Cobra Venom

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Cobras (genus *Naja*) are widely distributed over Asia and Africa, and cobra envenomation is responsible for a large number of mortality and morbidity on these continents. Like other elapid venoms, cobra venoms are neurotoxic in nature; however, they also exhibit local cytotoxic effects at the envenomed site, and the extent of cytotoxicity may vary from species to species. Cobra venoms are predominated by the non-enzymatic three-finger toxin family which constitutes about 60-75% of the total venom. Cytotoxins (CTXs), an essential class of the non-enzymatic three-finger toxin family, are ubiquitously present in cobra venoms. These low-molecular-mass toxins, contributing to about 40 to 60% of the cobra venom proteome, play a significant role in cobra venom-induced toxicity, more prominently in dermonecrosis (local effects).

membrane perturbations necrosis cobra venom antivenom neutralization

1. Epidemiology of Cobra Bites in the World

Snake envenoming is a devastating health issue that affects millions of individuals across the globe, particularly in the developing countries of tropical and subtropical regions. Global epidemiological data suggest 81,000–138,000 snakebite-associated deaths from 1.8–2.7 million cases of envenoming yearly, thereby highlighting the urgency of research into this neglected public health concern [1][2]. Moreover, region-wise distribution of snakebite data suggests most of the cases of snake envenoming are concentrated in the rural areas of South Asia, Southeast Asia, and East Sub-Saharan African countries [3].

The majority of the medically critical venomous species of snakes belong to the Viperidae (340 species), Elapidae (360 species), and Atractaspidae (69 species) families [4]. Accordingly, the World Health Organization (WHO) has recognized venomous snakes under categories 1 and 2 depending upon their distribution, venom lethality, and incidences of envenoming and deaths. Category 1 medically essential species are of the highest medical importance, and the WHO has recognized at least 109 species under this category. Furthermore, it has been observed that most medically relevant species are represented by only a few genera. For instance, about 25 Category 1 medically important snake species in Africa belong to only five genera—*Naja*, *Dendroaspis*, *Echis*, *Bitis*, and *Cerastes* [5].

Cobras, represented by the genus *Naja* (nāgá, meaning ‘snake’ in Sanskrit), belong to the Elapidae family of snakes, and most of their species are classified under Category 1 by the WHO. There are nearly 30 species of cobra (*Naja*) (**Table 1**) that are widely distributed in Africa and Asia [6][7], and they are responsible for a considerable number of snake envenoming cases on these continents. For various reasons, most global epidemiological studies have not discretely recorded the exact estimates of cobra envenoming in Africa and Asia. While neurotoxicity is one of the vital clinical manifestations to distinguish cobra envenomation, other elapid snakes, for example, mambas (*Dendroaspis* sp.), kraits (*Bungarus* sp.), or even some viperids, for example, berg adders (*Bitis atropos*) [8], and Russell's vipers (*Daboia russelii*) from southern India and Sri Lanka [9][10][11] have also been reported to inflict neurological disorders in patients. Therefore, identifying the inflicting species based solely on clinical manifestations might not always be accurate.

Table 1. Geographical distribution of different *Naja* species and their WHO medical importance category. Data presented in this table were retrieved from snakebite information and the data platform maintained by the World Health Organization (https://www.who.int/teams/control-of-neglected-tropical-diseases/snakebite-envenoming/snakebite-information-and-data-platform/overview#tab=tab_1). The data were accessed on 5 October 2022.

Snake Species	Common Name	Medical Importance/ Category	Region of Distribution	Number of Countries	Human Population (2020) in This Species' Range
N. anchietae	Anchieta's cobra	Highest, Secondary	Africa	6	19,008,230
N. annulata	Banded water cobra	Highest, Secondary	Africa	10	114,642,902
N. annulifera	Snouted cobra	Highest	Africa	8	70,731,878
N. ashei	Ashe's spitting cobra	Highest	Africa	6	32,513,269
N. atra	Chinese cobra	Highest	Asia and Australasia	5	570,266,425
N. christyi	Christy's water cobra	Secondary	Africa	3	15,111,896
N. guineensis	Black forest cobra	Highest, Secondary	Africa	7	55,106,930
N. haje	Egyptian cobra	Highest, Secondary	Africa	21	443,884,351
N. kaouthia	Monocled cobra, Thai cobra	Highest, Secondary	Asia	11	976,884,863
N. katiensis	Mali cobra, West Africa brown spitting cobra	Highest, Secondary	Africa	12	123,542,818
N. mandalayensis	Mandalay spitting cobra	Highest	Asia and Australasia	1	14,774,047

