Chapter

Toxicosis of Snake, Scorpion, Honeybee, Spider, and Wasp Venoms: Part 1

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Abstract

Toxicosis is a poisoning caused by venomous animals such as snake, scorpion, honeybee, spider, and wasp. Their poisons contain amino acids, peptides, proteins, enzymes, and metallic ions that are responsible for neurotoxicity, hemotoxicity, and myotoxicity. Because of in vivo therapeutic challenges posed by toxicosis, there is need for ideal therapeutic agents against envenomation caused by venomous animals. Findings have shown that toxicosis could be treated symptomatically. Snake and scorpion antivenins could be used for treatment of poisoning caused by snake, scorpion, honeybee, spider, and wasp. The amount of antivenin is dependent on the quantity of venom injected into the affected individuals. More so, symptomatic treatments are also done according to the systems affected. Hospitalization is necessary for assessment of therapeutic success.

Keywords: toxicosis, snake, scorpion, toxin, antivenin, lethality, hemotoxicity, neurotoxicity, myotoxicity, hospitalization

1. Introduction

Venomous animals such as snake, scorpion, honeybee, spider, and wasp constitute very significant health hazard in the world. The snake venom contains many toxic and non-toxic molecules [1]. Forty-seven out of 50 US States have venomous snakes. Southwestern US are mostly affected. About 4700 venomous snakes bite human and 150,000 primarily dogs and cats are bitten by venomous snakes every year in the US, with human mortality of 0.06% and that of dog is 1–30% [2]. Scorpionism is caused by many poisonous scorpions including Tityus species endemic to Panama, whereas *Centruroides* are endemic to Guatemala, Belize, El Salvador, Nicaragua, and Costa Rica. They are wildly toxic via unchannel active toxins. In Panama, the incidence was 52 cases per 100,000 in 2007 and 28 deaths were recorded between 1998 and 2006, respectively. *Tityus* species present in the Atlantic coast of Costa Rica is responsible for fatalities in Panama. *Tityus pachyurus* [3] and *Parabuthus granulatus* are of the most medical importance in the Western Cape of South Africa. *P. transvaalicus* venom is used for production of *P. granulatus* venom [4]. About 200,000 cases of scorpionism are reported in Mexico and cause 310 deaths every year and 20,000 out of 38,068 affected persons were successfully treated using equine antiserum (serotherapy) and no life was lost [5]. The first case of scorpionism was reported in Canada in a 36 year old man in 1962. The rate of scorpionism in Amazon region of Brazil is 8.14–273 cases per 100,000. Most species involved in envenomation belong

to the genus of Tityus [6]. *M. gibbosus* is endemic to a small geographic area of Erbalj on terra rossa soil [7]. The incidence of scorpion sting in Iran was 61.2 per 100,000 populations [8], as against 1.2 million people with estimated 3250 death per year. The mean annual rate was 17.4 per woman population [9]. The highest rate of sting occurred in Iran among individuals of 25- to 34-year-old [8]. The global mortality rate was 10 per 1000 cases. Most of the stings were seen on lower limbs (58.6%) and upper limbs (34.3%) during the hot season [10]. The scorpion that had envenomated for the first time may have less toxic envenomation for the second time as reported in the case of sting from *Leiurus abdullahbayrami* [11]. In India, envenomation was more common in males than in females [12].

Honeybee (*Apis mellifera*) constitutes a significant nuisance and of medical importance in Africa, Europe and other parts of the world. Other subspecies are *A. mellifera carnica*, *A. mellifera ligustica*, and *A. mellifera scutellata* [13]. Honeybee stings reported in Ceara, Brazil showed 1307 cases affecting men between 20 and 29 years of age [14] translating to 19 cases per 100,000 in Campina Grade [15]. Bee envenomation is a problem in India, China, Latin America, Middle East, and North and South Africa [16]. About 200 stings from *Apis mellifera* could cause envenoming syndrome in children and elderly [17] as multiple stings, not increased venom potency or delivery cause serious reactions [18]. Bee venoms differ in weight and concentrations of phospholipase and melittin [19]. Unfortunately, no specific antivenom for bee envenomation; hence, proper removal of stings, first aid treatment and chemotherapy should be considered as medical emergency [20]. Administration of hydrocortisone, calcium, analgesic, and 0.9% sodium chloride and application of ice to the site of stung pregnant woman resulted in recovery from the pain and the fetus was stable and delivered 3 months after treatment without sequela [21]. There are 42,473 species of spiders grouped into 110 families (Platnick) [22]. *Hadronyche formidabilis* and *H. cerberea* have very high envenoming rates [23]. Black widow spider (*Latrodectus mactans*) and brown recluse spider (*Loxosceles reclusa*) are of most concern [24]. In view of the increased challenges and negligence of envenomation caused by venomous snake, scorpion, spider, wasp, and bee, there is need for thorough search for their therapeutic regimens with a view to having lasting solution against fatality.

2. Methodology

Literatures were searched on venomous snakes, scorpions, honeybees, spiders, and wasps with an intent to identifying their toxicity potentials, epidemiology of their toxicosis, signs of toxicity, treatment, and development of vaccines against their venoms. Sought also are information on medicinal plants, phytochemicals and other therapeutic agents, structures of some chemicals present in the venoms, and their medical applications and medicinal uses. Mathematical formulas were also derived for calculation of body weight, body surface area, packed cell volume, hemoglobin, total blood volume, lost blood volume, median lethal dose (LD_{50}), median effective dose (ED_{50}), number of bee stings, total dose of bee venom, and relationship between renotoxicity and hemotoxicity.

3. Results

Findings have shown that venoms from poisonous species of snakes, scorpions, honeybees, spiders and wasps are highly toxic and could cause various degrees of hemotoxicity, myotoxicity, and neurotoxicity including death (**Tables 1** and **2** and **Figures 1**–77).

System	Age (year)	Sting(s)	Sex	Signs	Treatment
Nervous	6,70 70	1 each 1	Female Male	Axonal polyneuropathy, seizure Brachial plexitis, Parkinsonism	Immunoglobulin I.V., anti-inflammatory, oxygen
Muscular	34	3	Male	Rhabdomyolysis, muscle pain, allergy	Analgesic, anti-inflammatory
Circulatory	35–42	Many	Male	Myocardial infarction, ischemic attack, cardiac arrest, Kounis syndrome, anaphylaxis	Angioplasty, steroids, antihistaminics
Renal	2	1	Male	Nephrotic syndrome, anasarca, acute renal failure	Corticosteriod
Ocular	21–50	1	Male Female	Cataract, glaucoma	Surgery, keratoplasty, antibiotics, corticosteroid
Miscellaneous	40	Multiple	Male	Intravascular coagulopathy, coma	Hydrocortisone, analgesic, pheniramine

Table 1.
Toxicity signs of honeybee sting in human.

