

## MINI-REVIEW

# KAMBÔ: an Amazonian enigma

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### ABSTRACT

The secretions of the Giant Monkey Frog *Phyllomedusa bicolor* are used by populations in the Amazon regions (mainly the indigenous Katukinas and Kaxinawás). The so-called “toad vaccine” or “kambô” is applied as a medication for infections and to prevent diseases, and also as physical and mental invigorator, and analgesic. Since the 1980s, researchers and companies have been interested in the composition of these secretions. Phyllomedusin, phyllokinin, caerulein and sauvagine are the polypeptides in these secretions that can cause intense effects on smooth muscles, vessels provoking, nausea and vomiting, arterial hypotension, flushing, palpitations, nausea, vomiting, bile secretion and angioedema. These actions are similar to bradykinin. However, the feeling of well-being and improvement of motor skills described by the users seems to be associated with dermorphine, caerulein or deltorphin – peptides with analgesic properties – and their affinity for the opiate receptor systems. Caerulein is a peptide that increases digestive secretions. Phyllomedusin and Phyllokinin lead to blood pressure and digestive effects. Sauvagine release corticotropin and mimics the physiological reactions of exposure to stress. Deltorphins and dermorphins have high affinity for the opiate receptor system and can lead to analgesia. The fame acquired by the therapy motivated the use by individuals from urban areas worldwide, without safety considerations. While in indigenous communities, there is an entire cultural tradition that provides relative safety to the application, however, the extension of use to individuals from urban areas worldwide is a problem, with reports of severe adverse effects and deaths. Undoubtedly, the skin secretions of the *Phyllomedusa* genus contain substances of intense pharmacological action and that can lead to research for therapeutic uses, but control over their application in rituals outside the forest is needed due to the risks presented.

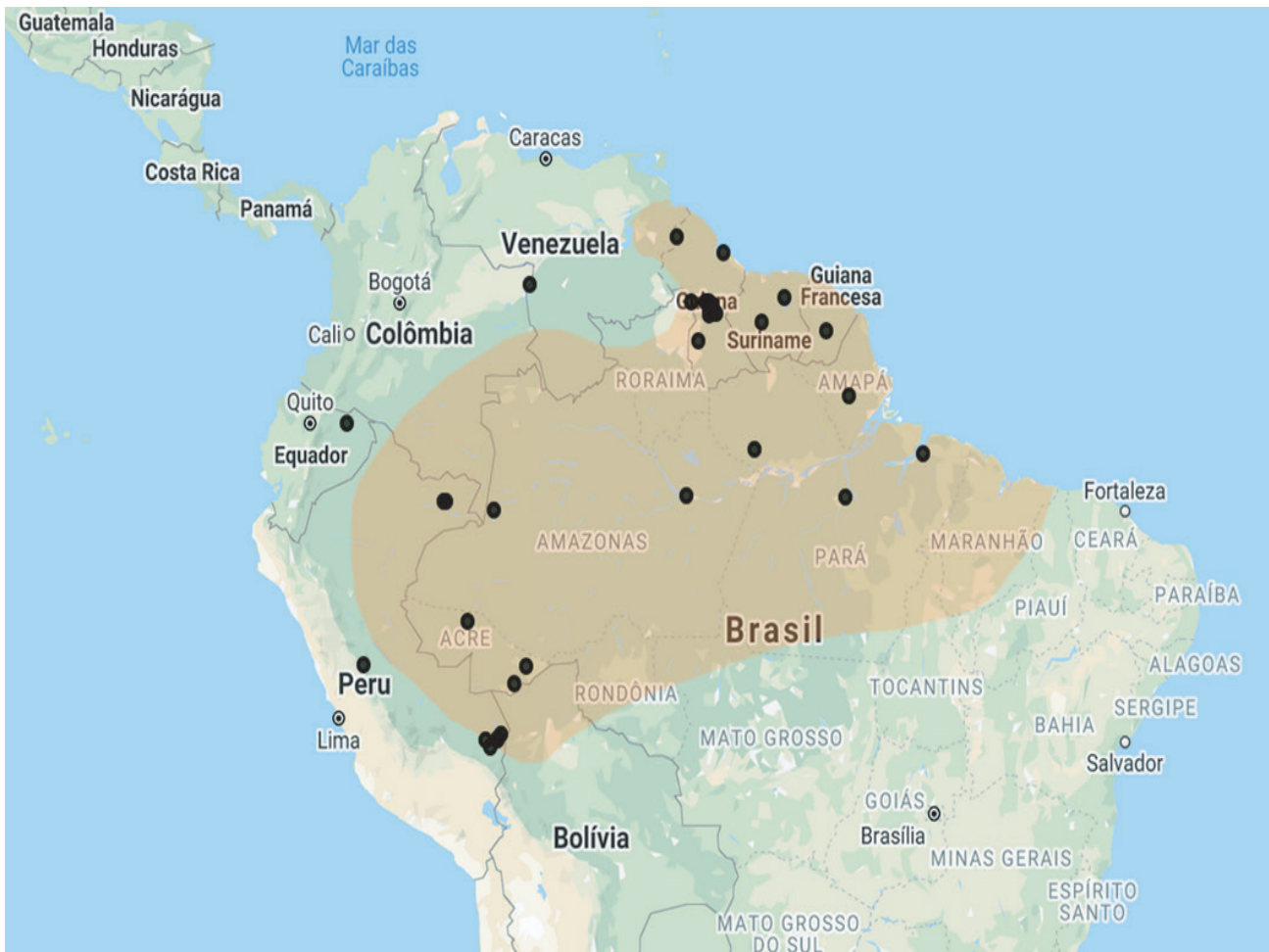
**KEYWORDS:** Frog venoms, amphibians, indigenous medicine, pharmacological and toxicological phenomena, toxinology

