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Review Article

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Snakebite Envenoming: A Comprehensive Review on Epidemiology, Diagnosis, Potential Treatments Role of Proteomics and Bioinformatics

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ABSTRACT

Since snakebite has been a medical problem for many decades, very little progress has been made in reducing the number of people who die. Snakebite kills millions of people worldwide each year, and many more are severely harmed. A wide range of bioactivities, including bleeding, inflammation, and discomfort, as well as cytotoxic, cardiotoxic, and neurotoxic effects, are involved in snake venom's envenomation. Numerous toxin-rich proteins may be found in the venomous snake species whose antivenoms collectively include hundreds of poisons. Despite extensive research efforts, most snake venom toxins are still unidentified. Recently developed bioinformatics techniques for mining snake venom have facilitated an experimental study on the most interesting potentially toxic substances. Several computational approaches can predict toxin molecular targets and the binding manner to these sites. Modern bioinformatics is utilized to examine snake venom proteins, in addition to the usage of herbs in their therapy is also discussed in this study. Efforts should be made to ensure the availability of safe and effective antivenoms in low-income tropical countries at reasonable rates and to ensure their correct clinical usage in these nations.

Key words: *Snakebite envenoming, Medicinal plants, Cardiovascular, Viperidae, Bioinformatics*

INTRODUCTION

Envenoming from snakebite is an often overlooked tropical condition [1]. It is caused when a venomous snake injects its highly specialized and lethal secretion venom into a human, typically inadvertently [2]. Fangs are modified teeth attached to a venom gland in the snake via a conduit. Venom is injected into the victim through the fangs [3]. Because of the great level of complexity and diversity present in the composition of snake venoms, these substances have diverse biochemical and toxicological profiles, which in turn define a broad variety of analytic symptoms [4]. Some venom poisons produce local tissue damage injury, frequently leading to long-term consequences.

On the other hand, other toxins cause systemic effects, such as neurotoxic manifestations (which can result in, for example, paralysis of the respiratory muscles), acute renal damage, rhabdomyolysis (which refers to generalized destruction of muscle tissue), injury of heart muscle, central and peripheral nervous system disorder, or thrombosis are all possible complications [5-7]. Viperidae snakes belong to the Viperidae family, producing venom that can cause local effects and systemic signs such as loss of blood, coagulopathies, and hypovolemic breakdown [8]. Venom from snakes of the Elapidae family (also known as elapids) is primarily responsible for inducing neurotoxic symptoms, such as neuromuscular paralysis [9]. The superfamily Colubroidea, often known as advanced snakes, comprises more than 2,500 species [10]. These snakes have a broad geographical range and a long evolutionary history. All poisonous snakes are included in this superfamily since they belong to the taxon Caenophidia, which is part of the order Squamata and the suborder Serpentes [11]. The families Viperidae (which

includes real vipers and pit vipers), as well as Elapidae (which includes crocodiles), are home to some of the world's most lethal animals Cobras, kraits, sea snakes and mambas are examples of elapids [12, 13]. Because snakes are ectothermic, you will find a greater number of them in warmer climes. This means that the countries of the developing world that are most at risk for snakebite are tropical (particularly in various Latin American, African, and Oceanic nations) [14].

To some extent, interactions between humans and snakes are prevalent in those nations. This is particularly true during the rainy season, which corresponds with the mating season of snakes and is also a peak time for human agricultural activities. The significant load of snakebite envenoming in terms of mortality and sequelae is underscored by epidemiological evidence acquired from hospital records [15]. According to community-based surveys conducted in certain countries, the true death toll is significantly higher than the estimations derived from hospital-based statistics. In contrast, people living in nations with higher incomes, such as North America and Europe, have a much lower risk of being bitten by poisonous snakes. They are mostly unaware of the global epidemic caused by snakebites in other parts of the world [16]. As a direct result, financial agencies, public agencies, the pharmaceutical business, and health advocacy organizations have paid no attention to snakebite envenoming. As a result, it has been difficult to devise effective strategies to lessen the social burden of snakebites. Envenomation from snakebite is a form of morbidity and mortality common in tropical areas but often overlooked [17]. As a result of the low incidence of cardio-toxicity and the lack of reliable information, the effects of snakebites on the heart are not well recognized. This is mostly attributable to the fact that most snakebites happen in distant and rural locations [18]. This review aims to evaluate the effects of snakebite envenoming on the cardiovascular system and offer an algorithm for screening cardiovascular symptoms. After completing a systematic review, several studies pertaining to cardiovascular involvement in snakebite envenomation were selected for further study. It would appear that cardiovascular involvement is somewhat uncommon. However, when it does occur, it can lead to a broad variety of complications, including myocarditis, myocardial infarction, ventricular dysfunction, hypotension, and even cardiac arrest [19]. The cardiovascular symptoms were responsible for severe adverse outcomes in a sizeable number of the cases that were examined (24.39 percent) (cardiac arrest, myocardial infarction, malignant ventricular arrhythmias, or death) [20]. Patients showing signs of a systemic illness should have careful clinical surveillance, a thorough physical examination, and an early EKG. These should all be considered to be critical markers for detecting cardiovascular involvement. An overview of the review headings presented in the study was demonstrated in **Figure 1**.