Animal	Weight (kg)	Number of stings	Dose of stings (mg)	LD_{50} (mg/kg)	ED_{50} (mg/kg)	Lethal time (hour)
Child	10	94	28.2	1.41	11.2	2.10
Adult	60	1000	300	2.5	7.5	3.72

Table 2.
Calculated median lethal dose and effective dose 50 of honeybee venom and antivenom in human.

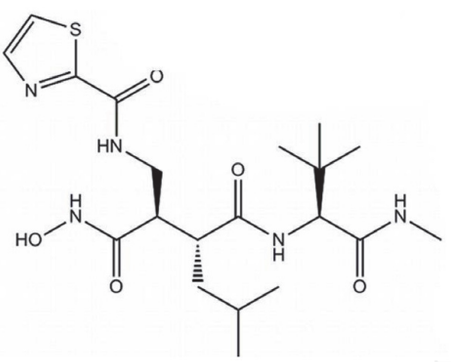

Figure 1.
Metalloproteinase of rattlesnake's venom.

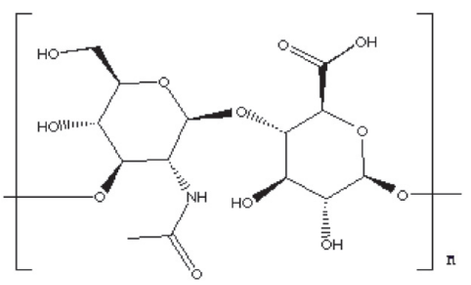

Figure 2.
Hyaluronidase of black mamba's venom enzyme.

Figure 3.
Eastern diamondback rattlesnake *(*Crotalus adamanteus*) found in southeastern United States.*

Figure 4.
Western diamondback rattlesnake *(*Crotalus atrox*) can be found, from California to West Texas, Oklahoma, the southern parts of New Mexico and Arizona and northern parts of Mexico. This species is also found in several islands in the Gulf of California.*

Figure 5.
Mojave rattlesnake *(*Crotalus scutulatus*) found in the deserts of the southwestern United States and central Mexico.*

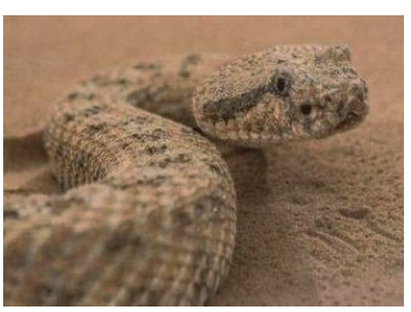

Figure 6.
Sidewinder *(*Crotalus cerastes*) found in the desert regions of the southwestern United States and northwestern Mexico.*

Figure 7.
Timber rattlesnake *(*Crotalus horridus*) also commonly known as canebrake rattlesnake or banded rattlesnake found in the eastern region of the United States.*

Figure 8.
Pigmy rattlesnake *(*Sistrurus miliarius*) found in the southeastern part of the United States.*

Figure 9.
Massasauga rattlesnake *(*Sistrurus catenatus*) found in several states of the United States, southern Ontario in Canada and in northern Mexico on the border with Texas.*

Figure 10.
Prairie rattlesnake *or* ***Great Plains rattlesnake*** *(*Crotalus viridis*) found in the western United States. They are also found in southwestern Canada and northern regions of Mexico.*

Figure 11.
Inland taipan *(*Oxyuranus microlepidotus*) found in semi-arid regions of central east Australia.*

Figure 12.
Coastal taipan *also known as the common or eastern taipan (*Oxyuranus scutellatus*). It's found throughout the coastal regions of northern and eastern Australia and also on the island of New Guinea.*

Figure 13.
Central Ranges taipan *(*Oxyuranus temporalis*).*

Figure 14.
King cobra *(*Ophiophagus hannah*). King cobras live in Southeast Asia mainly in the plains and rainforests of India where they are abundant and revered in some places, southern China, Malaysia, and the Philippines.*

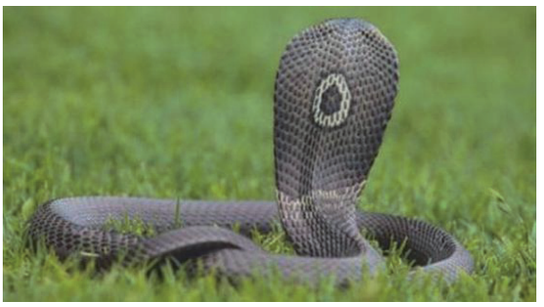

Figure 15.
Monocled cobra *(*Naja kaouthia*) can be found in China, India, Vietnam, Nepal, and Cambodia, but also Malaysia, Bangladesh, Bhutan, Laos, Myanmar, and Thailand.*

Figure 16.
Indian cobra *(*Naja naja*). They are found in several countries including India, Pakistan, Sri Lanka, Myanmar, southern Nepal, Bangladesh, Bhutan, and possibly in the extreme eastern Afghanistan in the Kabul River Valley.*

Figure 17.
Egyptian cobra *(*Naja haje*) is found throughout most of North Africa north of the* ***Sahara desert****, and also south of the Sahara through West Africa, in the Congo Basin, Kenya and Tanzania and the southern part of the Arabian Peninsula.*

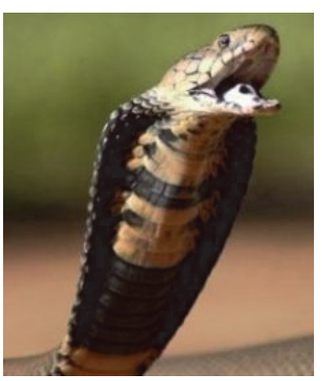

Figure 18.
Mozambique spitting cobra *(*Naja mossambica*)—eastern parts of southern Africa, most of Mozambique, Swaziland, Zimbabwe, southern Angola, Zambia, Malawi, northeastern Namibia, northern Botswana, and southern Tanzania including Pemba island.*

Figure 19.
Cape cobra *(*Naja nivea*) found in southern Africa, particularly in South Africa and in parts of Botswana and south part of Namibia.*

Figure 20.
Common krait *(*Bungarus caeruleus*) found in the Indian subcontinent. These snakes are found almost all over Peninsular India but not in the offshore Islands. They are also found in other neighboring countries such as Pakistan, Bangladesh, Nepal, and Sri Lanka.*

Figure 21.
Blue krait *is also known as the* ***Malayan krait*** *(*Bungarus candidus*). These snakes are found in Peninsular Malaysia, central Vietnam, Thailand, Bali, Lao People's Democratic Republic, Indonesia, Singapore, and Sumatra.*

Figure 22.
Black mamba *(*Dendroaspis polylepis*). The black mamba lives in the savannas and rocky hills of southern and eastern Africa. Its fragmented range includes many African countries like the Democratic Republic of the Congo, Sudan, Ethiopia, Eritrea, Somalia, Kenya, Uganda, Tanzania, Burundi, Rwanda, Angola, Mozambique, Swaziland, Malawi, Zambia, Zimbabwe, Botswana, Namibia, and South Africa.*