### INTRODUCTION

Toads, frogs and tree frogs are animals present in the folklore and culture of almost all places where they exist. Although they are associated with rainfall and fertility, part of this presence is associated with the fact that they produce or accumulate toxic substances, capable of promoting their defense and causing serious poisoning in predators. Toad poisons most often cause manifestations similar to digitalis poisoning, being represented in the Mayan, Chinese and Vietnamese cultures, in addition to playing an important role

in Europe in the Middle Ages, where they were associated with potions and recipes from alchemists and witches. In Brazil, the muiraquitã is an amulet of a green stone shaped like a frog or toad that is found in watercourses and is considered to bring luck to those who find it. The kambô, which also is a green tree frog, is associated with healing rituals in the Amazon rainforest, rituals that have spread to urban centers around the world.

An old legend from the Amazon region says that once many Indians from the village of Kaxinauá once got seriously ill



**Figure 1.** Geographic distribution of *Phyllomedusa bicolor* in the Amazonian basin. Map BerkeleyMapper/AmphibiaWeb. 2020. <<http://amphibiaweb.org>> University of California, Berkely, CA, USA.

and the shaman was unable to do anything to cure them with the herbal medications. In one of his rituals using ayahuasca, the shaman received a message to enter the forest and there he found a deity holding a green frog. The shaman was shown how to shave the frog's back and remove a whitish secretion, which should be applied to patients. The shaman used these secretions successfully and since it became a routine in the Kaxinauá and many other tribes. The different names for this treatment in the various tribes include kambô in Katuquinas, 'kambu in Kaxinawás, and kampu or kempô in other tribes. (Lima et al, 2006; Venâncio and Melo-Sampaio, 2010).

