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REVIEW

Bongkrekic Acid—a Review of a Lesser-Known Mitochondrial Toxin

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Abstract
Introduction Bongkrekic acid (BA) has a unique mechanism of toxicity among the mitochondrial toxins: it inhibits adenine nucleotide translocase (ANT) rather than the electron transport chain. Bongkrekic acid is produced by the bacterium *Burkholderia gladioli* pathovar *cocovenenans* (*B. cocovenenans*) which has been implicated in outbreaks of food-borne illness involving coconut- and corn-based products in Indonesia and China. Our objective was to summarize what is known about the epidemiology, exposure sources, toxicokinetics, pathophysiology, clinical presentation, and diagnosis and treatment of human BA poisoning.
Methods We searched MEDLINE (1946 to present), EMBASE (1947 to present), SCOPUS, The Indonesia Publication Index (http://id.portalgaruda.org/), ToxNet, book chapters, Google searches, Pro-MED alerts, and references from previously published journal articles. We identified a total of 109 references which were reviewed. Of those, 29 (26 %) had relevant information and were included. Bongkrekic acid is a heat-stable, highly unsaturated tricarboxylic fatty acid with a molecular weight of 486 kDa. Outbreaks have been reported from Indonesia, China, and more recently in Mozambique. Very little is known about the toxicokinetics of BA. Bongkrekic acid produces its toxic effects by inhibiting mitochondrial (ANT). ANT can also alter cellular apoptosis. Signs and symptoms in humans are similar to the clinical findings from other mitochondrial poisons, but they vary in severity and time course. Management of patients is symptomatic and supportive.
Conclusions Bongkrekic acid is a mitochondrial ANT toxin and is reported primarily in outbreaks of food-borne poisoning involving coconut and corn. It should be considered in outbreaks of food-borne illness when signs and symptoms manifest involving the liver, brain, and kidneys and when coconut- or corn-based foods are implicated.

Keywords Bongkrekic acid · Mitochondrial toxin · Bacterial toxin · Food-borne illness · *Burkholderia cocovenenans*

Background

Bongkrekic acid (BA), a little-known mitochondrial toxin produced by the bacterium *Burkholderia gladioli* pathovar (strain or set of strains with the same or similar characteristics that have been shown to be pathogenic to certain plants) *cocovenenans* (*B. cocovenenans*), has been implicated in various outbreaks of severe food-borne illness [1–12]. Human illness from BA exposure is reported from consumption of contaminated food, particularly fermented coconut tempe (a traditional food made of fermented coconut pulp) and corn products [13]. These outbreaks have occurred mainly in Indonesia and China [4]; however, one was recently reported in Mozambique [12]. *B. cocovenenans* proliferation and BA toxin production increases when these food products undergo incomplete fermentation. Bongkrekic acid is odorless and tasteless; affected food products can have a normal

The findings and conclusions in this article are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention or the Agency for Toxic Substances and Disease Registry.

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appearance, smell, and taste [5]. Published epidemiological and toxicological reports about outbreaks and human illness from BA are scarce.

Methods

We searched for references in MEDLINE (1946 to present), EMBASE (1947 to present), SCOPUS, The Indonesia Publication Index (http://id.portalgaruda.org/), Pro-MED alerts, and ToxNet. Our search terms were: ((bongkrek) OR flavotoxin) AND (cocovenenans OR (farinofermentans)). We manually searched reference lists of identified articles and performed Google searches for other online sources of information using the terms *Burkholderia gladioli*, *cocovenenans*, bongkrekic acid, *asam bongkrek*, flavotoxin, tempe bongkrek, fermented corn flour, *Tremella*, and diaojiangba (hanging syrup cake). Sources were reviewed and selected for inclusion if they contained biochemical, epidemiologic, toxicological, or clinical information. On manual review of the references from articles and book chapters, the most original articles were identified and included. Websites were used if they were referred to in Pro-MED alerts or were from established and reliable news sources. The single PowerPoint presentation was included from the Chinese Center for Disease Control and Prevention where they have experience with BA. Once we reviewed a source and extracted the pertinent information to answer questions in each section, we did not include other sources if it contained the same information.