Figure 23.
Eastern green mamba *(*Dendroaspis angusticeps*). Their range stretches from the eastern Cape in South Africa through Kenya, Mozambique, Tanzania, eastern Zimbabwe, and southern Malawi.*

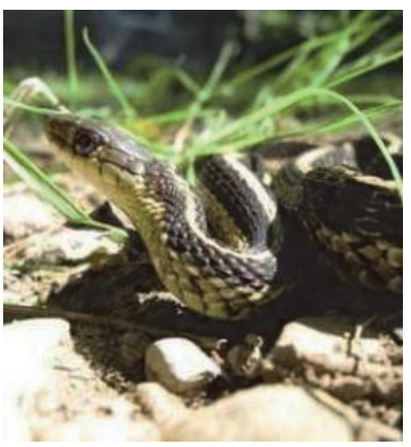

Figure 24.
Eastern gartersnake *or* ***Eastern garter snake****(*Thamnophis sirtalis sirtalis*). They have a wide range across eastern North America, extending as far north as southern Ontario and Quebec in Canada, to the Gulf of Mexico in the south, along the eastern shores of America to the Mississippi River.*

Figure 25.
California red-sided garter snake *(*Thamnophis sirtalis infernalis*) found in California.*

4. Discussion

4.1 Signs of ophidism

Difference between cobra and viper venom in terms of molecular weight, route of administration and nature of toxin could account for differences in their venoms

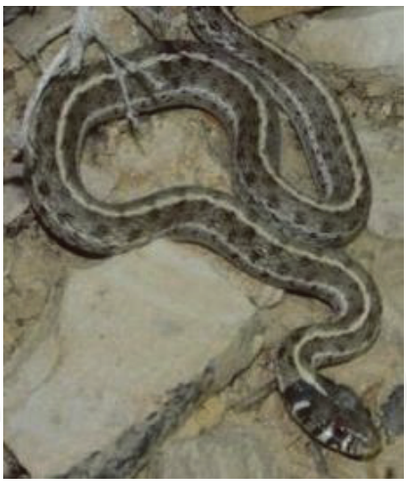

Figure 26.
Checkered garter snake *(*Thamnophis marcianus*) found in the southwestern United States southwards into Mexico and Central America as far south as Costa Rica.*

Figure 27.
Eastern brown snake *(*Pseudonaja textilis*) found in the eastern half of Australia, except in Tasmania.*

Figure 28.
King brown snake *or* ***mulga snake*** *(*Pseudechis australis*) found over most of mainland Australia, except for the extreme south and the southeast coastal regions.*

lethality. Venom of *Cerastes cerastes* is more toxic than that of *Bitis arietans* and *Macrovipera lebetina* and toxin of *Naja haje* is more toxic than that of *C. cerastes*, *M. lebetina* and *B. occitanus*. Vipers have toxins with high molecular weight [25]. Therefore, venom quality has to be standardized for development of efficient antivenom, [26]. When the time of injected antivenom is shorter than fatal limit time,

Figure 29.
Death adder *(genus* Acanthophis*) found in Australia, Indonesia, New Guinea and its nearby islands.*

Figure 30.
Red-bellied black snake *(*Pseudechis porphyriacus*) native to eastern Australia. The red-bellied black snakes are found in a more or less continuous range from southeastern Queensland south through eastern New South Wales and Victoria.*

Figure 31.
Gaboon viper *(*Bitis gabonica*) found along the equatorial belt of Africa, East and Central Africa, and southeast Africa. In the African Portuguese-speaking countries, it can be found in Guinea-Bissau, Angola, and northern Mozambique.*

Figure 32.
Tiger snake *(*Notechis*) found in Australia.*

the envenomated may be protected by increasing the dose of antivenom. But when the antivenom is injected closer to the fatal limit time, the chance of death is one-half [27].

4.2 Treatment of snake envenomations

Rational dosage of snake antivenom requires larger randomized controlled trials and further strategies are required to reduce morbidity in children bitten by *Naja atra* [28]. Neurotoxic envenomations and complications thereafter correlate positively with snake antivenom dosage; hence higher doses are required which may

Figure 33.
Puff adder *(*Bitis arietans*) found in African savannah and grasslands.*

Figure 34.
Horned viper *(*Cerastes cerastes*). It is found in many north African countries like Morocco, Mauritania, Mali, eastward through Algeria, Niger, Tunisia, Libya and Egypt, Chad, Sudan, Ethiopia, Somalia, and northern Israel.*

Figure 35.
Boomslang *(*Dispholidus typus*) found in sub-Saharan Africa in the central and southern regions of the continent. The boomslang is most abundant in Botswana, Swaziland, Namibia, Mozambique, and Zimbabwe, but the species has been reported as far north as southern Chad and Nigeria, and as far east as eastern Guinea.*

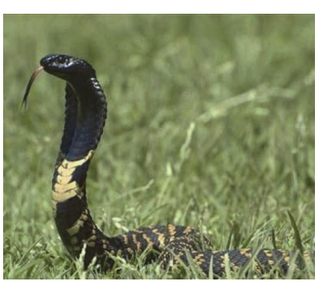

Figure 36.
Rinkhals *(*Hemachatus haemachatus*). The rinkhals is found in most provinces of South Africa, like western and eastern Cape along the south coast, Mpumalanga, Free State, southern Gauteng and Kwazulu Natal.*

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Figure 37.
Copperhead *or* ***water moccasin*** *(*Agkistrodon contortrix*). These snakes are found in the United States and in northern Mexico. In the USA, they are found in the states of Alabama, Arkansas, Florida, Georgia, Illinois, Connecticut, Delaware, Indiana, Iowa, Kansas, Kentucky, Louisiana, Ohio, Mississippi, Missouri, Oklahoma, Maryland, Massachusetts, New Jersey, New York, North Carolina, Tennessee, Texas, Pennsylvania, South Carolina, Virginia, and West Virginia. In Mexico, it occurs in Coahuila and Chihuahua regions.*

Figure 38.
Cottonmouth *(*Agkistrodon piscivorus*) found in the southeastern United States.*

Figure 39.
Mamushi *or* ***Japanese Mamushi*** *(*Gloydius blomhoffii*) found in Japan, China, and Korea.*

also cause adverse reactions [29]. Neutralization capacity of antivenom may be related to geographic proximity of snake species [30]. *Cerestes cerestes* antivenom and *Macrovipera mauritanica* antivenom cross react with *Bitis arietans* antivenom due to presence of antigens common to them [31]. Tenerplasminin-1 (TP_1), a plasmin inhibitor isolated from *Micrurus tener tener* venom was similar to Kunitz-type serine peptidase inhibitors [32]. *Rauwolfia serpentina* inhibits *Daboia russelii* venom [33].

The therapeutic dose of antivenom is relative to the quantity of venom [34]. Therefore, postmortem lesions are required to provide the cause of death [35].