Snake Species	Common Name	Medical Importance/ Category	Region of Distribution	Number of Countries	Human Population (2020) in This Species' Range
N. melanoleuca	Black and white cobra, Forest cobra	Highest, Secondary	Africa	11	244,375,176
N. mossambica	Mozambique spitting cobra	Highest, Secondary	Africa	10	130,049,980
N. naja	Indian cobra, Spectacled cobra	Highest, Secondary	Asia and Australasia	5	1,656,817,409
N. nigricincta	Western barred spitting cobra, Zebra cobra	Highest, Secondary	Africa	4	11,381,021
N. nigricollis	Black-necked spitting cobra	Highest, Secondary	Africa	33	727,256,279
N. nivea	Cape cobra	Highest	Africa	4	17,651,152
N. nubiae	Nubian spitting cobra	Secondary	Africa	5	39,843,095
N. oxiana	Central Asian cobra, Transcaspian cobra	Highest, Secondary	Asia and Australasia, Middle East	8	242,127,307
N. pallida	Red spitting cobra	Secondary	Africa	6	59,847,176
N. peroescobari	Sao Tome cobra	Highest	Africa	1	189,185
N. philippinesis	Northern Philippine cobra	Highest	Asia and Australasia	1	592,982,107
N. sagittifera	Andaman cobra	Secondary	Asia and Australasia	1	373,959
N. samarensis	Southern Philippine cobra, Visayan cobra	Highest	Asia and Australasia	1	30,350,207
N. savannula	West African banded cobra	Highest, Secondary	Africa	16	151,894,138
N. senegalensis	Senegalese cobra	Highest, Secondary	Africa	13	84,781,768

Moreover, except for Australia, no other countries currently employ snake venom detection kits to identify the encountered snake species [12]. Therefore, keeping track of exact numbers of envenomation by a particular snake species becomes quite challenging to identify the inflicting species taxonomically. In addition, discrepancies in

Snake Species	Common Name	Medical Importance/ Category	Region of Distribution	Number of Countries	Human Population (2020) in This Species' Range
N. siamensis	Indochinese spitting cobra, Siamese spitting cobra	Highest, Secondary	Asia and Australasia	5	119,240,121
N. sputatrix	Southern Indonesian spitting cobra	Highest, Secondary	Asia and Australasia	2	167,089,984
N. subfulva	Brown forest cobra	Highest, Secondary	Africa	22	377,545,129
N. sumatrana	Equatorial spitting cobra	Highest, Secondary	Asia and Australasia	6	124,654,470

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...enzymatic ...ein (toxin) [10][19][20][21][22][23][24][25][26]. ...t-synaptic neurotoxins (NTX) dictates the lethality of cobra venoms [24][27].

2. Composition of Cobra Venom: A Summary

Biochemical and pharmacological analyses of crude *Naja* venom and their purified toxins are crucial in highlighting the variation in venom composition owing to the different geographical locations of these species [28][29]. However, these conventional methods are not apt for the characterization of non-enzymatic proteins, and with cobra venoms being primarily dominated by non-enzymatic toxins, a comprehensive cobra venom composition has yet to be unraveled. Recent developments in mass spectrometry-based snake venom toxin profiling have enabled thorough analysis of cobra venom composition. Proteomic findings have suggested that cobra venoms are predominated by enzymatic phospholipase A_2 (PLA_2) (~13–15 kDa) and non-enzymatic 3FTXs (~6–9 kDa); together, they constitute about 90% of the total cobra venom. Other enzymatic proteins in cobra venoms include L-amino acid oxidase, serine proteases, metalloproteases, phosphodiesterases, 5′-nucleotidases, cholinesterases, phospholipase B, hyaluronidases, and aminopeptidases. In addition, the minor non-enzymatic classes of toxins in cobra venoms include Cobra venom factors, Kunitz-type serine protease inhibitors, nerve growth factors, cystatin, natriuretic peptides, cysteine-rich secretory proteins, ohanin-like proteins or vesprysn, vascular endothelial growth factors, and C-type lectins or snaclecs (reviewed by [4][30][31]).

