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REVIEW ARTICLE

Computational exploration of Plant Ribosome Inactivating Proteins (RIPs) in countering Snake venom: A novel therapeutic opportunity and challenges

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Abstract

Snakebite envenoming represents a critical global health challenge, particularly prevalent in regions with limited access to healthcare resources, where venomous snakes pose a significant threat to human populations. Antivenom therapy which mainly rely on antibody production by immunization of large animals with venom components is labour intensive, time consuming and associated with various ethical concerns. Consequently, access to quality and affordable antivenom remains limited in many affected regions with high mortality associated with snakebites. In traditional medicine, many plant species have been ethnobotanically reported for their antivenom properties and are used to neutralize animal toxins. Ribosome-inactivating proteins (RIPs) are a diverse group of toxins found in various organisms, including plants that possess the ability to inhibit protein synthesis by irreversibly damaging the ribosomes. Even though considered to be harmful, the biological role of RIPs has gained increasing attention in recent years due to their potential therapeutic implications. With these insights, this review underscores the potential of RIPs as promising candidates for adjunct treatments in snakebite management strategies. *In silico* analysis by molecular docking of RIPs with major snake venom proteins resulted in effective binding and shows the interface residues involved in the interaction. This integrative approach enhances our understanding of snakebite pathophysiology, accelerating the development of novel next generation antivenom therapies that are safer and more effective.

Keywords: *in silico* analysis; interface residues; major snake venom proteins; molecular docking; neutralizing snake venom; next generation antivenom; Ribosome Inactivating Proteins (RIPs); snakebite envenoming

Introduction

Certain species in the animal kingdom have evolved with production of toxic compounds in various parts of their body for the purpose of defence, predation or competition (1). When humans are attacked by these animal species, they inject venoms or poisons that cause various inflammatory reactions leading to short-term and long-term effects on human health (2). Since these venomous bites are considered as a medical emergency, allopathic treatments are often employed for recovery. In traditional medicine, many plants were ethnobotanically reported neutralizing these animal toxins. But the bioactive compound present in these plants acting against the animal toxins were not completely characterized. By understanding those compounds, we would be able to produce an alternative medicine.

Nature has always blessed human beings with numerous plant species. Plants, being used as food, feed, medicine, fuel and even as poison are subjected to various stresses from the surrounding environment. To overcome stress and survive, they undergo several defence mechanisms and one such interesting mechanism adopted is producing toxic bioactive compounds (Fig. 1) (3).

These toxic compounds range from low molecular weight phytochemicals to high molecular weight proteins (4) such as RIPs, plant protease inhibitors, lectins, α-amylase inhibitors, canatoxin like proteins, ureases, arcelin, pore-forming toxins and antimicrobial peptides undergo specific activities in plants to give resistance against several biotic and abiotic stresses aiming to a persistent life (5). These phytotoxins when consumed by humans may lead to numerous side effects.

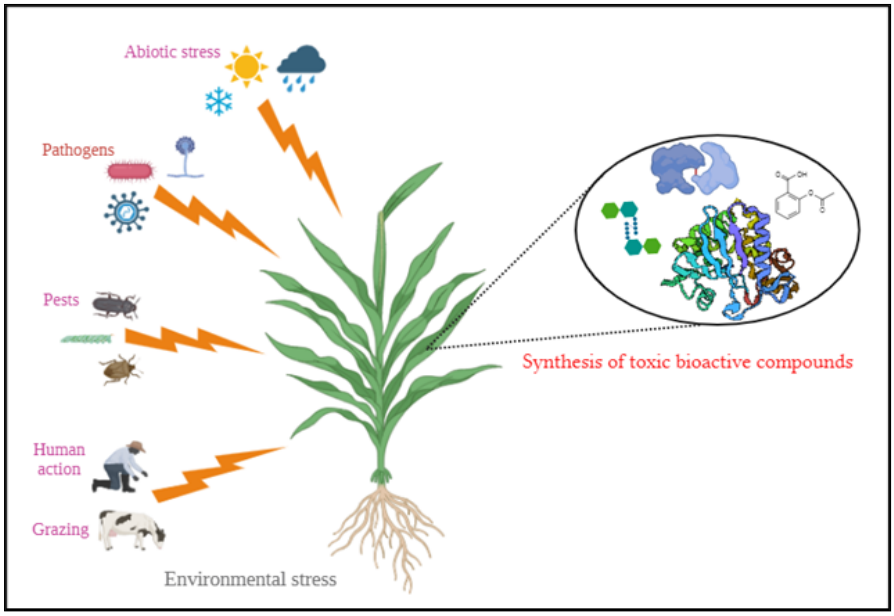


Fig. 1. Synthesis of toxic bioactive compounds by plants to mitigate environmental stresses.