Figure 1. Graphical representation of Snakebite Envenoming

Epidemiology

Snakebites seriously threaten public health in many regions of the developing world. Mortality and morbidity in the subordinate regions of the tropical and sub-tropical hemispheres include Sub-Saharan Africa, south to Southeast Asia, Latin America and Papua New Guinea. Snakebites cause envenoming in at least 1.8–2.7 million individuals annually around the world, with a higher level of death, approximately extending from 81,410 to

137,880 **(Figure 2)** [21]. There is relatively forty-six thousand mortality occurring only in India [22]. The yearly mortality rate in sub-Saharan Africa is about seven thousand and thirty thousand; however, these estimates perhaps were not accurate [23].

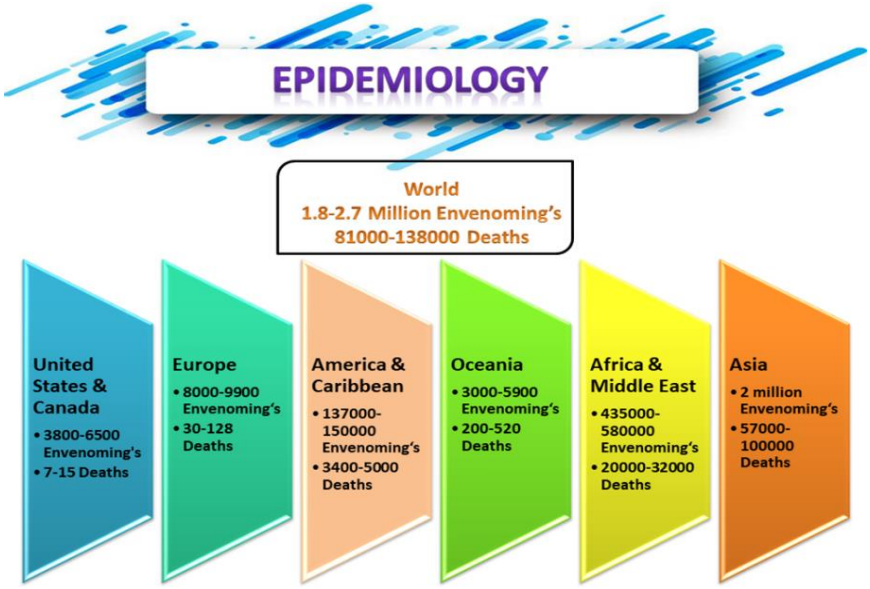

Figure 2. A global overview of snake envenoming and deaths

Snakebites disproportionately afflict lower socioeconomic segments of society, those whose home is substandard, and those with inadequate access to medical education. The most severely impacted nations are those with lower levels of lower human development index, low GDP (a measure that combines average lifespan, education, and earnings), and below levels of consumption on health care. Due to the exorbitant expense of treatment, the need for compelled borrowing, and the loss of income, the disease drives impoverished people farther into poverty. Indeed, those between the ages of 10 and 40, who make up the most productive members of rural communities, have the highest incidence of both bites and fatalities [24, 25]. Those under 5 years old have been found to have a higher case fatality rate. For instance, between the ages of 5 and 14, the proportion of people who died due to snakebite envenoming was the greatest in India. When children participate in agricultural tasks, play, or place their hands in the burrows of rodents, they risk being bitten by a snake [26].

Envenoming from snakebite is a disease that primarily affects young people and agricultural workers due to environmental and occupational factors. The exact people that are vulnerable vary widely from country to country. South African, Saint Lucia, and Martinique sugar cane farmers are in danger, as are tea pickers in southern India. Snakebite envenoming is the fifth largest cause of mortality in Myanmar, and it primarily affects people who work in the rice paddy farming industry. Families of agricultural workers are at risk. In warmer tropical seas, fishermen utilize hand traps and ropes [27]. Also at risk are fishermen who work in agricultural environments. Pregnant women are in a particularly precarious position, and it has been established that snakebite envenoming is a significant contributor to fetal and maternal mortality, as well as abortions and antepartum hemorrhages, in Nigeria and Sri Lanka [28].

Envenoming from a snakebite is another environmental hazard that affects native nomadic peoples, hunter-gatherers, tribal members, people who collect firewood, and the impoverished (those who are incredibly needy). This hazard has been identified in South America, Africa (particularly in the Hadza hunter-gatherers of Tanzania, the African Bushmen of the Kalahari Desert or southern Africa, and the nomadic Fulani and Turkana pastoralists (sheep or cattle farmers) of the savanna in West Africa and Kenya), India, and Sri Lanka [29]. In Africa, the Hadza hunter-gatherers live in Tanzania, the African Bushmen live in southern Africa, and the Fulani and Turkan Hadza people are hunter-gatherers who inhabit Tanzania, which is located in South America. In the native society of Australia, the seaside plains of New Guinea, and the Amazon rainforest, envenoming has been a major factor in the high fatality rates observed (the Yanomami and Waorani ethnic groups).