Figure 40.
Russell's viper *(*Daboia russelii*) is found throughout Asia, in the Indian subcontinent, much of Southeast Asia in southern parts of China and Taiwan. The species is found in many countries India, Pakistan, Sri Lanka, Myanmar, Bangladesh, Nepal, Thailand, Cambodia, China, Taiwan, and Indonesia.*

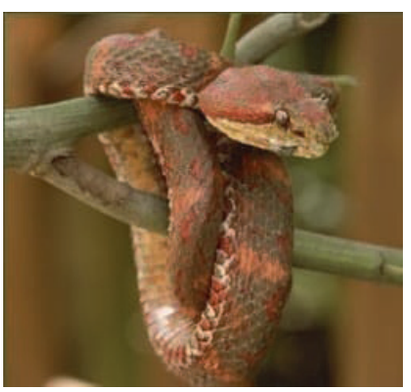

Figure 41.
Eyelash viper or eyelash palm-pit viper *(*Bothriechis schlegelii*) found in central America and northern South America.*

Figure 42.
Golden lancehead *(*Bothrops insularis*).*

Figure 43.
Jararaca *(*Bothrops jararaca*). They are found in southern Brazil, northeastern Paraguay, and Misiones province in northern Argentina. It is also found in several islands off the coasts of Argentina and Paraguay, some as far as 35 km offshore.*

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Figure 44.
Fer-de-lance *or* ***terciopelo*** *(*Bothrops asper*) inhabits the region from southern Mexico to northern South America.*

Figure 45.
Bushmaster *(*Lachesis muta*) found in southern Central America and the northern half of South America including the island of Trinidad.*

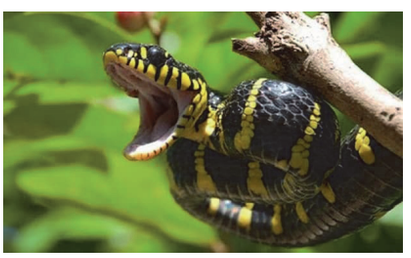

Figure 46.
Mangrove snake *(*Boiga dendrophila*) found in Indonesia, Malaysia, Thailand, Singapore, Vietnam, Cambodia and Philippines.*

Figure 47.
Ringneck snake *(*Diadophis punctatus*) found in southeastern Canada and throughout most of the United States southward into Central Mexico.*

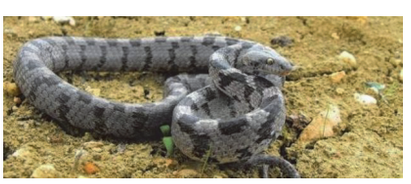

Figure 48.
European cat snake *or* ***European Catsnake*** *(*Telescopus fallax*).*

Hence, neutralizing capacity of antivenins must be standardized [36] because of complex nature of venom composition [37]. Pro-coagulant is used to assess anti-venom activity and the results of antivenin test in rodents may not prove efficacious in human [37] which is considered very important [38]. Hence, changes in dosing

Figure 49.
Indian red scorpion *(*Hottentotta tamulus*) found throughout most of India, eastern Pakistan and the eastern lowlands of Nepal.*

Figure 50.
Deathstalker scorpion *(*Leiurus quinquestriatus*). The deathstalker scorpion's range covers a wide sweep of territory in the Sahara, Arabian Desert, Thar Desert, and Central Asia, from Algeria and Mali in the west through to Egypt, Ethiopia, Asia Minor and the Arabian Peninsula, eastward to Kazakhstan, and western India.*

Figure 51.
Arabian fat-tailed scorpion *(*Androctonus crassicauda*) found mainly in the Palaearctic region. It is commonly found in Saudi Arabia, Kuwait, Qatar, Iraq, Iran, Turkey, and in north African nations.*

Figure 52.
Yellow fat-tailed scorpion *(*Androctonus australis*). The yellow fat-tailed scorpion is found in north and west Africa, the Middle East, and eastward to the Hindu Kush region. Countries where* Androctonus *species live include Armenia, Morocco, Algeria, Tunisia, Libya, Egypt, Togo, Palestine, Israel, India, Lebanon, Turkey, Jordan, Saudi Arabia, Yemen, Oman, United Arab Emirates, Qatar, Kuwait, Iraq, Iran, Afghanistan, Bahrain, and Pakistan.*

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Figure 53.
Black spitting thick-tailed scorpion *(*Parabuthus transvaalicus*)—southern Africa.*

Figure 54.
Striped bark scorpion *(*Centruroides vittatus*) is distributed throughout the South-Central U.S. states and throughout northern Mexico. Beginning in the northern Mexico Border States, Chihuahua, Coahuila, Nuevo León, and Tamaulipas,* C. vittatus' *range extends upward longitudinally through Texas, Oklahoma, and Kansas, to reach as far north as Thayer County, Nebraska.*

Figure 55.
Arizona bark scorpion *(*Centruroides exilicauda*) found in the deserts of Arizona, California and Utah.*

Figure 56.
Brazilian yellow scorpion *(*Tityus serrulatus*)—South America.*

and development of new antivenins have been recommended [39]. However, low effective dose can be used with beneficial results [40]. The most effective treatment for snake envenomation is the specific heterologous serum [41] and additional dose is unnecessary in brown snake envenomation [42]. Antivenom cause anaphylactic

Figure 57.
Yellow-legged burrowing scorpion *(*Opistophthalmus glabrifrons*)—southern Africa.*

Figure 58.
Tanzanian red clawed scorpion *(***Pandinus cavimanus***)—Tanzanian, Africa.*

Figure 59.
Emperor scorpion *(***Pandinus imperator***) found living in the rain forest or wet savannah, throughout Africa from Mauritania to Zaire.*

Figure 60.
Brown widow spider *(*Latrodectus geometricus*) found throughout the world, including Africa, the United States, Europe, Asia, the Middle East, and South America.*

Figure 61.
Yellow sac spider *(*Cheiracanthium*) is a species endemic to the Americas.*

Figure 62.
Indian ornamental tarantula *(*Poecilotheria regalis*) is a species of spider found in South Asia, as well as southeastern India.*

Figure 63.
Brown recluse *(*Loxosceles reclusa*) primarily found in North America (throughout the Midwest and Southern United States in particular).*

Figure 64.
Black widow spider *(*Latrodectus*) found on every continent of the world (with the exception of Antarctica).*

Figure 65.
Sydney funnel-web spider *(*Atrax robustus*) is native to eastern Australia.*

Figure 66.
Chinese bird spider *(*Cyriopagopus hainanus*) is found predominantly in China and Southeast Asia.*

Figure 67.
Redback spider *(*Latrodectus hasseltii*) found predominantly in Australia, Southeast Asia, and New Zealand.*

Figure 68.
Brazilian wandering spider *(*Phoneutria fera*) endemic to the tropical regions of South America.*

Figure 69.
Six-eyed sand spider *(*Hexophthalma*) is found predominantly in the deserts of southern Africa.*

Figure 70.
Tarantula hawks *(*Pepsis *species) found across South and Central America and in the southern United States.*

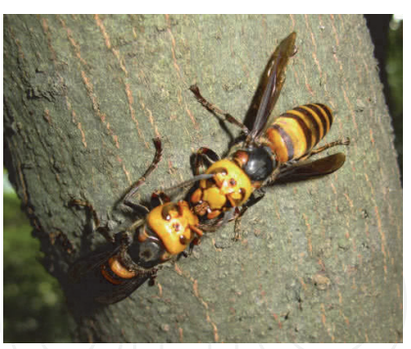

Figure 71.
Giant Japanese hornet.

