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Why there are no effective herbal antidotes against snake venom available in India?

Snakebite is one of the major causes of death and disability in the tropical countries[1]. The antidote [anti-snake venom serum (ASVS)] developed in 1894 by Calmette[2] remains the only therapeutic intervention despite having several limitations[3-5]. Before the development of ASVS, herbal antidote existed in nature, mentioned in age-old folk-traditional literature (Ayurveda, Unani, *etc*.) whose scientific validation began in the early 19th century[6]. An exhaustive research was done by Mhaskar and Caius[7] (1898-1928) at Haffkine Institute, Bombay (now Mumbai), India, on the herbs active against snake venom. They concluded that none of the herbs/herbal combination tested was found effective against snake venom. One of the major causes of the failure of Mhaskar and Caius was that the concept of dose-response relationship [LD_{50}/MLD (median lethal dose)] was not established at that time. Pharmacological-toxicological methodologies were available from the early 19th century, and a new dimension of research venture was started with herbs-snake venom. Our group at Kolkata (1981-2018) has established the efficacy of the herbal extract/compound active against Cobra and Viper venoms in animal models[8-14], but an antidote could not be developed. In the present communication, some of the major constraints are discussed and analyzed for the future young researchers working on snake venom.

The starting material of this kind of research was the authentic snake venom, which was often not available in countries such as India, Nepal, Pakistan and Bangladesh. The term authentic means that (*i*) the snakes shall be captured from different parts (east, west, south and north) of the country and should be identified by a zoologist (taxonomist); (*ii*) age, sex, length and health status of the snakes should be recorded and kept at temperature-controlled serpentarium. Further, the snake from wild catch and snakes from captive breed should be kept separated because of venom qualities; (*iii*) the venom should be collected once in a month by a trained personnel in a sterile container with a record of the yield/snake and lyophilized immediately; (*iv*) lyophilized venom should be stored in amber-coloured screw-capped sterilized glass vials, labelled properly and stored in a cool temperature (8-15°C); and (*v*) biological testing (LD_{50}/MLD in mice through intravenous, subcutaneous, intramuscular route) and biochemical properties (protein content, gel banding pattern, *etc*.) should be recorded. There is a need to establish National Snake Venom Bank (NSVB) for the above activity. The NSVB shall provide certificate of authentic venom for the bona fide buyers (for research), institute and industry (for ASVS production). The young researchers should be careful about the starting material and should go for certified authentic snake venom. Several other countries also supply certified authentic snake (of their country origin) venom at a high cost that will not serve our purpose of research. Therefore, there is a need to develop the NSVB and such efforts are in progress by the Department of Biotechnology [Biotechnology Industry Research Assistance Council (BIRAC)], India. One study has reported that ASVS manufactured by Indian companies fail to provide sufficient protection in snakebite victims[15]. The reason could be non-availability of certified authentic snake venom in India.

The research on herbal antidote against snake venom needs a multidisciplinary approach where botanist, pharmacologists-physiologists, toxicologists and chemist-phytochemists may be involved. However, there are many hurdles among which procurement of authentic herbal resources is the main, which is also a basic need for any herbal research programme[16].

The collection of authentic herbal portions/ parts (whole plant, root, stem, leaf, tuber, flower, *etc*.) requires the following: (*i*) the herbs should

be identified by a plant taxonomist and a herbarium prepared should be preserved for future reference, (*ii*) age of the herbs, region and season of collection need to be recorded, and (*iii*) the herb washed with water, dried in sunlight, powdered and preserved in dry container at room temperature (15-22°C).

In the laboratory experiments, it is desirable to use aqueous extract (per oral), except when there is a need to purify the herbal pure compound, solvent (ethanol, methanol, chloroform, *etc*.) extracts may be used. Phytochemical purification, done by phytochemists, requires long protocols and skilled hands. It happens that purified compounds may have low-yield and low-activity, as compared with the whole extract. On several occasions the toxicity of the pure compound played a negative role[17]. Therefore, for all herbal extracts/pure compounds toxicity studies are essential before safe human trials.

Herbal extracts/herbal compounds alone were not found to be effective in snake venom neutralization studies. It was established that herbal extracts/compounds when combined with nanoparticles may enhance the action of herbs[18]. Gold nanoparticle with herbs increased the action of the herbs against snake venom[18-22]. Nanoparticles conjugation may decrease the action of the herbs and may show toxicity. The use of biodegradable and biocompatible nanoparticles (calcium, polymer, albumin nanoparticle) may be an alternative to avoid the toxicity. Newer methodologies such as *in silico* studies using molecular docking and modelling gained importance in snake venom research[23].

At present, there are no research training centres in India although snake venom research started in 1860 at Calcutta Medical College, Kolkata[24]. Later, in 1930-1940, snake venom research continued at the Pharmacology Department of the Calcutta School of Tropical Medicine[25]. In 2010, a registered society was formed in Kolkata with the name 'Toxinological Society of India' to promote snake venom research. There is a need to establish a Snake Venom Research Institute in India to fulfil the lacunae.

The knowledge gap, lack of facilities and funds in snake venom research are the major constraints in herbal antidote development against snake venom. Snake venom herbal antidote may be possible in the near future, provided there are cooperative hands between scientists, policy-makers and industry.

***Conflict of Interest*:** None.

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