Chapter 1

INTRODUCTION
Since time immemorial, snakes have been one of the most feared and dreaded animals in the world. The presence of venom in some of the species, generates this fear. History tells us the importance of snakes in people's lives. They are worshipped and have given birth to many myths and legends.

Snakes are present almost everywhere between Arctic and Antarctic circles. The tropical and temperate regions are the primary breeding ground of deadly snakes, thus exposing a huge population to snakebite which are fatal. The major venomous snakes found in India are Indian Cobra (Naja naja sp), Russell's viper (Daboia russellii russellii), Saw scaled viper (Echis carinatus), Common krait (Bungarus caeruleus) and Banded Krait (Bungarus fasciatus).

Snakebite is a serious health problem worldwide and specially in the tropics (Swaroop and Grab, 1954). Approximately 15,000-25,000 people die in the Indian subcontinent alone (Hati, 1979; Warrell, 1996). The number of snakebite deaths in the state of West Bengal, India, reported annually between 1969-1974 was 384, 194, 205, 225, 280 and 359 (Hati et al., 1992). However most of the snakebite statistics are based on hospital records, and a majority of the snakebites occur in remote, inaccessible rural areas, where they often remain unreported. Thus the available data may not reflect the real magnitude of the problem (Swaroop and Grab, 1954). The situation is greatly aggravated, especially in a country like India, due to lack of medical practitioners and the existence of the so called traditional healers who take undue advantage of the illiterate rural folk (Hati et al., 1990; Hati et al., 1992). Patients generally reach the health centre or a district general hospital between 1-10 hours after the bite. Poisonous snakebites predominate between months of June and September and more so during the night time. Bites occur mainly on legs, about 55%-80%, while those on the arms are significantly less (Kamad and Shikarkhane, 1996; Jerald and Arole, 1996).
The venoms of true vipers and pit vipers are cytolytic and haemolytic causing swelling and necrosis of tissue, spreading from the site of the bite, often with intravascular coagulation and haemorrhage. The cobra venom is highly neurotoxic. The venoms of sea snakes are mainly myotoxic that causes necrosis of muscle accompanied by severe pain. The important signs of systemic poisoning for vipers include blood tinged sputum (haemoptysis), low blood pressure (hypotension), bleeding from nose (epistaxis), passage of darkened feces due to the presence of blood pigments (melena), passage of RBC with urine (haematuria), sub-conjunctival haemorrhage, convulsions followed by defibrination syndrome with non-clotting blood. In case of a cobra bite the patient has drooping eye lids (ptosis), glossopharyngeal palsy, nasal intonation, paralysis of extrinsic muscles of eyes, nausea, incoordinated speech, salivation, drooping of head, uncontrollable desire to sleep, cyanosis, asphyxia and finally paralysis of the lower extremity accompanied by respiratory failure.

The first step towards poisonous snakebite management is to make a tight ligature near the site (Wallace, 1994). Though some doubt the value of a ligature, it would still be advisable because of the psychological boost it would confer to the patient. Without wasting much time the patient should be taken to the nearest hospital where antiserum is available. In 1894, Albert Calmette developed the antiserum, the only specific treatment available till date. The antiserum is given i.v. drip in normal saline. Antiserum though considered the most viable antidote has numerous drawbacks. It does not provide enough protection against venom induced haemorrhage, necrosis, nephrotoxicity and often develops hypersensitivity reactions (Sutherland, 1977; Corrigan et al., 1978; Stahel et al., 1985). Antiserum development in animals is very time consuming and it requires ideal storage conditions which are not necessarily met with. The greatest disadvantage in a developing country like India is the high cost of the antiserum specially for the rural people.

To overcome these drawbacks, studies have been conducted to find an alternative treatment. One of the most important resource of India is its medicinal plants. Many Indian medicinal plants are mentioned in the literature, which are
used to treat snakebite victims specially in rural areas (Chopra et al., 1956; Biswas and Ghosh, 1977). Very few scientific reports on the active constituents from plants are there, which inhibit snake venom action (Nazimuddin, 1978; Sudarsanan et al., 1975; Leung 1980; Morton 1981; Duke 1985; Mors 1991; Martz, 1992). From this laboratory, an active compound 2-hydroxy-4-methoxy benzoic acid was isolated from root extract of Hemidesmus indicus R.Br, which effectively neutralized Vipera russellii venom induced pathophysiological changes (Alam et al., 1994).

Mother Nature has given us the antidote of snake venom in the form of medicinal plants. Once the Queen Hatshepsut of Egypt collected saplings of trees from equatorial Africa in exchange of valuables like gold, ivory, ebony and many other things to decorate the temple she was building to enclose her own tomb (Dobelis, 1990). So, plants were worshipped and regarded as more valuable than gold. In the earlier days, the application of plants in medicine was based on empirical observations. The progress of science has enabled the establishment of the usefulness of herbal medicine on a firm footing. Many important synthetic drugs had their origins in the plants. The Asian subcontinent is the storehouse of numerous medicinal plants. The ancient medicine men prescribed roots, seeds, stems and leaves of numerous plants to treat snakebite victims. Usefulness of these plants have been recorded in ancient literature.

The present investigation aims for the first time to study the antisnake venom properties of a few selected Indian medicinal plants. Eighteen medicinal plants were selected on the basis of literature survey and geographic availability of these plants in this region (Indian subcontinent). These plant extracts were studied against snake venom (viper and cobra) induced lethal action in experimental animals. Out of the eighteen plant materials, ten were found to effectively neutralize venom induced lethal action. The observation clearly validates the claims of traditional literature and medicine men, that Nature has provided us with the antidote of snake venom in the form of herbs. There are very few scientific evidence of these claims and the present study attempts to provide that.
Of the ten plant materials identified as potential snake venom antidotes, three of them, the roots of *Pluchea indica* and *Hemidesmus indicus* and seeds of *Strychnos nux vomica* were found to be most potent. They were taken for a further detailed investigation against venom neutralization. Crude extracts (methanolic/ethanolic) of the three plants were tested for neutralization against snake venom. Isolation and purification of the active component responsible for snake venom neutralization was then conducted. The isolated fraction was then studied for the neutralizing capacity, its structural elucidation and the mechanism of action. The information from the present thesis may add knowledge in the area of snake venom research and snake envenomation management, at least in the rural parts of India.