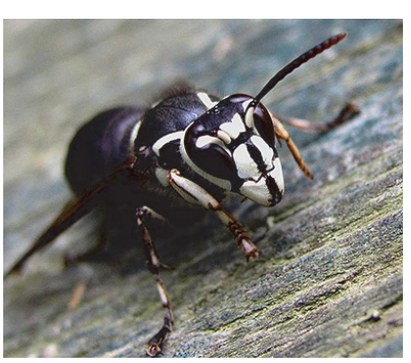

Figure 72.
Bald-faced hornet *(*Dolichovespula maculata*) is found throughout North America.*

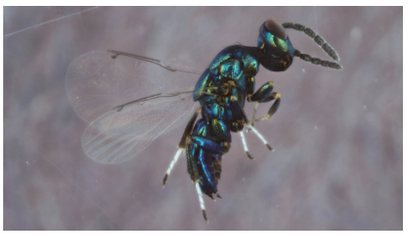

Figure 73.
Crypt-keeper wasp *(*Euderus*).*

Figure 74.
German yellowjacket Paravespula germanica *(Linnaeus) found throughout North America.*

Figure 75.
Paper wasps *(*Polistes *species)—southern United States.*

Figure 76.
Africanized honey bee *(*Apis mellifera scutellata *Lepeletier) occurs naturally in sub-Saharan Africa but has been introduced into the Americas.*

Figure 77.
Bumblebee Bombus terrestris.

reactions [43] and serum sickness necessitating balance between treatment benefit and the risk of adverse reactions [42]. Failure of snake antivenin may be due to the fact that different snake venoms contain varieties of potent hemotoxins, neurotoxins, and other toxins [44]. Therefore, the viper venom is more toxic than elapine venom due to the nature and molecular weight of toxins. Geographical variability, the species of snakes, body weight, and the route of administration of antivenin are very vital to successful treatment [45]. Toxins with molecular weight (<7KDa) diffuse quickly into the blood stream [25], which may not affect efficacy of snake antivenin IgY elevated by ion exchange chromatography [46].

But antivenin affects pharmacokinetic and pharmacodynamic properties of venom. Hence, the quality of preparation and optimization of the use of antivenin must be standardized [47]. The amount of antivenin is determined by clinical signs, size of snake, and the known efficacy of available antivenin [9]. The route of administration of antivenin is controversial, but intravenous route has been considered the most efficient [47]. Polyclonal antibodies are more effective against *Cerastes cerastes* snake venoms in laying hens than in mammals [48]. Chicken immunoglobulin (IgY) is more sensitive, easy to assay, does not activate human complement system and does not react with human anti venomous IgG antibodies or human Fc receptors [49]. The immunoglobulin IgY offers protection against embryo infections [50]. The effective IgY dose required to prevent mortality in rabbit was four times the dose of injected venom using Lowy's protein assay [51]. Milk whey lactoferrin increased antibody levels and immune-stimulatory effects against snake venom [52] whereas adjuvant sustains the release of antigen, interacts with immune cells [53], activates nonspecific mediators of the immune system and enhance macrophage phagocytic activity. IgG antibody neutralized activity against *T. alholabris* venom [54]. Thai neuro polyvalent antivenin is considered second-line treatment for *Hydrophis schistosus* and *Hydrophis curtus* [55]. Both IgG and $F(ab')_2$ antivenins activated human complement system with IgG having significantly higher anti-complementary activity than $F(ab')_2$ antivenin [56]. *Agkistrodon halys* antivenin is more efficacious than green pit viper antivenin [30]. Anti-Cc and Anti-Mm $F(ab')_2$ cross reacted extensively with *Bitis arietans* venom, perhaps due to the presence of venom antigens common to the both snakes [57]. Gamma irradiated *Naja haje* antivenin showed higher neutralizing capacity [58]. Equine antivenom neutralized coagulant and hemorrhagic activities against *Rhabdophis tigrinus* snake venom [59]. *Pseudo naja* antivenin could not neutralize afbrinogenemia with serious consequences [60]. Hence clotting factor replacement therapy using fresh frozen plasma is associated with afibrinogenemia [61]. Gold nano-particle-based lateral flow assay is used for detection of snake envenomation [62]. Therefore, pharmacokinetics may be useful in design and optimization of antivenins [63]. Purification and characterization of new bioactive compounds in snake venoms would be of help in diagnosis and treatment of snake envenomation [64]. Sea snakes such as

Hydrophis schistosus and *Hydrophis curtus* produce venoms that could be neutralized by their neuropolyvalent antivenom (NPAV) and cross neutralization should serve as basis for antivenom purification [55]. Non-irradiated and gamma-irradiated polyvalent antivenoms could neutralize *Naja haje* [65]. Lack of potent monovalent and polyvalent antivenins could be responsible for gross disparity in the management of snakebite. Treatment of snake envenomation was introduced by Albert Calmette of the Institute Pasteur Saigon in the 1890s. The antivenom is either whole IgG or pepsin refined F(ab) fragments of IgG derived from plasma of horse, donkey, mule, sheep immunized with venom of one or more species of snakes lyophilized venoms that have shelf-life of about 5 years and should be stored at $\leq 25^{0C}$, whereas liquid antivenom have shelf-life of 2–3 years and should be stored at 2–8°C and not frozen. Antivenoms against *Naja naja*, *Bungarus caeruleus*, *Daboia russelli* and *Echis carinatus* are produced in India [66]. About 8–10 vials of antivenom against Russell's viper that injects 63 mg of venom is required. Each vial neutralizes 6 mg of the snake venom. Children should receive the same dose as adults, but should be observed closely for antivenin post administration reaction. Normalization of blood pressure in 15–30 minutes, stopping of coagulopathy in 6-hour, reversal of neurotoxicity in 30 minutes and recovery within 24–48 hours are the characteristics of effective snake antivenom. If there is coagulopathy, administration of anti-snake venom can be repeated every 6 hours or after 1–2 hours of the initial dose. Worsening of cardiovascular signs requires repeating dose of snake antivenom every 1–2 hours [67]. About 70% of all snakebites are by non-venomous snakes and 50% of bites by venomous species are dry bites [68]. Serum produced from irradiated *Naja haje* is more potent in venom neutralization than the serum produced from native venom. The two sera inhibit cardiotoxic and hepatotoxic effects [58]. *Crescentia cujete* fruit has significant neutralizing capacity against Vipera russelli venom [69]. Snake envenomation detection immune assay (SEDIA) is a potential diagnostic test for snake envenomation [52]. Milk whey (lactoferrin) could be an adjuvant to snake antisera [52]. Pharmacokinetics of venom from *Hypnale hypnale* are not changed by intramuscular injection of the venom, although may reduce systemic bioavailability of the venom [63]. Structures, cytotoxicities, and affinities to phospholipids of cytotoxins from the venom of *Naja haje* differ [70]. *Acorus calamus* and *Withania somnifera* root extract have neutralizing potential against venom of *Echis carinatus* [71]. Isolated chicken immunoglobulin (IgY) could neutralize viper venom [51]. Low dose snake antivenom with supportive treatment is effective, less cost, and has low level of adverse reactions [72]. IgY antibody could neutralize venom of *Trimeresurus albolabris* [54] and *Cerestes cerestes* venoms [48]. Indian snake antivenoms (VINS and BHARAT) are effective against *D. russelli*, *E. carinatus*, *B. caeruleus* and *N. naja* with VINS being more superior to BHARAT [37]. Serum harvested from polyvalent venom from different species of snakes could neutralize snake venom such as *Rhabdophis tigrinus* [59]. Too small initial doses of snake antivenom could not neutralize venom of *Pseudo naja*; hence the patient remains afribrinogenemic for long period of time [60]. Neutralizing potential of snake antivenom (IgY) could be improved by ion exchange chromatography. Therefore, IgG antivenom has significant complementary antivenom activity than F(ab′)2 antivenom [56].