However, when the intake is restricted to a certain level these biomolecules have highly significant therapeutic properties in human life (6). Why not use these toxic proteins to serve as a potential antidote? Here in this review, preliminary discussions were made regarding the role of a phytotoxic protein in neutralizing the animal toxin.

An overview of Ribosome Inactivating Proteins (RIPs)

One among the toxic protein family is the RIPs that are mostly present in plants and studies have revealed that they are also present in some bacteria, fungi, mushrooms, algae and insects. The discovery of ribosome-inactivating proteins in the nineteenth century occurred when the scientist Stillmark isolated ricin from *Ricinus communis* and observed its toxic effects. (7). However, the characterization of these proteins came into the spotlight only from the 1970s (8). In the group of eminent researchers who contributed to the discovery of RIPs from plants, Professor Fiorenzo Stirpe and his team had detected, isolated and characterized many RIPs including the purification and characterization of immunotoxins from RIPs (9). He is the pioneer to have documented the various biological roles of RIPs for human welfare (10). Based on the previous studies, N-glycosylation in 60S ribosomes is the enzymatic mechanism by which ribosome inactivating proteins remove a particular adenine at position A^{4324} from the rat 28S rRNA (11). This adenine is located within the α-sarcin/ricin loop (SRL), a conserved 14 nucleotide sequence found in major rRNAs across diverse organisms, from bacteria to humans. The core of this loop features a GAGA sequence, where the first adenine residue acts as RIP's substrate (Fig. 2). This irreversible modification of the targeted adenine residue inhibits the GTPase activities of elongation factors EF-1 and EF-2 subsequently impeding the process of translation and leading to cell death in eukaryotes (12). This mechanism of targeted cell death may be employed for the detoxification of animal toxins in the human body.

Origin and types of RIPs

In nature, RIP genes were more widely distributed among plant species. Many different types of plants produce numerous isoforms of RIPs, which have evolved through a range of molecular mechanisms such as gene duplication, gene deletion, gene fusion with other genes and horizontal gene transfer between species (13). According to the available data, the RIP domain about 30 kDa in size made up of a single polypeptide chain with N-glycosidase activity formed at least 300 million years ago and are currently classified as type I RIPs (14). Pokeweed antiviral protein (PAP) was the first type I RIP which was isolated from *Phytolacca americana* (American pokeweed) (15). Moreover, there exists a single domain protein exhibiting N-glycosidase activity with arginine/glutamate rich polypeptides (AGRPs) at their N-terminal sequences that have a lower molecular weight than that of normal type I RIPs are termed as small type I RIPs. These small type I RIPs are most commonly present in the *Cucurbitaceae* family (16). Later, it is said that a plant managed to combine the RIP domain with a lectin domain duplication led to all current type II RIPs. The A domain with N-glycosidase activity is approximately 30 kDa which is structurally like type I RIPs, while the B domain with lectin characteristics is approximately 35 kDa and has the capability to bind specifically to galactosyl terminated structures on the surface of the cells, aiding the entry of A domain into the cell (Fig. 3). For example, ricin and abrin belong to the category of type II RIPs which are highly toxic and not all type II RIPs are toxic. The absence of the B domain in type I RIPs accounts for their comparatively lower toxicity than type II RIPs. Type III RIPs being less prevalent were descended from the resulting ancestor type II RIPs through domain fusion and deletion containing a N-terminal domain like the A domain of type I RIPs, fused to an unidentified functional C-terminal domain (14). Proteins belonging to this type are produced as single domain proenzymes such as barley JIP60 and maize b-32 (16, 17). Plants tightly express these RIP genes only in specific tissues or in response to stress leading to the synthesis of RIPs and are localised extracellularly as well as in subcellular compartments such as vacuoles and endoplasmic reticulum undergoing various post translational modifications allowing the RIPs to function effectively in host cells and ensure to prevent the self-toxicity of native proteins (12, 18-20).