Some people evolve chronic morbidity, disability, and psychological sequelae after being envenomated by a snake. These sequelae include amputations, PTSD, myopia, loss of parental and fetal life, contraction (a condition of shorting and hardening muscle), cancerous ulcers and prolonged infectious disease. In sub-Saharan Africa, at

least 6,000 amputations are performed annually as a direct result of snakebite envenoming [30]. This number does not include amputations performed in other parts of Africa. Even when chronic disability is not considered, it is estimated that the cost of immature mortality simply due to snakebite envenoming in India is 2.97 million disability-adjusted life years, in contrast to the burden of snakebite envenoming worldwide is predicted to be 6.07 million disorder life years. In India, the cost of early mortality due to snakebite envenoming is calculated to be 2.97 million disability cases [31]. The worldwide death count of snakebite envenoming is more than twice as high as the cost proposed for efforts that were included below the category of having contact with venomous animals in the research conducted in 2013 for the global burden of disease study [32]. This brings to light the well-known problem of inadequate reporting of snakebite incidents in official records. The combined burden from snakebites is greater than the global burden for other neglected tropical diseases such as Buruli ulcer, echinococcosis, leprosy, trachoma, yaws, yellow fever, and podoconiosis. This is the case for 16 countries in West Africa [33]. Snakebites cause both early mortality and disability, which is a factor in the combined burden of snakebites [34]. This is because the total burden from snakebites includes both premature mortality and disability from snakebites. In sub-Saharan Africa, the combined burden of trypanosomiasis, leishmaniasis, and onchocerciasis is larger than the burden of snakebites [35].

Pathophysiology

Venoms have independently developed in various species, including spiders, jellyfish, snakes, and scorpions. Venoms serve predatory and offensive functions found in a vast spectrum of phylogenetically diverse organisms. Venom is an example of a trophic adaptation that is essential for foraging by poisonous snakes [36]. Fundamentally, the development of venom has played an important part in the biological environment and evolutionary history of splendid snakes. Venoms are made up of protein combinations of various complexities as a direct consequence of Strong Darwinian selection resulting in fast progression. These protein complexes can either work independently or as part of a combined phenotype to slay or slaughter the prey or unintentional victim [37, 38]. Venom, both within and across species, appears to be a property shared across all taxonomic groups; even though these characteristics exhibit only in terms of the number of genes that encode poisons, there is a modest level of genetic complexity. Genomic reorganizations and other changes in genes encoding toxins and poison expression patterns might have had a role. However, the methods that generated such a diverse array of organisms are still a mystery to scientists [39]. Convergent structural and functional evolution has played a role in the formation of animal venoms, just like in forming eyes, fins, and wings, each developed separately in their respective lineages [40]. Genes that produce proteins with specific structural patterns have been repeatedly chosen as templates for neofunctionalization, the process by which a gene acquires a new function following the duplication of another gene through convergence. Specific structural motifs are encoded by these genes, which produce proteins. Snake venom becomes more complicated when genes are duplicated and quaternary linkages are made in homomer or heteromer multiprotein complexes. Only a small subset of multigenic protein families is represented by these protein mixtures. There is a lot of variation within and amongst several of these protein families [41]. Toxin effect of the snake venom was demonstrated in **Figure 3**.

It is essential to have a solid understanding of the evolutionary processes and ecological constraints that led to the range of snake venoms that exists today to correctly define species' phylogentic and graphical borders. One way to accomplish this goal is by demonstrating the spatial and temporal distribution of venom composition changes within and between species. It is possible that shedding light on the interdependence of evolutionary and clinical toxicology can be accomplished by gaining insights into the selection variables formed in the process of local adaptation and species-level diversity in venoms [42]. The most medically significant toxins in a human envenoming are often those that cause the greatest incapacitation in prey. A better understanding of the molecular mechanisms by which venomous snakes adapt to their natural habitats will guide the development of next-generation snakebite therapeutics that are more effective at neutralizing snake venom [43].

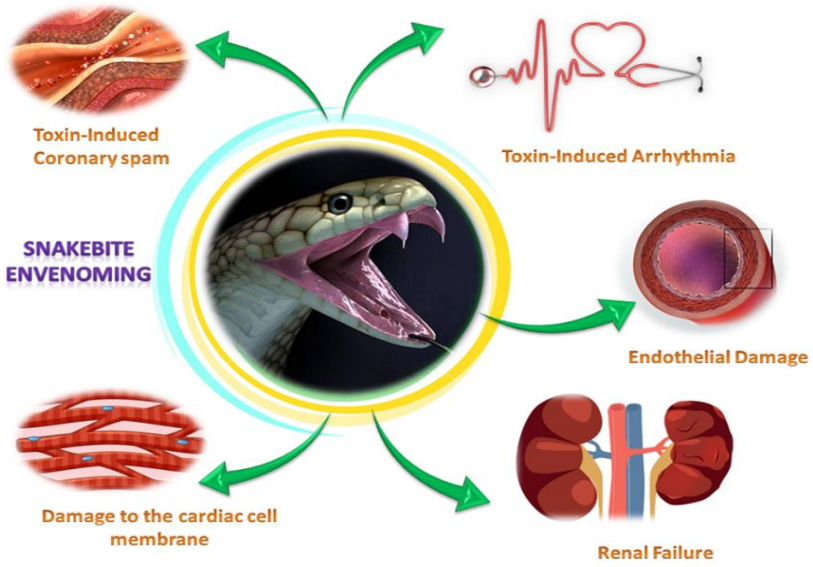

Figure 3. Toxic effects of snake venom toxins on the human body. Venoms have a wide spectrum of poisonous effects on the human body, and the venom's makeup determines the most harmful effects. Neuromuscular paralysis caused significant tissue damage to the victim and increased permeability of the blood vessels caused by viperid venoms, and cardiovascular shock might occur.