4.3 Medicinal plants and phytochemicals against ophidism

Andrographis paniculata and *Aristolochia indica* could neutralize venom of *Daboia russelli* [41]. Higher dose of Haffkine polyvalent antivenom could neutralize venom of *Naja sumatrana* [40]. *Calotropis gigantea* could neutralize venom of *Vipera russelli* [73]. Brown snake, *Pseudo naja* causes venom induced consumption

coagulopathy with over one-third of patients having serious hemorrhagic collapse and microangiopathy. The venom is neutralized by one vial of antivenom [42]. *Androctonus crassicauda* antivenom could neutralize *Mesobuthus* venom found in Aegean region of Turkey [74]. Lectins from *Abrus precatorius* may be tried against snake and scorpion venoms. Because native and denatured agglutinin from the plant has immunomodulatory potential [75]. Hence, clinical studies of the effectiveness and safety of antivenoms have to be intensified because most currently marketed antivenoms were registered without any formal clinical or preclinical safety and effectiveness testing [76]. Change in amino acid sequence of a venom component can lead to a change of new compounds. Alpha bungarotoxin is cholinergic. Therefore, venom proteomics and genomics could lead to discovery of new therapeutic agents including antivenoms [77]. Natural and synthetic inhibitors of snake venom metalloproteinases are phenols and rosmarinic acid which inhibits hemorrhage caused by venoms of *Trimeresurus flavoviridis*, *Crotalus atrox* and *Gloydius blomhoffii*, *Agkistrodon bilineatus*, *Deinagkistrodon acutus* and *Bitis arietans*. Apigenin also inhibits venom of *Echis carinatus* and gallic acid inhibits venom of *Daboia russelli*, isoquercitrin, myricetin-B-O-glucoside and gallocatechin from *Schizolobium parahyba* leaves neutralized venoms of Bothrops species including *B. jararacussu* and *B. alternatus* [78, 79]. Matrix metalloproteinase inhibitors such as that of zinc-binding group, marimastat, prinomastat and tanomastat inhibit venom of *Echis ocellatus*. They are hydroxamic acid derivatives. Matrix metalloproteinases are grouped as astacins, serralysins and reprolysins under metzincins [80, 81]. Zinc containing endopeptidases and calcium ions could be chelated by ethylenediamine-tetraacetic acid, o-phenanthroline [82, 83], N,N,N,′N′-Tetrakis (2-pyridylmethyl) ethane-1,2-diamine (TPEN), diethylene triamine pentaacetic acid (DTPA), tetraethylthiuram disulfide (TID) in hemorrhage and myotoxicity caused by venom of *E. carinatus* [84]. Bisphosphonate clodronate, tetracycline and doxycydine inhibit hemorrhagic, proteolytic, coagulant and defibrigenotic effect of venom from *B. asper* [85]. A clerodane diterpenoid from *Baccharis trimera* caused inhibition of *B. neuwiedi* and *B. jararacussu* venoms [86]. Triacontyl p-coumarate from *Bombacopsis glabra* inhibited venom of *Bothropoides pauloensis*, *B. leucurus*, *B. jararaca* and *B. pautoensis* [87]. Macrolobin A and B (triterpnoid saponins) from *Pentaclethra macroloba* inhibited venom of Bothrops [88]. Linearol and isolinearol (secodolastane diterpenes) from *Canistrocarpus cervicornis* inhibited venom of *B. jararaca* [89]. Lupeol and lupeol acetate (terpenes) inhibited *E. carinatus*-venom induced damage [90]. Quinolones including 2-hydroxymethyl-6-methoxy-1,4-dihydro-4-equinolinone inhibited venoms of *B. jararacussu*, *B. moojeni* and *B. alternatus* [78]. N-acetyl cysteine inhibited gelatinase, hyaluronidase, hemorrhagic and defribrinogenating activities of *Vipera russelli* and *E. carinatus* venoms [91]. A derivative of citalopram (DFD) neutralized venoms of *E. carinatus*, *E. ocellatus*, *E. carinatus sochureki*, *E. carinatus leakeyi* and *Crotalus atrox* [92]. However, *Allium cepa*, *Securidaca longipedunculata*, *Carica papaya*, *Harrisonia abyssinica* and *Nicotiana tobaccum* are frequently used in treatment of snakebite. Low dose of snake antivenom is highly cost-effective as compared to the high dose [92].

4.4 Signs of scorpionism

Scorpion species of medical importance are represented by the genera *Androctonus*, *Tityus*, *Mesobuthus*, *Hottentotta*, *Parabuthus*, *Centruroides* and *Leiurus*. *Leiurus abdullahbayrami* caused hyperexcitability, agitation, aggressiveness, squeaking, fighting, tachypnea, weakness, convulsions and death due to cardiac and respiratory failure [93]. Envenomation of *Leiurus quinquestriatus* showed degranulation of eosinophils, fever, edema of cerebrum and myocarditis in rabbit [94].