Results

We identified 109 articles, five book chapters, four Pro-MED alerts, one PowerPoint presentation, and 12 websites using the search criteria listed in the Methods section. We included 18 articles, five book chapters, two Pro-MED alerts, one PowerPoint presentation, and three websites in this review.

Biochemistry

Bongkrekic acid is a heat-stable, highly unsaturated tricarboxylic fatty acid with a molecular weight of 486 kDa (Fig. 1) [14, 15]. It is thought to be a polyketide. Polyketides are biologically active secondary metabolites produced by bacteria, fungi, and plants to impart a survival advantage such as inhibiting the growth of other bacteria, fungi, viruses, parasites, or tumor cells. Doxycycline, erythromycin, and many other antibiotics are examples of polyketides [15].

The gram-negative, aerobic, rod shaped bacteria *B. cocovenenans* produces BA. *B. cocovenenans*, like other species in the *Burkholderia* genus, is ubiquitous in the soil and plants. The *Burkholderia* genus includes more than 60 species, but *B. cocovenenans* is the only pathovar thought to produce BA [13]. *B. cocovenenans* was originally thought to belong to the *Flavobacterium* and *Pseudomonas* genera, but genetic sequencing studies have confirmed its classification as a *Burkholderia* species [13].

B. cocovenenans and the other *B. gladioli* pathovars also produce toxoflavin, an electron carrier that generates hydrogen peroxide and subsequent toxicity related to free radical formation. Its toxicity is relatively mild and secondary to that of BA [13]. Early studies reported that *B. cocovenenans* may produce a toxin called flavotoxin A. Later studies confirmed it has the same molecular formula as BA and may be the same molecule as BA or be a BA metabolite [4, 16]. The authors of the original paper later state that they are the same molecule [17].

Epidemiology

Outbreaks to date have been reported in only two settings: in Indonesia, among people who eat tempe bongkrek, a traditional food made of coconut pulp fermented by *Rhizopus oligosporum* [18], and in China, among people who eat fermented corn flour products or *Tremella fuciformis* mushrooms (Table 1) [2].

Tempe bongkrek is a locally produced, inexpensive protein source in Java, Indonesia. It is made by pressing the coconut meat by-product from coconut milk or oil production into a cake that is then inoculated with *R. oligosporum* mold for fermentation [1]. The final product is sliced or cubed for frying or cooking in soup. If fermentation is incomplete, *B. cocovenenans* and BA can proliferate [1, 18]. Deaths from BA poisoning related to tempe bongkrek consumption were first reported in 1895 [18]. Since 1975, consumption of contaminated tempe bongkrek has resulted in almost 3000 cases of BA toxicity, including at least 150 deaths [13]. In

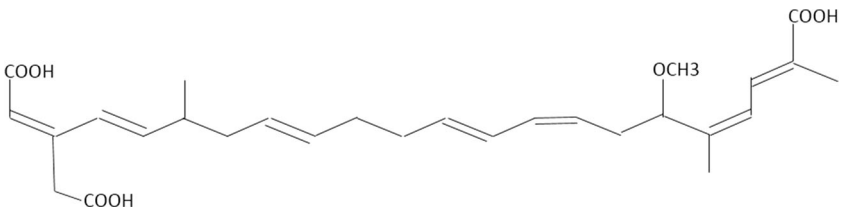

Fig. 1 Structure of bongkrekic acid

Table 1 Summary of outbreaks, year, number affected and fatalities related to bongkrekic acid poisoning [1–12]

