In 1932, it was the most common cause of childhood poisoning. Most recently, the toxin is an adulterant of recreational drugs, commonly used to lace or bulk cocaine, heroin, and amphetamines. The drugs remained on the market for many years. Even by 1946, when the organic chemist Sir Robert Robinson finally determined the structure of strychnine in his Nobel Prize-winning research on alkaloids, the true mechanism of strychnine was not fully understood.

![Figure 1. Strychnos nux-vomica Tree from Foster Botanical Garden (photo credit H. Keahi Mookini Horowitz)](image-url)
understood. Soon after Dr. Robinson’s discovery, Dr. Robert B. Woodward and colleagues received the 1954 Nobel Prize for their research on synthesizing strychnine, marking a giant step forward in synthetic chemistry and broadening the understanding of the compound. This new appreciation of strychnine eventually allowed for evaluation of its function. When ingested, inhaled, or otherwise introduced into the body, strychnine targets and inhibits the glycine receptors of the Renshaw interneurons of the nervous system. As a result, there is a loss of the normal inhibitory control performed by the Renshaw cells, leading to disinhibited and prolonged motor neuron activity. Within 15-30 minutes of ingestion, patients may subsequently develop the characteristic tetanic-like posturing (opisthotonos) in response to even minor stimuli. The repeated muscle excitation can lead to hyperthermia, muscle breakdown such as rhabdomyolysis, and even seizures. Death often results from respiratory failure secondary to spastic contraction of the respiratory muscles. Perhaps most alarmingly, the patient remains aware of all these symptoms as they progress. As such, it is important to control symptoms immediately with supportive care, benzodiazepines (often in high doses), and isolating the patient in a dark, low-stimulus environment, preferably in the intensive care unit. Given the risk for respiratory failure, there should be low threshold for sedation, intubation, and mechanical ventilation.

With regards to S. nux-vomica itself (unlike other sources of strychnine), the plant also contains brucine, which is structurally similar to strychnine and exerts similar effects. Thus, this apparently innocuous plant has two lethal toxins hidden in the berries and bark that can prolonging or worsening its toxicity. So, should a patient present with tetanic-like spasms, it is important to keep the differential diagnosis broad and inquire about recent exposures to or ingestions of this toxic plant.

The second toxic plant highlighted in the book is yellow oleander (Thevetia peruviana), a relatively common plant with a characteristic spiraling, trumpet-shaped yellow flower that is typically found in tropical regions and often cultivated as an ornamental shrub (Figure 2). Despite its attractive outward appearance, nearly every part of the plant contains thevetin, thevetoxin, and other naturally occurring cardiac glycosides. At one point in history, yellow oleander was utilized to treat heart failure, Hansen’s disease, malaria, ringworm, and indigestion. However, due to its significant gastrointestinal side effects (ie nausea and vomiting), its use gradually decreased, particularly as other drugs were introduced to the market. However, yellow oleander remained an important agricultural plant for pest control and has even been investigated for potential chemotherapeutic effects. Beyond its aesthetic appeal, yellow oleander is famous for its toxicity, especially for suicide and suicide attempts - a reputation that has garnered it the nickname of the “Be Still Tree” (Figure 3). From multiple reports, ingestion of even 8-10 seeds can be fatal, but most agree that
the amount of glycoside absorbed is widely variable based on how it is consumed and what part of the plant is ingested.\textsuperscript{12,13,15-17} Shortly after ingestion, patients start to experience gastric upset, nausea, vomiting, and then progress to weakness, cardiac dysrhythmias, possibly neurologic symptoms, and eventually death.\textsuperscript{12} Like digoxin (arguably the most well-known and most used cardiac glycoside), the toxins of yellow oleander act to competitively bind and inactivate sodium-potassium exchangers (Na/K ATPases) on muscle cells.\textsuperscript{18} This results in two main pathogenic pathways. First, the inhibition of sodium exchange results in increased intracellular sodium, activating a sodium-calcium exchange enzyme. Intracellular calcium then increases, leading to depolarization of the cell and activation of intracellular secondary messenger cascades. Gastric motility, cardiac conduction, and cardiac and other muscle contractility becomes quickly abnormal, resulting in the symptoms above. Second, the inhibition of potassium exchange results in hyperkalemia, hyperpolarizing muscle cells, leading to muscular weakness and cardiac dysrhythmias.\textsuperscript{12,18} Symptoms may start as soon as 3 hours after ingestion. Unfortunately, the patient’s symptoms may be so severe at initial presentation that they would be unable to provide any history of ingestion or exposure. Unless there is sufficient information, it is critical to suspect yellow oleander toxicity alongside digoxin toxicity in patients who come from areas where the plant is available and have signs and symptoms of cardiac glycoside toxicity. Treatment is largely supportive, with close attention to electrolyte abnormalities, cardiac dysrhythmias, and hemodynamic instability. Close cardiac monitoring is essential with particular attention to when to administer atropine in bradycardic and hypotensive patients and when to intervene on tachyarrhythmias, especially ventricular tachycardia.\textsuperscript{19} For this same reason, correction of hyperkalemia is potentially lifesaving. Digoxin immune Fab fragments can also be tried for toxic ingestions of oleander as there may be some cross reactivity.\textsuperscript{12,18}

Chinaberry (\textit{Melia azedarach}) is commonly used in traditional Chinese medicine as antiparasitic or antifungal and represents an uncommon cause of human toxicity. However, in Micro, it becomes an essential component of the curare the adventurers concoct to defend themselves in the wilderness on Tantalus.\textsuperscript{1} Meliatoxin from the fruit and toosendanin from the bark of the chinaberry tree are both limonoid tetranortriterpenes whose mechanism of action is still poorly understood but have known toxicity in many animals. Intoxicated animals often experience gastric upset, dry mouth, nausea, vomiting, and general agitation. However, in more extreme causes, more severe symptoms have been noted, including arrhythmias, hypotension, respiratory depression, cyanosis, blurred vision, perioral or extremity numbness, generalized weakness, inability to masticate and swallow, ataxia, loss of reflexes, seizures, and progression to respiratory arrest and death.\textsuperscript{19} Unfortunately, without a clear understanding of the toxic mechanism of action of this plant there has been no elucidated antidote, so supportive care remains the mainstay of therapy. Diagnosis relies heavily on history of exposure and ingestion, which may often be incidental given the bright and potentially enticing appearance of the fruit itself. Close monitoring for decomposition is important, but severe human toxicity is rare.\textsuperscript{19}

With equal parts work and imagination, the island of Oʻahu yields an impressive bounty of toxins, and, certainly the toxic compounds discussed above have clinical implications. As such, toxins should remain a consideration for clinicians encountering patients with any risk of exposure and self-harm attempts. The true clinical threat remains more science fiction than fact, as rates of ingestion and exposure to these toxins are infrequent. Still, one cannot deny the potential danger that lurks in the forests of Oʻahu, giving a whole new meaning to ʻmālama ʻāina (to care for the land).

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