Tityus pachyurus polock envenomation was characterized by sialorrhea, respiratory distress, profuse sweating, ataxia, restlessness, somnolence and hypoglycemia [95]. The toxicity of venom is relative to the maturity and weight of the scorpion [96]. *Tityus stigmurus* caused, cardiogenic shock, pulmonary edema, severe neurological symptoms and death [9]. Spontaneous glycinergic and glutamatergic post synaptic currents, suggest that scorpion toxin act on inhibitory and excitatory presynaptic nerves. *A. australis* venom is more toxic followed by *T. pachyurus*, *A. crassicauda*, *L. quinquestriatus*, *M. eupeus*, *L. abdullahbayrami* and *H. sauleyi* [93]. *A. crassicauda* scorpion venom could induce activation of human monocytes leading to promotion of expression of IL-12 [97] with molecular peptides (Acra 1 and Acra 2) that are similar to known sodium-channel specific toxins of other scorpions [98]. *M. gibbosus* endemic to Mediterranean area causes scorpionism characterized by pain, pulsating and gloving sensations, cold, sweat, paleness, excitation, occasional spasm of the affected part, tortuousness of the vein, which lasted for more than 4 years. Periodical tingling, and occasional muscle twitches were observed during night. The treatment was symptomatic [99].

4.5 Treatment of scorpionism

Local anesthetic is effective, while opioids are ineffective and increase the risk of respiratory depression. Non-steroidal anti-inflammatory drugs may be disappointing. Bio 10 ml of 10% calcium gluconate administered over 5–10 minutes relieves muscle pain and cramps and the effects last 20–30 minutes, hence safe limit dose is required. SA IMR scorpion venom antiserum is equine anti-scorpion globulin supplement in 5 ml per ampoule and 5–10 ml is required for adults and children. Its plateau effect is achieved in 2–6 hours, hence respiratory support is of paramount importance during the period. If case-response to first dose is inadequate, another 5 ml could be administered. The victim should be kept under close observation for at least a period of 6–12 hours. Electrolytes, pH, acid-base balance arterial blood gases, and electrocardiography should be used for assessment of scorpionism to avoid fatality. The rule of thumb is that scorpions with thick tails and slender pincers (e.g. Buthidae) produce more venoms than those with slender tails and large pincers. Hence speed of scorpion and a wave of potential neurotoxic effects are very important. Bioclon and Butantan are very effective antivenins against scorpionism [95]. Treatment of scorpion envenomation requires specific antiserum. Antiserum against *Buthus quinquestriatus* from immunization of horses with crude venom as antigen has been proven to be effective [100], and high amount of antivenins is required to achieve satisfactory neutralization [101]. *A. crassicauda* antivenin could prevent, neutralize and cure *M. eupeus* scorpionism if applied at optimum time, dose, and route [102]. The LD_{50} of *A. crassicauda* venom (1.1 mg/kg) and 39.19 mg/kg [103] make it highly toxic. The long half-life of venom in the body might require antivenin that has long half-life [101].

In Saudi Arabia, scorpionism is treated using 5 ml of antivenom diluted in 5–20 ml of saline and the solution was administered intravenously. Adjunct chemotherapy could be instituted when required. However, a 12-year-old boy inadequately treated with antivenom died from pulmonary edema, hematemesis, severe neurotoxicity, and circulatory failure. All the patients treated in Saudi Arabia stayed in hospitals for 1–2 days. The incidence of antivenom reaction was 1.7–6.6%, low protein level of antivenom, and high quality of catecholamine could lead to antivenom failure [101].

Two purified toxic fractions of *Mesobuthus eupeus* toxin were quickly eliminated from tissue [104] signifying that *M. eupeus* toxicity may not last long in the body. Dissociation of the toxin-channel complex during depolarization is determined by the difference between electrical energies of the activated states of normal and

toxin-modified channels [105]. The partially purified toxic fractions, when injected to rabbits, gave rise to more potent antivenoms against whole venoms as compared to presently commercially available antivenoms [106]. *A. crassicauda* has LD_{50} of venom (15.45 μg/kg) in mice, making it one of the highly toxic species of scorpions in the world [103]. *A. crassicauda* antivenom could neutralize *M. gibbosus* venom (20 LD_{50}) in Aegean region of Turkey [107]. Thus, highly potent antivenom could be produced from about 238 telsons in 51 days [74].

Comparing the calculated ratio of $\frac{292}{13.6}$ and $\frac{330}{13.6}$ which gives equivalent weight of 21.5 kg and 24.3 kg respectively shows that Butantan (292 μg/ml) and Bioclon (330 μg/ml) can be used effectively in the treatment of human weighing 21.5 and 24.3 kg body weight, respectively. Signifying that age plays role on the disposition of *Tityus* toxin, the toxic principle of Tityus species. Therefore, the difference in severity of symptoms observed in children and adults may be due to difference in pharmacokinetics of the toxin. *Mesobuthus eupeus* venom can be neutralized by nanovalent, polyvalent and anti-idiotype antivenom, respectively. They are non-toxicants and can be used as a vaccine in people at the risk of scorpion stings [108]. Scorpion anti-venoms are specific antigens, detoxified venoms or toxins, purified venom fractions, natural toxoids, recombinant toxins, synthetic peptides, monoclonal and recombinant antibodies [100]. Using peptides derived from the sequence of scorpion toxins, the penetration of antipeptide antibodies can neutralize the cognate venom [109]. Turkish antivenom against *A. crassicauda* is effective against other species of scorpions. Minimum lethal dose and minimum effective dose were used to evaluate the effect of Turkish antivenom on *M. gibbosus* envenomation [96] suggesting applicability of the new formula for calculation of effective dose for antivenoms. Scorpion sting results in adult morbidity and pediatric mortality [110]. The most lethal species are *T. serrulatus*, *T. bahiensis* in Brazil, *Centruroides suffusus*, *C. lionpidus*, *C. sculpturatus* in Mexico, *Leiurus quinquestriatus*, *A. crassicauda*, *A. australis*, *A. amoreuni*, *Buthus occitanus* in Middle East and North Africa, *Parabuthus grauntatus* and *P. transvaalicus* in South Africa, *Mesobuthus tamulus* and *Palamneus swammerdance* in India [111], respectively. One milliliter of *Androctonus crassicauda* antivenom could neutralize *Mesobuthus eupeus* venom. The antivenom is monovalent with immune activity and neutralizing capacity. The venom is produced by Refik Saydam Hygiene Centre in Turkey [103]. Also *A. crassicauda* antivenom could neutralize *Mesobuthus gibbosus* venom [96]. Stings from *Leiurus abdullahbayrami* causes hyperexcitability, agitation, aggressive behavior, squeaking, fighting, tachypnea, weakness, convulsions, and death due to cardiorespiratory failure. However, the venom has two kinds of protein with molecular masses of 4 and 6 kDa, respectively [93]. The condition was treated by dipping the affected hand in ice water, adrenaline (1:1000) was injected around the site of the sting and chlorpheniramine was injected intramuscularly into the upper arm. Snake antivenom made by J. Wyeth and Brother Ltd., Canada was administered intramuscularly [112] and produced desired therapeutic effect against scorpionism. Scorpion envenomation may be more dangerous in pregnant woman [113]. However, Meu TxKα3, a scorpion toxin-like peptide could undergo mutation at site 30 and help improve its K^+ channel-blocking and antibacterial function [114]. The designed bispecific NbF12–10 neutralized AahI and AahII toxins and could be used in the treatment of *Androctonus australis* envenomation. About 100-kDa horse antivenom serum could neutralize 7 kDa scorpion toxin and 15 kDa antivenom could neutralize AahI toxin. The NbAch1′ F_{12} fully neutralized 100 LD_{50} of AahI toxin [115]. Children with abnormal electrocardiography may require high dose of antivenom [116]. Aminotoxin could activate T lymphocytes and may be used as immunomodulators in infection and cancer [117] whereas Ca^{2+}-activated K^+ channel (ISK_2) is sensitive to apamin [118]. Nevertheless alpha-KTx peptides from the venom of *Centruroides*