Snake venom composition

The increased interest in various aspects of venom biology has catalyzed the development of approaches known as "-omics," which aim at the qualitative and quantitative characterization of venom poisons. One such methodology is the proteomics of venoms. Particularly, the integration of next-generation transcriptomics and proteomics techniques has shown that it can characterize venom in unprecedented detail. This article provides a synopsis of the relative distribution of the primary classes of poisonous components found in the venoms of viperid and elapid snakes [44, 45].

The investigation of the immunological response of antivenoms (also known as antivenins, antivenenes, anti-snakebites, and anti-snake venom serum), a range termed 'antivenomics,' against venoms is an easy translational application of the corpus of knowledge collected through venomics. Antivenomics is a methodology based on proteomics used to quantify the degree to which antivenoms respond cross-reactively with homologous and heterologous venoms. When used together, antivenomics and in vivo neutralization testing make up an effective toolset for determining the potential therapeutic usefulness of antivenom before it has even been tested on humans **(Figure 4)** [46].

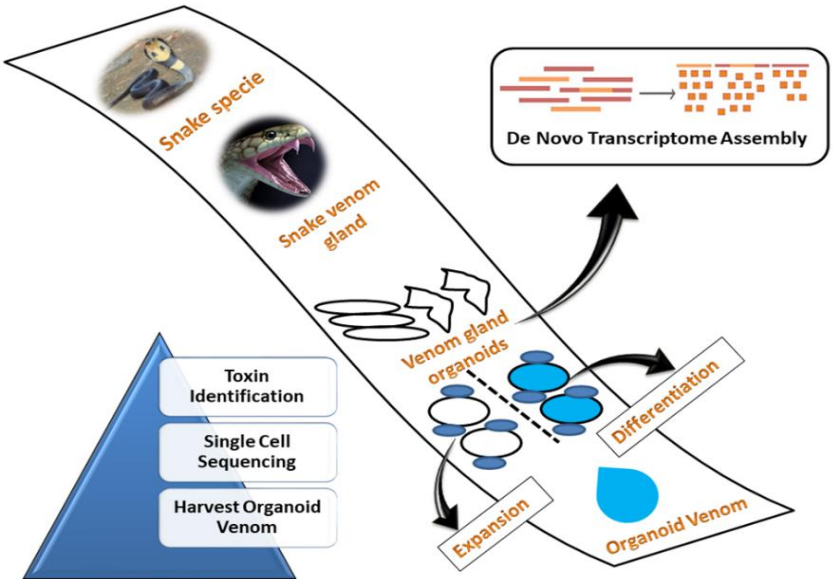

Figure 4. Different steps involved in the composition of snake venom

Diagnosis & prevention

Aside from snakebites, medical crises present a significant clinical challenge because they can be fatal very quickly. The process of decision-making is made more difficult by the existence of unanswered questions concerning the identity of the species, as well as the quantity of venom injected and its composition, both of which can change depending on the age of the snake as well as within the species itself across its geographical range [47]. Registered nurses or health assistants treat most snake bites at health centers, pharmacies, clinics, and medical centers in regional and remote regions [48]. Depending on the severity of the patient's condition, it may be feasible to transfer them to a tertiary hospital in the province, which offers specialized medical care as well as critical care units and laboratories.

Diagnosis

If envenoming is suspected, it is necessary to get a detailed history of the patient's symptoms and look for any evidence of it immediately to administer the most effective, life-saving treatment. In order to rule out hypovolemia, vital signs must be included in a fast clinical examination, Postural heart rate measures, investigations performed for ptosis and indications of progressive immobility, such as respiratory failure, and examination for sudden systemic bleeding. In the middle of the night, patients who are bitten by kraits (Bungarus spp., family Elapidae) generally wake up aware that they have been bitten. Arthropod (such as a spider), lizard, rodent, or fish bites; hymenopteran (such as a scorpion or centipede) stings; or punctures caused by plant spine or thorn, nail, or other sharp object are all differentiating factors for snakebites [19, 49]. It is possible that venomous or non-venomous snakes inflicted 'dry bites' (i.e. transcutaneous bites without envenoming) inflicted these bites, resulting in negligible or no symptoms. A professional herpetologist can identify the snake species if the dead snake or an image of it is available [38, 50]. Snakebite victims and spectators can provide useful information if they can describe their symptoms in detail and identify characteristic patterns (syndromes) in their symptoms.