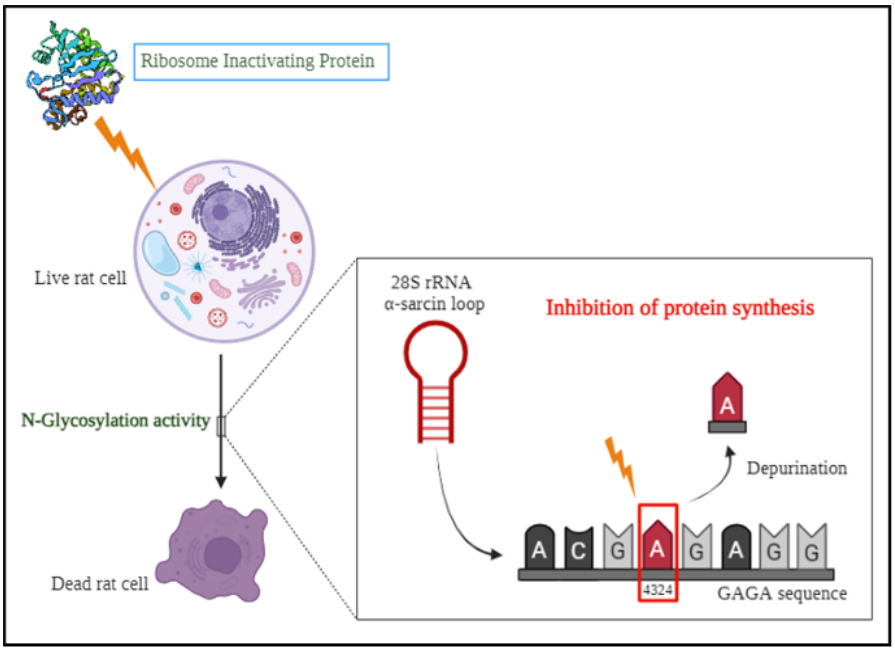


Fig. 2. Mechanism of action of RIPs.

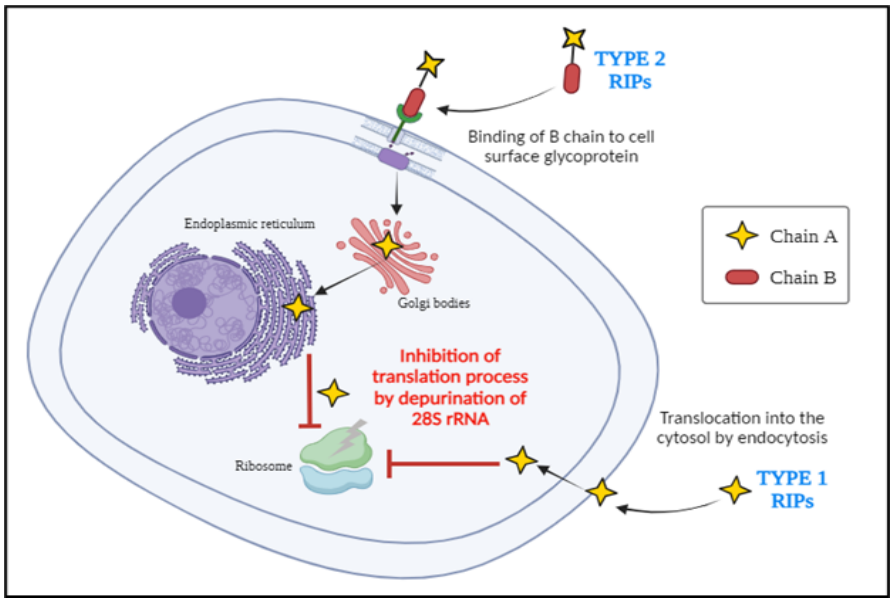


Fig. 3. General hypothetical model for mechanism of entry of RIPs into cells.

Applications of RIPs

Despite having the highly toxic effect of RIPs on pathogens and pests to overcome stress in plants (16), their N-β-glycosylase activity inhibiting translation seems to trigger the pathways activating caspases leading to the induction of apoptosis in mammalian cells (21). The high toxicity of type II RIPs to humans and animals through ricin poisoning (22), abrin poisoning (23, 24) and other toxicity analyses were studied previously (8). The Type I RIPs being less toxic than Type II RIPs when administered at higher doses may induce toxic symptoms and even cell death in rats (25). Consequently, many RIPs were isolated and used by criminals in assassination plots or in the event of murder leading to mass destruction (26, 27). Considering this deadly activity, the US government in 1997 classified several toxic biological compounds including some RIPs as category B biological warfare agents.

Besides being a toxic weapon, RIPs also have many other biological roles in the field of agriculture as anti-plant viral activity, antifungal activity (28) and insecticidal activity and in the field of medicine as anticancer activity, embryotoxic activity, abortifacient activity, antimicrobial activity, antiviral activity, anti-HIV activity and various other applications in the area of neuroscience research and developing immunotoxins as a therapy against cancer (Fig. 4) (10, 29). Here, in this review, the effect of RIPs on snake venom proteins was studied using *silico* approaches and their role against snake venom envenoming was discussed.