Outbreak location	Year	Number affected	Deaths
Indonesia			
Java	1895	Unknown	Unknown
	1951–1975	7216	850
	1975	1036	125
	1977	400	70
	1983	450	42
	1988	200	14
Magelang regency	2007	30	10
Banjarnegara	2013	4	1
China			
Heilongjiang	1953–1974	665	288
Jilin	1956–1975	991	373
Liaoning	1959–1965	186	42
Northeastern China	1961–1979	327	105
Guangxi	1990–2006	121	76
Chengdu	2010–2014	47	16
Yunnan	2014	22	5

Indonesia, the reported mortality rate averages 60 % among those affected by BA toxicity [5]. After an outbreak in 1988, production of tempe bongkrek was banned, but production and occasional outbreaks continue to occur [1, 13].

In northeastern China, fermented corn products used to make breads, noodles, and dumplings appear to be the primary source of BA poisoning [2]. In southern China, diaojiangba (hanging syrup cake) has been linked to BA poisoning events [3]. In addition, half of the *Tremella fuciformis* mushrooms consumed in China and other Asian countries might be contaminated with *B. cocovenenans* possibly from the soil [2]. Outbreaks due to BA usually occur during warm summer months in both Indonesia and China.

In 2015, the first outbreak of BA toxicity outside of Asia was reported. An outbreak in 2015 in northwestern Mozambique killed 75 people and sickened many who drank pombe, a homemade, fermented corn flour-based beverage (Table 1) [12].

Exposure

Bongkrekic acid production depends on two distinct and sequential environmental conditions: those that support bacterial growth and proliferation, followed by those that favor BA production (Table 2). Bongkrekic acid is produced in warm environments (22–30 °C) with a neutral pH, the same conditions under which tempe is made [14]. Production is also dependent on the presence of fatty acids, particularly those found in coconut and corn [1]. Bacterial growth media containing oleic acid produced the highest concentrations of BA [1]. When *B. cocovenenans* is cultured on coconut medium under ideal conditions, toxin production can reach 2–4 mg/g by the second day of culture [4]. Lauric, myristic, and palmitic acids make up 71.5–74.5 % (by weight) of the fatty acids in coconut oil, and oleic acid can be found in varying concentrations in corn [1]. Interestingly, *R. oligosporum* has a suppressing effect on BA production and can reduce BA concentration when allowed to form adequate numbers of fungal colonies [4, 6, 7].

Toxicokinetics

There is scarce information on the toxicokinetics and lethal dose of BA in humans. One source suggests that 1–1.5 mg can be fatal in humans [14] and another suggests an oral LD_{50} of 3.16 mg/kg [20]. Studies on mice suggest an oral LD_{50} of 0.68–6.84 mg/kg [16] and an intravenous LD_{50} of 1.41 mg/kg [15]. Another study in rats showed that a 2 mg/100 g oral dose caused death within 2–5 h. In the same study, rats survived an initial 1 mg/100 g, but a repeat dose after 48 h caused death [21].

The absorption profile and volume of distribution for BA is unknown, although BA likely has a large volume of distribution because it is a highly unsaturated fat and is highly lipid soluble [22]. We do not know how BA is metabolized. Early studies reported Flavotoxin A (a toxin also thought to be found in *B. cocovenenans*) and BA to be the same organic chemical compound according to nuclear magnetic resonance spectra, ultraviolet spectra, molar extinction coefficients, and mass spectra [17], but more recent studies theorize that flavotoxin A is possibly a metabolite of BA [4]. The route of elimination of BA is unknown.