Laboratory and other investigations

Laboratory tests can help detection of systemic envenomation and management of snakebites. Envenomation is confirmed by peripheral neutrophil leukocytosis, which is indicative of a general inflammatory reaction. A hemorrhage with an HCT (a low red blood cell count) indicates severe bleeding. At the same time, hemoconcentration from plasma leakage into tissues due to enhanced capillary permeability is indicative of high hematocrit [51]. Microangiopathic hemolysis, identified by schistocytes in a blood film, can cause acute kidney injury when severe thrombocytopenia goes hand in hand with severe bleeding diathesis. Viperids, Seas elapids, and colubrid snakes with no front fangs can all inflict systemic envenoming on humans, and incoagulable blood is a telltale symptom of that. Twenty minutes of room temperature, undisturbed waiting time is all it takes for the easy 20-minute whole-blood clumping test to reveal whether or not a little amount of venous blood has coagulated. If coagulation is impaired, it suggests that the animal has been poisoned with anticoagulant venom, which is extremely dangerous [52]. Scientific tests such as prothrombin and activated clotting times, fibrin breakdown enzymes, and D-dimer can detect disseminated intravascular coagulation. Severe muscle damage can be seen if creatine kinase levels are greater than 10,000 units/liter in the bloodstream. All individuals with signs or symptoms of acute renal damage should have their potassium levels checked. Blood and other proteins should be detected in the patient's urine upon admission. Slight atrioventricular block or signs of myocardial ischemia can be seen on an ECG, as can sinus bradycardia, ST–T alterations, and other abnormalities. Patients with pre-existing coronary artery disease are at risk for myocardial infarction, which can occur due to shock. Pericardial effusion, myocardial failure, and pleural and peritoneal hemorrhage can all be detected by echocardiography [31]. It has also been suggested that wound ultrasonography can detect tissue damage. Intracranial hemorrhages and infarcts can now be assessed using CT and MRI.

Detection of venom

Retrospective confirmation of species identification, prognosis prediction, and antivenom therapy efficacy can all be derived from enzyme immunoassays, which detect and quantify venom antigens in the body fluids of snakebite victims. Commercial venom detection kits can identify high amounts of antigens within 15–30 minutes, but these kits are only accessible in Australia (produced by Seqirus) [53]. In order to identify between venoms from closely related species, venom detection tests are very sensitive but not specific enough. It is unnecessary to treat the patient with antivenom simply because venom was found in a wound sample. Tissue around the fang puncture wounds, incision and blister aspirate, serum, and urine samples should be saved for enzyme immunoassays In

forensic instances [54]. Reverse transcription PCR and snake-derived DNA in bite-wound swabs are used to identify the venom gland mRNA of the biting species, among other approaches.

Prevention

The most efficient way to avoid snakebites is to have educational initiatives driven by the community and aimed at the people most likely to be bitten [55]. Utilizing radio, television, cell device apps, social networks, banners, magic shows, or public gatherings in smaller towns are all effective methods of communication that should be used [56]. It is necessary to raise public awareness about the dangers of envenoming from snakebites and provide direction on walking, working, and sleeping more safely. Even in places where traditional ambulances are unavailable, patients bitten by snakes can still be transported to medical facilities where they can be treated. This can be accomplished, for instance, by using boats or by having volunteer village-based motorcyclists transport the patients. It is critical to prevent people from wasting time using traditional therapists because this practice is inefficient.

Management

First aid

If someone has been bitten, they or witnesses should administer immediate first aid. Important features include assurance, immobilization, removal of rings and other tight objects, pressure pads or pressure bandages over the bite incision to minimize the spread of the venom through the veins or lymphatic system, and reassurance. To go to the nearest medical facility, the patient needs to be transferred as quickly as possible, ideally quietly. Paracetamol (also known as acetaminophen) or opioids should be used to manage pain; aspirin or NSAIDs should not be used because they can increase the risk of bleeding [57]. Place the patient in the recovery posture and implant an oropharyngeal airway to minimize the danger of lethal shock and upper respiratory obstruction (via bulbar paralysis or fluid aspiration) during transit (a tube to maintain the airway). Avoiding harmful therapies, including incisions, suction, and tight tourniquets, must be avoided. Atropine, an antimuscarinic, and neostigmine, an acetylcholinesterase inhibitor, have been suggested as first aid for suspected cases of neurotoxic snake bites from Acanthophis species, some Micrurus species from Latin America, and other elapids whose venoms mostly act on postsynaptic receptors of the neuromuscular junction [58].

Administration of a healthcare facility

There should be at least 24 hours of clinical assessment for patients who claim to have been bitten by snakes. Before removing an in situ compression bandage or tourniquet, ensure you have an intravenous line and all the resources you will need for urgent resuscitation. As soon as a patient cannot breathe and is cyanotic (blue lips, tongue and mucosae), the airway should be reopened and any available source of oxygen administered. Intravenous fluids should be administered as soon as possible if the patient is in shock. As previously said, the severity of pain might vary, but if it is severe, it should be managed as per the guidelines [59]. Patients who initially appear uninjured might suddenly and abruptly decline for only a few minutes or hours. Inherently inaccurate or harmful, published severity scores are typically based on artificial criteria. The enzyme immunoassays used to measure venom antigen concentrations in blood or plasma have been demonstrated in various trials to be useful in predicting prognosis. Snakebite victims should be closely watched for signs of envenomation, including ptosis and spontaneous bleeding, as well as the degree and severity of local edema. Urine output should also be closely checked. Intra-compartmental pressure should be monitored if clinical compartment syndrome (substantial swelling of muscles trapped in a tight fascial compartment that could endanger blood flow) is suspected. Patients with neurotoxic envenoming may be difficult to assess because of their generalized flaccid paralysis, which makes the commonly used Glasgow Coma Scale deceptive for their degree of consciousness measurement. A patient may not be able to open their eyes, speak, or accept directions; nevertheless, if cardiorespiratory support is adequate and their upper eyelids are elevated, they may be able to express 'yes' or 'no' by flexing a toe or finger. Antivenom is the most critical decision to be made after the patient has been revived and a species diagnosis has been attempted. Antivenom. Snakebite envenoming's systemic consequences can only be treated with antivenom, the only specialized antidote that works [60, 61]. Horses, sheep, or other large domesticated animals such as camels that have been hyper-immune to one or more venoms for months to years are the source of antivenom. Since removing the Fc molecule from an antigen-binding (Fab) fragment is thought to reduce the likelihood of an allergic reaction, most antivenom manufacturers worldwide use enzyme digestion with pepsin to refine entire IgG taken from animals' plasma. Other antivenoms are made using papain to reduce