elegans block Kv1.3 of T lymphocytes [119] whereas Tst26 peptide from *T. stigmurus block* Kv1.2 and Kv1.3 channels [120] respectively. *T. serrulatus* could be detected using molecular mass of the venom [121]. *Androctonus mauretanicus mauretanicus* toxin could cross-react with the serum of *Androctonus australis* [122]. *Androctonus mauretanicus* and *Buthus occitanus* contain mycotoxins and post synaptic neurotoxins with the first being more toxic. But the polyclonal antivenom prevented lethality from *A. mauretanicus, B. occitanus* and *A. crassicauda* venoms [123]. Venom of *A. mauretanicus* is more toxic than that of *A. australis* hector that is more toxic than that of *B. occitanus*. Lethality of scorpion venom in mammals is dependent on age and species of the animals [124]. That is why the pharmacokinetics of a *Tityus* toxin from *T. serrulatus* scorpion venom is dependent on the age of affected individuals [125]. Death due to scorpionism is secondary to cardiorespiratory failure [126]. Hence quick detection and quantification of venom is necessary for rational therapy, which is highly beneficial to reduce management costs and patients risk [127]. Equine F(ab′)2, IgG recombinant toxin, synthetic apitoxin, mAb, Fab, ScFv, chFab and rFab are of great benefit in treatment of scorpion and spider envenomation [128]. Minimum effective dose of antivenom is administered precociously by intravenous route to achieve efficient immunotherapy [129].

A. australis has complex venom that contains cytotoxic principles with very fast resultant fatal effects [130]. The effective monoclonal antibodies (mAbs) specific for the α-neurotoxin 1 (Aah1) from *A. australis* hector venom has been reported [131]. *A. australis* has recombinant toxin II with immunological and biological properties [132]. In addition, *Androctonus australis* hector (Aah) envenomation is mediated by cytokines and complement system, which in turn activate leukocyte to damage tissue [133]. But kinins are involved in cardiovascular toxicity and lethality of *L. quinquestriatus* venom in rabbits. *Androctonus australis garzonii* venom (100 μg/kg) was neutralized by 4 mg/kg of antivenom injected intravenously [128]. Antivenoms against a number of scorpion venoms have been reported [127], suggesting that the potency of antivenom should be investigated in relation to the scorpion venom [93] and both LD_{50} and ED_{50} should be determined paradoxically and canonically [134].

Intravenous LD_{50} of *Vipera herus berus* (0.4 μg/kg) with signs including headdrop, floppy neck, flaccid paralysis of limb, respiratory paralysis and death [135] and that of *Laticauda colubrine*, 0.05–0.13 μg/g [136], Sri Lankan *B. caeruleus* 0.07 μg/g [137], and *Naja sputatrix* [138] disagree with the reported LD_{50} (0.5 ng) of *Androctonus australis* [93] signifying that the venom of *V. berus berus* is less potent than with that of *A. australis*. Similar signs were observed for *V. nikolskii* venom (1.0 μg/kg) but the signs caused by phospholipase A_2 were lost after the mice were injected strontium [139], which may become antivenom against *V. berus berus* and *A. australis* venoms in future. The newly developed dot-ELISA for detection of venoms of Indian venomous snakes, *Naja naja*, *Bungarus caeruleus*, *Daboia russelli* and *Echis carinatus* [140] with comparative proteomic enzymes [141] may be also used to detect scorpion venoms. High level of toxicity of *Montivipera raddei* and *Montivipera bubjardahica* venoms is responsible for, high activity against A549 human lung carcinoma [142] signifying that scorpion venom may have anticancer activity. Lethal doses of *L. quinquestriatus* were 0.5 mg/kg i.v. and 3 μg/kg i.m. [143]. The LD_{50} of *T. pachyurus* venom in monogastric animals show that mouse (4.8 μg/kg) is highly sensitive to *T. pachyurus* venom, Hamster (3.48 μg/kg), guinea pig (2.40 μg/kg), rat (2.32 μg/kg), rabbit (1.16 μg/kg), monkey (1.11 μg/kg), marmoset (2.40 μg/kg), squirrel monkey (2.08 μg/kg), ferret (1.99 μg/kg), cat (0.74 μg/kg), dog and baboon (0.70 μg/kg), child (0.56 μg/kg), micro pig (0.52 μg/kg), mini pig (0.40 μg/kg) and adult human (0.37 mg/kg) respectively [103] indicating that *Tityus pachyurus* toxin is more toxic to all the species of animals [139] as compared

to American pit viper venom [144]. The toxicity may be due to the presence of *Tityus* toxins that are also present in *Tityus pachyurus*, *T. stigmurus*, *Tityus obscurus* and *Tityus serrulatus* venom. The toxic principle acts via Na^+, K^+, Ca^{2+} and Cl^- channels signifying excitatory effects on heart, CNS and muscular fibers [142]. Hence, mini pig could be the best model for determination of LD_{50} and ED_{50} for *T. pachyurus* venom and antivenom respectively for human application [103].

5. Conclusion

The toxicity of snake and scorpion venom is dependent on the quantity of the venom, whereas apitoxicosis in human is dependent on the number of stings and dose of venom produced per sting. Snake and scorpion venoms are the most dangerous. However, venoms of some snakes and scorpions are equipotent and require 2 or more vials of antivenoms. LD_{50} of honeybee venom in adult man is 2.5 mg/kg which can be neutralized by 7.5 mg/kg ($3LD_{50}$) of antivenin. LD_{50} of honeybee venom in child is 1.41 mg/kg and can be neutralized by 11.2 mg/kg ($7.9LD_{50}$) antivenin. The venom can kill in less than 4 hours. Hence, children are more sensitive to honeybee toxicity than the adults are, and so may require higher dose of antivenom. Spider and wasp envenomation are less severe and could be treated symptomatically. All the organ systems could be affected and complications could follow multiple attacks. Hence treatment is by administration of antivenins, anti-inflammatory, analgesic and respiratory support. Neurological and cardiorespiratory signs may be considered as indices of therapeutic success or failure. Prompt therapeutic intervention and hospitalization of 1 or more days could either delay or avert death. In the cases of severe anemia, blood transfusion and fluid therapy may be evident.

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