Pathophysiology

Bongkrekic acid produces its toxic effects by inhibiting mitochondrial adenine nucleotide translocase (ANT). Adenosine triphosphate (ATP) synthesized in the mitochondria is exchanged for cytosolic adenosine diphosphate (ADP) by ANT to provide a continuous supply of ADP to the mitochondrial matrix (Fig. 2). Adenine nucleotide translocase is one of the most abundant mitochondrial proteins, comprising up to 10 % of the protein of the mitochondrion's inner membrane [23]. There are three isoforms of ANT found in humans and they occur to differing extents in the heart, skeletal muscle, fibroblasts, and liver [24]. It plays a role in coordinated (apoptosis) and uncoordinated (necrotic) cell death by becoming a part of a lethal pore in the mitochondrial membrane called the mitochondrial permeability transition pore (MPTP). The MPTP is a protein-based channel that regulates

Table 2 Optimal conditions for proliferation of *B. cocovenenans* and bongkrekic acid toxin production

Factor	*B. cocovenenans*	Bongkrekic acid
Temperature	30–37 °C [4]	22–30 °C [1]
pH	>5.5 [14]	6.5–8.0 [1, 7]
NaCl	<6 % [6, 19]	<1.5–2 % [6, 7]
Lipid type	Glycerol, oleic acid, coconut fat concentration <10 % [1, 7]	Glycerol, oleic acid, lauric acid, myristic acid, palmitic acid, coconut fat concentration 20–50 % [1]

the permeability of the mitochondrial membrane. Proteins, lipids, ions, pro-oxidants, and chemotherapeutic agents can all directly modulate the pore-forming activity of ANT [23, 24]. BA and its laboratory synthesized derivatives (with varying functional groups) have become tools in the study of apoptosis mechanisms, appearing in more than 700 publications [25].

In the earliest studies investigating the cellular pathophysiology of BA, Welling et al. showed dose-dependent decreases in glucose content and cellular oxygen uptake in sheep heart tissue, along with lactate accumulation and acidosis [21]. These findings led them to hypothesize that BA inhibits mitochondrial enzymes. Later research demonstrated that BA is a specific ligand for ANT, and inhibits the translocase by freezing ANT in its "m" (matrix-oriented) conformation [15, 23]. Just 1 μmol of BA per 1 mg of mitochondrial protein is sufficient to block phosphorylation of ADP completely [26]. About 10 μmol of BA per 1 mg of mitochondrial protein at 6 mmol ATP is required to block hydrolysis of ATP completely [26]. Other natural toxins that also inhibit ANT include atractyloside, apoatractyloside, apocarboxyatractyloside, epiatractyloside, carboxyatractyloside, aryl azido atractyloside, *n*-ethyl maleimide, agaric acid, and isobongkrekic acid [27].

Clinical Presentation

The latency period after exposure to BA-contaminated foods is reported to be 1–10 h [4, 13]. The primary target organs are the liver, brain, and kidneys [20]. Signs and symptoms in humans are similar to the clinical findings from other mitochondrial poisons, but they vary in severity and time course. Reported symptoms include malaise, dizziness, somnolence, excessive sweating, palpitations, abdominal pain, vomiting, diarrhea, hematochezia oliguria, hematuria, and urinary retention. Findings during patient examination include hypotension, arrhythmias, hyperthermia, icterus, jaundice, and rigidity of extremities, Cheyne-Stokes respirations, pulmonary rales, lethargy, delirium, shock, coma, and death [2, 4, 14]. Among fatalities, death can occur 1–20 h after the onset of signs and symptoms [4]. Mortality rates from past outbreaks are 40 % in China [20] and average around 60 % in Indonesia [5]. Laboratory abnormalities include an initial hyperglycemia