the size of Fab fragments and boost their distribution speed, but this has the drawback of making recurring envenoming more likely. Caprylic acid precipitation is commonly used to purify entire IgG molecules, which are then used in several antivenoms [62]. Affinity column purification can be used to extract antivenom antibodies, enhancing both the process's safety and cost. Antivenoms developed against the venoms of the most medically significant snake species in a single geographical area are known as polyvalent (polyspecific) antivenoms. Indian antivenoms that are effective against the 'big four' national species: the Naja naja (Elapidae family), the *Bungarus caeruleus* (Elapidae family), and the Viperidae family's *Daboia russelii* (*Echis carinatus*) (family Viperidae). Monovalent (monospecific) antivenoms, on the other hand, are developed to combat the venom of a particular species; for instance, European ViperaTab (Flynn Pharma) works against the venom of *Vipera berus* (family Viperidae). For more than a century, antivenoms have proven effective against many of venom's deadly and destructive consequences [63]. In addition to reversing anti-hemostasis, hypotension, and post-synaptic neurotoxicity, antivenom can prevent or reduce presynaptic neurotoxicity, rhabdomyolysis, and local tissue necrosis when given early. The most critical therapeutic choice in treating snakebites is whether to administer antivenom [64]. A specific antivenom must be chosen for each case of snakebite based on identifying the snake that bit the victim. Antivenoms are extremely specific and neutralize only the venoms used in their synthesis, along with those of a few related species. Antidotes can be expensive, hard to come by where they are most required and may need to be stored in a cold chain for transportation and storage. Syntax, Behringwerke, and Sanofi Pasteur are only a few major antivenom producers who have ceased production over the past few decades, mostly for business reasons, resulting in acute antivenom shortages in Africa. Only a small percentage of snakebites necessitate the use of antivenom. Adults and children alike receive the same dosage. Ideally, the beginning dose should be based on data from clinical trials. However, as these are rare, the manufacturer's estimate of neutralizing potency based on rodent median effective dose usually serves as a guide. The dose is raised and repeated if worsening neurotoxic or cardiovascular symptoms after 1–2 hours or the persistence of incoagulable blood after 6 hours. It is usually administered intravenously and takes anything from 10–60 minutes [65]. During the first two hours of antivenom treatment, patients should be continuously monitored for allergic and pyrogenic reactions. It is possible to lessen the frequency and severity of these dose-related early adverse antivenom reactions by giving adrenaline as a preemptive treatment. Reactions should be treated as soon as possible with intramuscular injections of adrenaline in the event that they occur (frequently itching and the formation of urticarial plaques; restlessness; nausea; tachycardia or tachypnoea).

Alternative treatment

Envenoming-induced organ and system breakdowns must be identified and treated. Both manually or mechanically, supraglottal or endotracheal intubation and assisted breathing are essential in treating patients with paralytic respiratory and bulbar dysfunction [66]. Acetylcholinesterase inhibitors, such as neostigmine, given with atropine, may improve neuromuscular transmission temporarily, but they are no substitute for antivenom in treating snake venoms. In patients with bilateral ptosis, the ice pack test (in which an ice pack is applied to one upper eyelid to lower local temperature and inhibit endogenous acetylcholinesterase) can predict response to acetylcholinesterase inhibition. Edrophonium is one such short-acting acetylcholinesterase inhibitor. A cautious fluid volume re-infusion and vasopressor medications, such as dopamine, are used to treat hypotension and shock that persist despite antivenom treatment. Renal replacement therapy is required if the acute kidney damage continues despite conservative treatment. While a tetanus toxoid booster is always recommended, prophylactic antibiotics have no place in this situation [66, 67]. However, a broad-spectrum antibiotic should be given if the wound has been incised or there is evidence of tissue necrosis, wound infection, or local abscess formation. Debridement (removal of necrotic tissue) and skin grafting may be required in some circumstances, and some gangrenous digits or limbs may necessitate amputation in some situations. Compartment syndrome (for example, the anterior tibial compartment) is a common complication in snake-bitten limbs, and surgeons are tempted to perform fasciotomies to treat it (a surgical procedure to improve circulation by incising fascial compartments) [68]. Fasciotomy is rarely warranted since intra-compartmental pressure normally remains within normal limits. Fasciotomy has proven catastrophic in patients whose anti-hemostasis has not been restored by enough antivenom. Unnecessary fasciotomies can exacerbate hospitalization and long-term morbidity.

Treatment

Polyherb combination medication therapy is becoming more popular because of its effectiveness and cost-effectiveness. Even if it has not been put into practice, this hypothesis should be looked into because of its low

cost, fewer side effects, lack of expiration, RT-storage, local availability, ease of administration, and double protection in the case of snake bite management in the presence or absence of AVS. However, like all other therapies, it has its drawbacks, such as limited yield, geographic variation, and toxicity [69, 70]. As a result, it is critical to protect the diversity of nature while also figuring out how the aforementioned herbal substances counteract the effects of snake venom. According to the findings of this review study, the peoples of the world have a wide variety and depth of traditional knowledge about medicinal plants.