Notably, the proportion of cobra venom CTXs was found to vary dramatically across different *Naja* species; it was ~13% in Taiwanese *N. kaouthia* venom, while it constitutes ~73% of *N. nigricollis* venom (**Figure 1**). In general, venoms from African spitting cobras have a higher proportion of CTXs than the Asiatic cobra ones, indicating geographical variation in snake venom composition. Interestingly, while the abundance of neurotoxins corresponds well to the severity of neurotoxicity in envenomed patients, the extent of local tissue-damaging effects of cobra venom do not correlate well with the proportions of CTXs, thereby suggesting variable cytotoxicity of the toxin isoforms as well as a contribution by other cobra venom toxins that can inflict local effects on their own or in complex with CTXs [32].

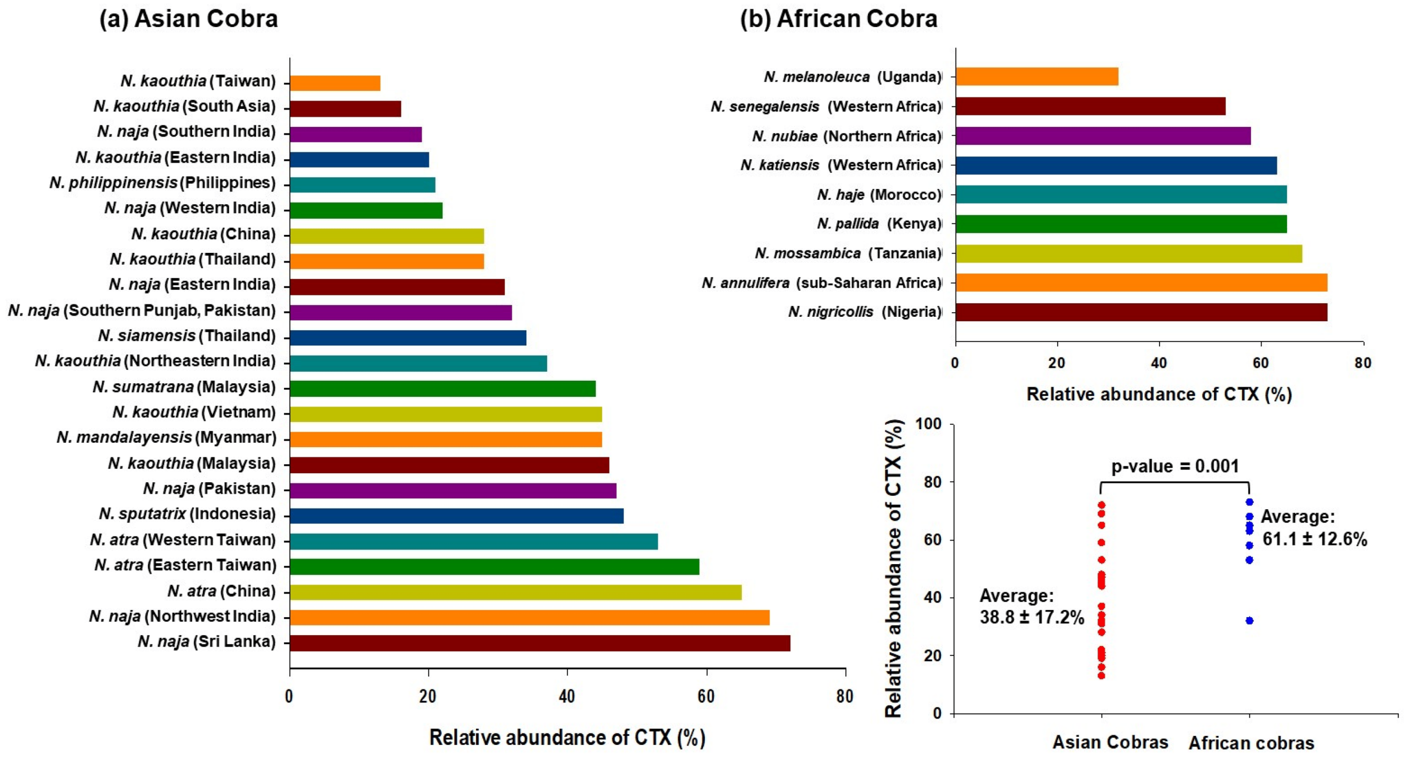

Figure 1. Proteomics analyses determined the relative abundance of CTXs in cobra venoms from diverse geographical locations (Source Kalita et al [33]). The mean relative abundance of CTX in African cobra venoms (61.1 ± 12.6%) is significantly higher as compared to Asian cobra venoms (38.8 ± 17.2%); p-value = 0.001.

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