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Commentary

Green medicine as a harmonizing tool to antivenom therapy for the clinical management of snakebite: The road ahead

Snakebite is declared as a "Neglected Tropical Disease" by the World Health Organization. As a result, this may be considered as a matter of global health concern for the people in general and the rural communities of the developing countries in particular. The reasons for the dearth of true statistical data on epidemiology of snakebite, particularly from some of these countries are mainly due to the lack of properly co-ordinated epidemiological survey programme. Therefore, the published data on snakebite based on hospital records were biased and did not reflect the true magnitude of the problem. Snakebite data based on diverse methodologies show that global incidence of snakebite is around 5,400,000 bites per year leading to over 2,500,000 envenoming and around 125,000 fatal cases annually[1]. As a result, snake envenomation warrants urgent medical attention and must be considered as a severe health issue.

India has rich assortment of snake fauna, of which only 242 species have been identified including 57 poisonous or harmful species. The four major species of venomous snakes ubiquitous in India know as "Big four" are considered responsible for life-threatening envenomation around the country. These include- Indian cobra (*Naja naja*), the common krait (*Bungarus caeruleus*), the Russell's viper (*Daboia russelii*) and the sawscaled viper (*Echis carinatus*). Although many other species of venomous snakes, for example, Indian Banded Krait (*Bungarus fasciatus*), *Naja kaouthia, N. oxiana*, *N. sagittifera*, *Echis sochureki*, *Hypnale hypnale*, are also responsible for fatal and/or mild envenomation in different parts of India[2,3], yet less attention has been paid in the supervision of snakebite wreaked by these neglected species of venomous snakes.

Snake venom, which is produced in a specialized salivary gland of the venomous snakes known as venom gland, contains numerous enzymatic and non-enzymatic proteins and toxins responsible for imparting toxicity in victims post-envenomation. Activity and number of enzymes present in snake venom vary from venom to venom. Elapidae venoms are rich in phospholipases, phosphodiesterase, nucleotidase, ATPase and cholinesterase[2,4] whereas Russell's viper and pit viper venoms contain proteases, coagulant, kinin-releasing and argininester hydrolyzing enzymes[5]. Many non-enzymatic toxins such as neurotoxin, cardiotoxin, myotoxin, and three-finger family of proteins present in snake venom also play an important role in venom toxicity.

The most effective and accepted therapy for snakebite patients is immediate administration of specific or polyvalent antivenom following envenomation. Unfortunately, this therapy carries an associated risk of anaphylaxis and serum reactions. Further, due to geographical variation in venom composition of snake, antivenom raised against the venom of a snake from a particular geographical origin may not be able to neutralize or prevent local effects of envenomation by snakes from other geographical locations[2,4]. Scarcity of sufficient amount of quality venom from authorized venom dealers also poses a challenge for a reasonable amount of antivenom production to meet the national requirement. Another problem encountered with the antivenom therapy is its failure to neutralize the low molecular weight, less immunogenic toxic components of the venom which cause local haemorrhage, necrosis and tissue damage in snakebite victims. In short, due to complex interplay of economic, epidemiological, therapeutic efficacy and safety issues of antivenom, the mortality of snakebite remains incongruously high in the developing countries. This propels that this problem must be re-addressed.

From the ancient days, human beings have explored many plants as a source of medicine to cure diseases

and various ailments. In fact, abundant plant species are used as folk medicine to treat poisonous snakebite all over the world. Ironically, in most of the cases these species are used without proper scientific validation. In India, about 50 such plants have been indexed[6] and many others (not included) have also been widely used against snakebite by villagers, snake charmers and traditional healers.

The limitations of antivenom therapy have prompted the scientists to explore the therapeutic use of natural products derived from plants or from other natural sources for the treatment of snakebite patients. However, questions have been raised on the validity of such treatments and, therefore, pharmacological reassessment of medicinal plants must be done very carefully and critically prior to their application as antidote for snakebite. During the recent years more attention has been paid to the ethnobotanical survey and pharmacological screening of medicinal plants traditionally used for the treatment of snakebite patients as well as isolation and characterization of active compounds possessing anti-ophidian property from natural resources.

A few of the well characterized active molecules from plants possessing antivenom activity and/or able to neutralize toxic enzymes of venoms include aristolochic acid from the medicinal plant *Aristolochia radix*[7], 2-hydroxy-4-methoxy benzoic acid and lepuol acetate from *Hemidesmus indicus* R. Br[8], AIPLI purified from methanolic leave extract of Neem, *Azadiracta indica*[9], isoquinoline alkaloid from a herbaceous plant *Cardiospermum halicacabum*[10], *etc*.

In this issue, Gomes *et al*[11] have demonstrated the efficacy of three synthetic herbal compounds *viz*. 2-hydroxy-4-methoxy benzoic acid (BA), p-anisic acid (PA) and salicylic acid (SA) in neutralizing the pathophysiological action of phospholipase A_2 (PLA_2) purified from *Bungarus fasciatus* (Indian Banded Krait). These compounds were found to neutralize the krait venom PLA_2 induced toxic effects with a variable extent[11]. However, the synthetic herbal compounds were found to be superior to the commercial polyvalent snake venom antiserum in neutralizing the toxic effect of tested PLA_2. The authors have concluded that in case of banded krait envenomation the combination therapy with the right choice of herbal antagonist and commercial polyvalent snake venom antiserum may provide better management against this snakebite[11].

Though many of the active plant constituents are promising contenders for the development of antivenom drug molecules in future, a single purified compound may not be sufficient to completely neutralize the toxic effect of snake venom. Therefore, pre-clinical studies to evaluate the antivenom activity of suitable herbal formulation(s) containing different combinations of these active molecules are essential. Moreover, considering the fact that plant derived secondary metabolites may not necessarily be benign molecules, assessment of bio-safety and *in vivo* toxicity of the anti-ophidian herbal formulation(s) must be addressed before advocating their safe therapeutic application in the clinical management of snakebite patients.

It is well understood now that development of green medicine for snakebite is a challenging task. Nonetheless, it is not an unworkable goal. To achieve this target, the scientists, clinicians, NGOs and government agencies must work coherently with a common objective to produce efficient and safe herbal medicine for snakebite treatment. Further studies should involve region-specific extensive ethnobotanical survey of our natural resources and creation of database of plants used as antidote for snakebite in ethno-medicinal practice. It is quite obvious that the high market demand of such plant derived medicines will build a pressure on our natural resources that might lead to the habitat loss, habitat degradation, and over harvesting of these medicinal plants resulting in a threat to our biodiversity. Hence, a well thought road map should be designed for the proper consumption as well as maintenance of our valuable natural resources. This in turn, will not only provide affordable and effective plant based curative molecule(s) for snakebite treatment but will preserve our indigenous knowledge as well.

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