In contrast, the antivenom providers are unreliable, and the products are quite expensive when accessible. Due to their tendency to trigger hypersensitivity reactions in sensitive people, antivenoms cannot be used to treat snake venom poisoning. An investigation into whether antagonizing snake venom's hepatotoxicity, anti-inflammatory, anti-oxidant, and anti-cancer properties are the same as antagonizing other systemic actions is important [71]. New plants must be tested regularly to further our understanding of complementary and alternative medicine. The theory of polyherb combination drugs (crude/pure) must also be improved. Herbal products, such as those used to treat snake bites, require a multidisciplinary approach in alternative medicine. Africa's ethnic rural cultures are heavily influenced by indigenous knowledge and plant use [72]. The primary goal of this study was to describe the traditional plants used by African healers to treat snake bites and, as a result, to compile a list of those plants. For all the researchers who have contributed so much to the vast body of knowledge on this subject, this is an earnest attempt at providing them with a stage. There are several areas where little is known about herbals for snake bites that require a significant amount of clinical investigation. There are several examples of medicinal plants in the herbal world that are useful against venom [73]. As a final note, the ultimate goal of health care services (traditional or modern) is to alleviate illness and avoid human or animal suffering; hence the following guidelines are made to achieve this goal.

Use of medicinal plants

As much research as possible must be conducted on the herbal remedies that traditional healers use to treat snake bites [74]. Based on the results of this research, decisions should be made, and instructions should be given to traditional healers regarding the safe use of herbal remedies, with particular emphasis on dose-related issues. Traditional healers should also be informed to take responsibility for their actions. Traditional healers use medicinal herbs, some of which effectively treat snake bites [75]. There should be a concerted effort to collect data on these plants. Investigations of the plants' phytochemical and pharmacological properties will undoubtedly lead, in the end, to the identification of those plants that have the potential to be beneficial as medicinal agents in the treatment of snake bites. Instead of criticizing traditional medicine as a whole as being ineffective and inferior, the government ought to encourage and create incentives for the most successful aspects of traditional healing rather than attacking traditional medicine as a whole [76]. This will be a powerful incentive for traditional healers to pass on their expertise to subsequent generations.

Table 1. Snake bites were traditionally treated using medicinal plants

Plant	Family	Local Name	Part of Plant Used	References
Cyphostemma junceum	Vitaceae	Etse Zewe	Chewing roots	[77]
Gossypium herbaceum L.	Malvaceae	Tit	Chewing root	
Pergularia daemia L.	Asclepiadaceae	Yeayit Hareg	Root	
Plumbago zeylanicum L.	Plumbaginaceae	Amira	Chewing Leaves	
Combretum molle G. Don	Combretaceae	Muama, Kiama	Root	[78]
Conyza sumatrensis	Asteraceae	Yadh asere, yadh	A leaf infusion of the plant	
Entada leptostachya	Fabaceae	Mwaitha	Crushed Stem	
Opilia amentacea Roxb.	Opiliaceae	Mutonga	Roots Crushed Powder	
Solanum incanum L.	Solanaceae	Mutongu	Stem and Fruits dried Powder	
Microglossa pyrifolia	Asteraceae	Nyabungodidi,	Chewing Leaves and Juice	
Boscia angustifolia	Capparidaceae	Kermed	Root Stem Bark	[79]
Nicotinia tabacum	Solanaceae	Timbhako	Leaves	
Solanum incanum	Solanaceae	Engulle/sengol	Root	

Role of proteomics and bioinformatics

In recent years, significant advances in proteomics have resulted in a rapid increase in knowledge of the peptides and proteins present in animal venoms, especially snake venoms. Snake venom is included in this category [80]. The quick detection of a nearly complete range of poisons found in a snake's venom now mainly owes to these methods. Previously, approaches that relied simply on reversed phase-high performance liquid chromatography (RP-HPLC) and mass spectrometry could not achieve this. Effective computational approaches are necessary to mine this massive volume of data. The number of poisons discovered by modern "omics" methods is enormous. This review will focus on databases that allow for the search and retrieval of information about snake toxins [50, 81]. This article will cover the computational approaches created to aid in investigating the activities of snake poisons. One of these computational techniques is the prediction of three-dimensional toxin structures and their interactions with molecular targets. In this lecture, we shall discuss the benefits and drawbacks of employing molecular modeling to forecast binding affinities and specificities and the future implications of combining this data. The biology of venoms, as well as poison target prediction in live creatures, finally, we will talk about how modern. Bioinformatics was used to analyze the function of a protein present in snake venom and the biological targets of this protein.