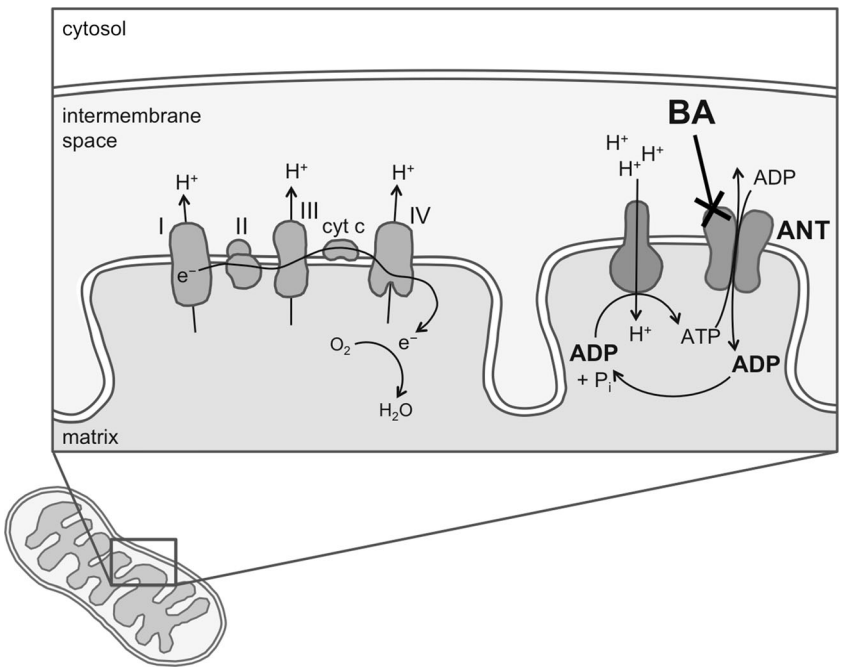

Fig. 2 Illustration of bongkrekic acid site of action showing inhibition of adenine nucleotide translocase in the mitochondrial matrix membrane

followed by hypoglycemia, abnormal liver function tests, normal red blood cell count and hemoglobin, and an increase in white blood cell count [2].

Data from animal studies show a variable timeline in the development of signs, symptoms and death. In one study, dogs fed contaminated food displayed restlessness, vomiting, hind leg paralysis, colonic spasms, coma, heart failure, respiratory paralysis, and death within 2–3 h [2]. In another study, dogs and rhesus monkeys fed *B. cocovenenans* culture supernatants died within 6–33 h and 15.5–35 h, respectively [6]. Mice died within 45 min when fed BA [5]. Test animals did not die when fed organs of animals poisoned with contaminated food [4].

Autopsies performed on three persons who died from a BA outbreak in China showed findings consistent with multi-organ failure and diffuse cellular dysfunction (Table 3).

Diagnostic Testing

Detecting *B. cocovenenans* and BA can be difficult and unreliable. *B. cocovenenans* has been isolated from contaminated food and vomit [8]. It can be identified using commercial test kits such as the Biologic GN2 System [13]. The most commonly used method for *B. cocovenenans* identification is 16S rDNA sequencing, but it can sometimes falsely identify other *Burkholderia* pathovars for *B. cocovenenans* [13].

Table 3 Reported autopsy findings from outbreaks of BA poisoning in China [2]

Organ	Macropathology	Micropathology
Liver	Glossless, hemorrhages on surface	Centrilobular necrosis, swelling, fatty degeneration
Kidney	Enlargement, adipose hemorrhage, thick cortex, medullar hyperemia, surface hemorrhage	Proximal and distal convoluted tubule cell disruption, granular and hyaline casts
Brain	Pia-arachnoid hyperemia, edema, herniation	Neuron degeneration, cerebellar necrosis
Heart	Left sided enlargement and dilation, hemorrhage on endocardium and epicardium	Swelling/hypertrophy of the myocardium, vacuolation, granular degeneration, nuclear damage
Lung	Pleural hemorrhage, hyperemia, edema, atelectasis	Expanded alveoli with red blood cells, monocytes, phagocytes, and leukocytes
Gastrointestinal	Lymphadenectasis, microhemorrhage, stomach dilation, incomplete mucous membranes	Edema, hemorrhage, necrosis
Spleen	Swelling	Stasis

B. cocovenenans can be identified using capillary electrophoresis-single strand conformation polymorphisms (CE-SSCP), microarray analysis, or probe-based cell fishing. The most reliable method might be the multiplex PCR protocol [13]. *B. cocovenenans* was isolated from lymphoadenoid and lung tissue from a man in Thailand and identified by 16s rDNA sequencing [13]. We found no other reports of *B. cocovenenans* isolation and detection from biological media.