The tree frog *Phyllomedusa bicolor* is a species of Amazonian tree frog belonging to the family Phyllomedusidae, which has eight genera: *Agalychnis* (14 spp.); *Callimedusa* (6 spp.); *Cruziophyla* (3 spp.); *Hylomantis* (2 spp.); *Phasmahyla* (8 spp.); *Phrynomedusa* (6 spp.); *Phyllomedusa* (16 spp.); *Pithecopus* (11 spp.). The *Phyllomedusa* genus, as well as others in this family, arouses great interest in the substances that it secretes in the skin for its defense. The *P. bicolor* or Giant Monkey Frog secretions are considered medicinal, being used routinely by indigenous populations in Amazon regions (Lima et al, 2006; Venâncio and Melo-Sampaio, 2010). *P. bicolor* can be found in the Amazon region of Brazil, Colombia, Bolivia, Peru, Venezuela and Guianas; It has also been reported in eastern Ecuador and

somewhat more rarely in the cerrado region or savannah-like area (Lima et al, 2006; Venâncio and Melo-Sampaio, 2010) (Figure 1).

Specimens of *P. bicolor* have a large body size (SVL: snout-vent length), the males with SVL 91-103mm and the females with SVL 111-119mm. The dorsum is dark green and the belly varies from white to yellow-white or cream. There are sparse white spots with dark frames on the lower lips, chest and front legs, and these are more dense on the flanks and hind legs. Fingers are transparent brown with large green adhesive discs. A prominent gland extends from behind the eye over the tympanum (Figure 2). The species is arboreal and nocturnal. Males usually call from high trees, and descend with the female to construct nests of 1- 3 meter above ponds. Reproduction occurs throughout the year in ponds near to, or far from streams, with a peak from November to May (rainy season) (Lima et al, 2006; Venâncio and Melo-Sampaio, 2010). The animals vocalize to demarcate territory at the time of mating when they are captured to extract skin secretions. The indigenous Amazonian ethnic groups Katukinas and Kaxinawás use as a medication for infections and as a physical and mental invigorator the so-called "toad vaccine", which has the names of kambô or kempô. This medication is obtained by the natives of these ethnic groups and some others indigenous communities by extracting and applying



**Figure 2.** *Phyllomedusa bicolor*, the tree frog kambô. Photo by: Marcelo Menin – Amazonia Federal University, Amazonas State, Brazil.

cutaneous secretions from the tree frog *P. bicolor* and from some other species (in lesser quantities) in order to obtain analgesic and antibiotic effects. This also gives the application a preventive character of diseases, according their culture. The white or yellowish secretion extracted from the back of the batrachians is dehydrated and reduced to a paste (or “vaccine”), which is applied to the skin and quickly absorbed by the body. The name kambô is used in general for the tree frog that provides the secretion, for the obtained secretion and for the method of inoculation of the substances in humans, in addition to denominating the ritual itself. The method is widely used by these indigenous communities, which credit the secretions of the eliminating of bodily impurities, the property of preventing illnesses and physical and psychic stimuli (increase of mood and elimination of “panema” or suffering of the mind) (Lima, 2005; Lima and Labate, 2007).