Bioinformatics and snake venom

Protein sequences and three-dimensional structures can be easily accessed through databases like UniProt, NCBI Genbank/GenPept, and the Protein Data Bank (PDB) [82-84]. This information is not standardized, especially regarding the naming of toxins and their pharmacological activities, and it is difficult to mine for snake venom peptides in these resources. In addition, the database relies on author submissions of information, which leads to numerous duplicate entries. A large body of work is being published in peer-reviewed articles but not submitted to the general databases. Some venomous animal databases are beginning to emerge. One can find information on cone snail venoms via Conoserver, Arachnoserver, and ISOB (Indigenous snake species of Bangladesh) [85]. The Swiss Institute of Bioinformatics (SIB) has developed a new resource, Venom Zone, which contains information on the venoms of six different species of organisms, including snakes. Taxonomy, activity, and venom protein families are used to organize the website's content, making it easy for users to find what they want. In addition, all of the data is linked to the venom protein information from UniProtKB/Swiss-Prot and UniProtKB/Trembl (which have been manually annotated and reviewed) (automatically annotated) [86, 87]. Uncharacterized peptides and proteins can benefit from the knowledge gained from studying the activity of peptides that have been thoroughly characterized. The use of specialized databases in this context is critical for accessing data, predicting toxins' three-dimensional structure and function, and identifying outstanding toxins with potential new characteristics **(Figure 5)**. As a result, the number of toxins in a particular animal's venom can be unreliably estimated because there is currently no widely accepted and standard method for annotating toxic substances from the abovementioned data. This issue could be solved using machine learning-based classifiers. Machine learning tool Tox Classifier distinguishes between the toxin and non-toxin sequences, allowing toxin proteins to be assigned to the most appropriate family, increasing the quality of these existing databases [19, 88].

Proteomic analyses of snake venom

Peptides and proteins make up the proteomes of snake venom. Recently, a review of proteomic approaches to studying snake venoms was published [89]. Electrophoresis, liquid chromatography, Edman degradation sequencing, amino acid analysis, enzyme digestion and mass spectrometry are some of the commonly used techniques in these approaches. High-performance liquid chromatography, Edman degradation, protein MALDI-TOF/MS, 1D or 2D PAGE, and digested protein ESI/MS/MS sequencing are the most widely used methods.

Venom extraction, which is done by "milking" a live snake, is the first step in studying the proteomes of snake venom. An effective method of snake milking is to force the snake to bite into an appropriate container. High-performance liquid chromatography (RP-HPLC), ultra-high performance liquid chromatography (UHPLC), and exchange chromatography are used to separate the proteins after venom collection [90]. Mass spectrometry and Edman degradation determine the peptide sequences after fractionating the crude venom. Several steps must be completed before a peptide can be subject to an MS/MS analysis, the most common of which are reduction, alkylation, and enzymatic digestion. Finally, nuclear magnetic resonance spectroscopy examines the tertiary structure [91].

Most of the cysteine residues in original sequences of snake venom peptides and proteins have cross-linked disulfide bridges. Snake toxins' ability to enhance activity, increase resistance to proteases, improve selectivity,

and stabilize secondary structural elements has been connected to the stabilization underpinning by the synthesis of disulfide bridges. Snake peptides also vary in the number of disulfide bonds they contain [92].

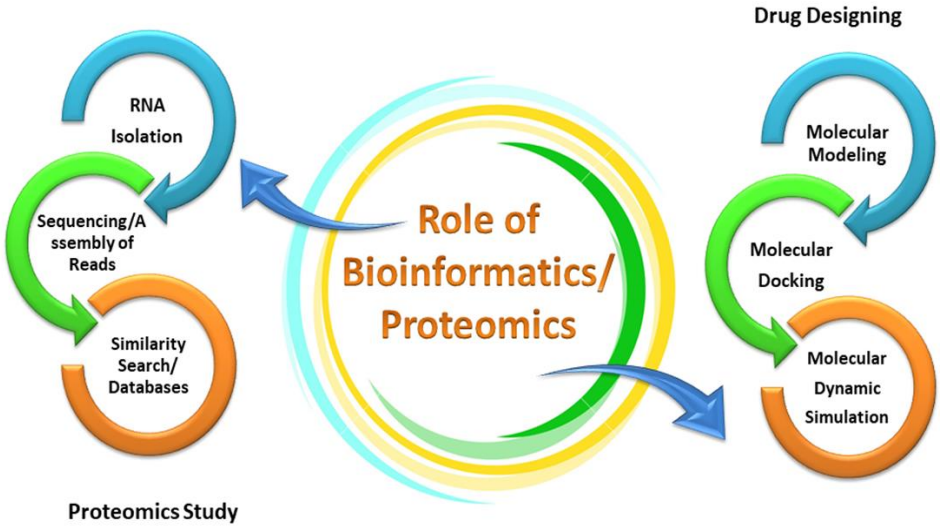

Figure 5. Role of Proteomics & Bioinformatics in snake envenoming's

CONCLUSION

In order to control snakebite envenoming, international cooperation is required to implement this multi-tiered roadmap coordinated by the WHO and engage many stakeholders. As a result, implementing such a comprehensive approach will necessitate a significant investment in terms of time, money, and other resources from United Nations Member States, donor organizations, snakebite experts, and other stakeholders. Bioinformatics has been utilized extensively to characterize the active chemicals in snake venoms, from discovering genes and proteins through their 3D structure and interactions with molecular targets. We have demonstrated this extensively here. Predicting the selectivity of toxins like snake toxins is difficult in molecular modeling and bioinformatics. Toxins, on the other hand, tend to target ion channels with various subtypes, each of which has a different effect on the body. Phenotypic screening procedures may have a better probability of discovering new medications than current pharmaceutical industry practices, which focus on modulating a specific molecular target. According to this approach, a pre-screen using bioinformatics could uncover molecules more likely to be different from the known poisons.

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