We could not locate any published reports of testing biological media for BA, but the presence and quantification of BA in environmental samples can be tested using liquid thin layer chromatography, chromatography-mass spectroscopy, and high-pressure liquid chromatography [16, 20, 21].

Management

Standardized guidelines for treatment of BA-poisoned persons do not exist. Management of patients is symptomatic and supportive. Treatment strategies may be extrapolated from recommendations for treatment of other mitochondrial toxins, such as carbon monoxide, cyanide, and hydrogen sulfide. However, antidotes used for other mitochondrial toxins (e.g., hydroxocobalamin, nitrites, or sodium thiosulfate) are not expected to have any significant benefit based on their different mechanism of toxicity and antidotal action. Dextrose might be helpful for patients who develop hypoglycemia, although it has not been reported to reduce mortality [13]. We expect that the volume of distribution of BA is likely too large to be amenable to extracorporeal removal, such as hemodialysis; however, hemodialysis should still be considered in the setting of renal failure to support organ function.

Discussion

Bongkrekic acid has a unique mechanism of toxicity among the mitochondrial toxins: it inhibits ANT rather than the electron transport chain. Much remains unknown about BA's pharmacokinetics. The limited data regarding the LD_{50} in animals cannot be extrapolated to humans or other species. Bongkrekic acid produces overt clinical toxicity similar to those of other mitochondrial toxins, although on a different timeline (delayed compared to agents like cyanide, which can cause illness within seconds to minutes). A high reported mortality rate may be due to difficulty accessing medical care in rural areas where outbreaks occurred and possibly due to limited resources in delivering the quality of supportive critical care necessary for treatment. Medical toxicologists should be aware of its existence for possible inclusion in the differential diagnosis of food-borne illnesses. Although illness from BA has not been reported outside of Asia until recently, this does not exclude the presence of BA-associated illness in

other parts of the world. It is unclear why it has not been detected in other parts of the world previously as *Burkholderia* and possibly *B. cocovenenans* is ubiquitous in soil [1, 13]. A lack of confirmatory testing capacity for detection of the bacteria or BA or a failure to consider the diagnosis could be contributing to misdiagnosis.

Bongkrekic acid poisoning appears to be somewhat rare, but it can significantly affect public health in those areas where fermented coconut or corn products serve as inexpensive sources of protein among largely food-insecure populations. Interventions aimed at exposure prevention and safer fermentation processes should be emphasized. Foods contaminated with BA can look, smell, and taste the same as non-contaminated foods [7], and no reliable, commercially available method of screening food products for *B. cocovenenans*, BA, or toxoflavin is available. Historically, prevention measures largely focused on discouraging the production and consumption of high-risk fermented foods. In spite of a ban on tempe bongkrek production in Indonesia, outbreaks have continued to occur [5]. Because *B. cocovenenans* is ubiquitous in soil [1], other prevention strategies may focus on inhibiting bacterial growth or toxin production. The risk for *B. cocovenenans* contamination might be decreased by using good sanitation measures throughout the production process [5, 11] and promoting conditions that favor fermentation [16]. Acidifying the fermentation environment or adding salt appears to decrease toxin formation [6]. This might, however, cause unacceptable changes to the appearance or taste of a fermented food product [7].

Conclusion

Bongkrekic acid poisoning should be considered as a possible etiology in food-borne outbreaks related to fermented coconut or corn products. This illness may be misdiagnosed for a variety of reasons including a lack of confirmatory testing capacity and/or failure to consider the diagnosis due to a lack of knowledge about it. Further work defining prevention messages, diagnostics, and potential treatment strategies is needed.

Compliance with Ethical Standards

Conflicts of Interest No conflict of interest to disclose.

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