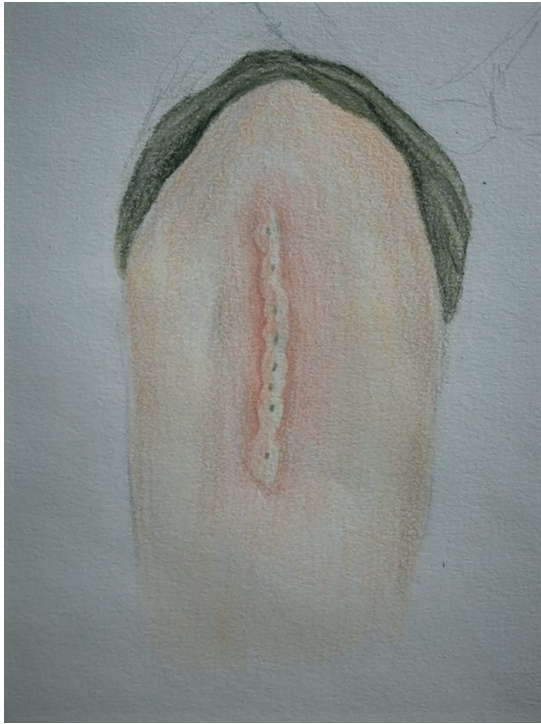
## TOXINOLOGY

Since the 1980s, several researchers and companies have been interested in the active ingredients present in the cutaneous secretion of *P. bicolor* and other species of the genus. Phyllomedusin, phyllokinin, caerulein and sauvagine are polypeptides cause intense effects in smooth muscles vessels: nausea, vomiting, arterial hypotension, flushing, palpitations, nausea, vomiting, bile secretion and angioedema. The actions of them are similar to bradykinin. However, the feeling of well-being and improvement of motor skills described by the users seems to be associated to the dermorphine, caerulein or deltorphin, peptides with analgesic properties and affinity for the opiate receptor systems. Caerulein is a peptide that increasing digestive secretions. Phyllomedusin and Phyllokinin lead to blood pressure and digestive effects. Sauvagine release corticotropin and mimics the physiological reactions of exposure to stress. Deltorphins and dermorphins

have high affinity to the opiate receptor system and can lead to analgesia (Tokuyama et al, 1969; Daly et al, 1992, Negri et al, 1992; Daly et al, 1993; Lacombe et al, 2000; Leite et al, 2005). The fame acquired by the therapy motivated the application of the secretion by individuals from urban areas in other regions of the country and worldwide, initially without any control and with the risks inherent to the use of several pharmacologically active substances.

With the dissemination and intense and little-proven application of therapy, ANVISA (National Health Surveillance Agency of Brazil) prohibited any form of use, trade, distribution or advertising of kambô as a medicine outside the villages (Resolution - RE nº 8), situation that currently stands (Lima and Labate, 2008). The illegal removal of secretions and frogs from villages and the country can be detected by a specific test (MALDI-TOF), developed by the Federal Police of Acre State, Brazil (Gomes et al, 2013).

The tree frog is identified by its vocalization in the trees. When captured, it is immobilized and has their poisonous secretion scraped from the back with a stick. The frog is later released. The secretion is applied on the arm of male individuals and on the calves of women. The shaman makes small punctual burns in sequence with the tip of a stick or incandescent vine (“titica”) and these serial and sequential inoculations are the entrance to the secretion, already hydrated again, which increases its viscosity and gives it an aspect of paste. This paste is applied in the exulcerations caused by the burns (Figure 3). The dose depends on the shamans and the patient. These healers themselves warn of the misuse of kambô, which in inexperienced hands can cause serious problems. With the potent actions of the substances demonstrated, it seems clear that use outside the tribes is very dangerous (den Brave et al, 2014; Hesselink, 2018; Labate and Lima, 2020).



**Figure 3.** Sequential perforations in the arm of a kambô practitioner after the applying the poison in the form of paste. Illustration by Ariadne Mendes V Haddad.

### CLINICAL ASPECTS AND CASE REPORTS

Numerous clinical effects are presented by the recipients of kambô. The initial state after application of the secretion is described as euphoric and happens fairly quickly. Together, a feeling of warming of the body is described. This is also accompanied by nausea, vomiting, diarrhea and swelling of the face (especially periorbital), probably linked to vasodilation. After 30-40 minutes, the user returns to normality, reporting a feeling of well-being and security. However, adverse reactions after its use have also been reported in several cases, some of which are described below:

In 2008, a 52-year-old trader, out of the four people receiving this treatment, died at a businessman's home after receiving kambô. The 'toad vaccine' in this case had been brought from the state of Acre (den Brave et al, 2014; Hesselink, 2018; Labate and Lima, 2020). Another reported death of a 42-year-old man, chronic consumer of Kambô, found dead near a small box labeled 'Kambô sticks' is likely to have been caused due to kambô. The individual had no history of any diseases and the toxicological screening was negative for ethanol and other drugs. Phyllocaerulein, phyllokinin, and deltorphin A were isolated from the Kambô sticks but, only deltorphin A was detected in his blood sample. (Aquila et al, 2018). Leban and colleagues (2016) reported a 44-year-old woman from Slovenia who used the dried skin secretion from *P. bicolor* in five points at her shoulder. She developed nausea and vomiting, confusion, lethargy, muscle weakness, spasms and cramps, seizure, decreased consciousness level and short-term memory loss. The initial laboratory tests showed profound plasma hypoosmolality, (251mOsm/kg) proportional to hyponatremia (116mmol/l), combined with inappropriately elevated urine osmolality (523mOsm/kg)

and high urine sodium concentration (87mmol/l), indicating a syndrome of inappropriate antidiuretic hormone secretion. Plasma osmolality and hyponatremia improved one day after exposure to the secretions (Leban et al, 2016). In another case, there was an association between liver damage and a ritual of Kambô in a 34-year-old man that was admitted to hospital due to icterus, skin itching, weakness, and pain in the upper abdomen. The patient had not previously consumed a significant amount of alcohol, but had performed the ritual of Kambô, using poison from *P. bicolor* to maintain abstinence of drinking, smoking, and with the aim to 'purify his body'. It seems that often damage to the liver occurs after activation of the various peptides and organic compounds in medicaments used in natural medicine (Pogorzelska and Lapinski, 2017). Yet another report of adverse effects occurred in a 32-year-old female with severe protracted vomiting after the application of the Kambô 'vaccine', with a degree of hyponatremia of 116mmol/l, which is severe enough to cause a seizure. The authors commented that the peptides dermorphin and deltorphin act as agonists of the  $\mu$ - and  $\delta$ -opioid receptors, respectively, which may result in symptoms of opioid toxicity and the opioid-mediated stimulation of the chemoreceptor trigger zone has been shown to induce nausea and vomiting (Kumachev et al, 2018). Li et al (2018) reported a patient who was attended in an emergency department with prolonged symptoms of vomiting, flushing, facial swelling, altered mental status, and intense agitation requiring chemical restraints, twenty-two hours after a Kambô ritual, which configures a prolonged time of the poison's actions, a fact not commonly observed in the ritual (Li et al, 2018). In 2018, Roy et al described a 33-year-old Caucasian female, who was brought to the local emergency room by the police with signals of psychosis. She had no significant psychiatric history prior to this incident and she claimed that she uses the kambô toxin up to nine times per month. She presented with characteristics of paranoia, anxiety, bizarre delusions, labile mood, and panic attacks. As part of her treatment plan, the patient was started on risperidone and she gradually improved after nine days in the hospital psychiatry unit (Roy et al, 2018).

In addition to the clinical implications, the use of toad vaccine also poses problems for the law-enforcement authorities; since such products are sold as natural products, the users consider them as safe to consume, while in reality these may lead to serious and harmful effects on the user, and even death. (Folha de São Paulo Agency, 2008; Menocchi, 2008). "There is no research that ensures the use of the toad vaccine for the aforementioned indications; therefore, the patient who consumes the product is subject to serious and unknown health problems", says the Anvisa ordinance, published on 30<sup>th</sup> April, 2004. Technical advice of Anvisa and the sanitary legislation further preaches that any input that you are not aware of the origin of, and which has no guarantee of therapeutic efficacy, the recommendation is that it should not be used.

### CONCLUSIONS

Although widespread, the habit of using the 'kambô' does not yet have safe methods of application, which can result in serious health risks for the users. There is an entire

cultural tradition in indigenous communities that provides relative safety to its application, but the extension of its use to urban areas worldwide, without previous profound knowledge of the applicators, has been increasing resulting in serious side effects, including deaths. Undoubtedly, the skin secretions of the *Phyllomedusa* genus contain substances of intense pharmacological action and that may have therapeutic potential, but the control over their application in rituals outside the indigenous settings is needed due to the intense risk posed by their use.

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## COMPETING INTERESTS

None declared.

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