Severity of snakebite and need for effective antivenom

Snakebite, the most serious Neglected Tropical Disease (NTD) is a potentially life threatening lethal medical emergency that is responsible for enormous suffering and disability in every continent caused by the toxins released by the venomous snakes (30). According to the World Health Organization (WHO), 1.8 to 2.7 million cases of envenomation occur annually among 5.4 million estimated snakebites worldwide. Every year there are around 81410 to 137880 deaths due to snakebites and in some cases, they also result in permanent impairment (31). Being a cold-blooded reptile most of the

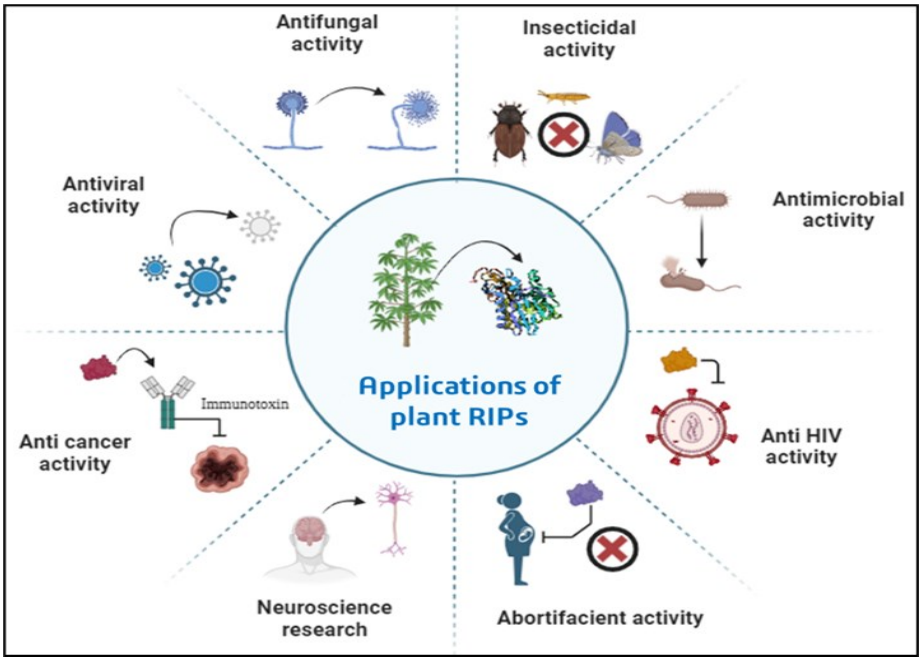


Fig. 4. Various applications of plant RIPs.

snake species rely on tropical climatic regions to survive and almost half of all snakebite deaths worldwide are said to occur in India, a tropical country where an estimated average of 50000 to 60000 deaths is reported each year (32, 33). Mainly rural and peri-urban communities involved in agricultural and other allied activities are highly vulnerable to snakebites (34). Among 3783 species of snakes which are distributed worldwide, only around 600 species are most dangerous and highly venomous in nature (35, 36). The venomous species mainly come under the families like Elapidae (401 species), Viperidae (383 species), Atractaspididae (69 species) and some in Colubridae (2105 species) (37, 38). In India, the medically important snakes which causes severe damage to the livelihood are termed as "The Big Four" and they are Indian cobra (*Naja naja*), Common krait (*Bungarus caeruleus*), Russell's viper (*Daboia russelii*) and Saw-scaled viper (*Echis carinatus*) (39). These venomous snakes have a special structure in their mouth region called fangs connected to the venom gland through venom duct. The venom gland which secretes venom is a modified salivary gland surrounded by the compressor muscles which aid in the delivery of the secreted venom fluid while biting. Generally, the evolution of these features was adapted by the snakes to capture, immobilise and digest their preys easily or attack their predators (40, 41).

Composition of snake venom

Snake venom is a complex mixture of organic and inorganic substances, including proteins, carbohydrates, lipids and metal ions, which elicit various pathophysiological effects (42). Its composition varies based on factors such as age, nutrition, climate, temperature and geography, both among and within species (43). Theo Tasoulis and Geoffrey K Isbister classified venom proteins into 59 families, categorized into five major toxin groups responsible for different physiological effects (Table 1) (117).

Snake venom exerts its toxicity through mechanisms such as neurotoxicity (flaccid paralysis), myotoxicity (muscle damage), hemotoxicity (coagulation disruption), necrotoxicity (tissue death), cardiotoxicity (cardiovascular damage) and nephrotoxicity (renal damage) (44, 45). Among venom proteins, the most dominant families include (42 - 45) Phospholipase A_2 (PLA_2). Phospholipase A_2 is one of the most abundant enzyme components in snake venom which are structurally characterized by a single polypeptide chain that is folded into a tight globular form by disulfide bonds with a conserved catalytic site containing a calcium ion (46). The main activity of PLA_2 is to disrupt the membrane integrity by hydrolysing the phospholipids in the cell membrane. This causes pain, inflammation and localized tissue damage at the envenomation site. As a result, other venom components can easily be disseminated into the bloodstream facilitating quick spread of toxicity (47). Certain PLA_2 have the direct ability to activate the elements of the blood coagulation cascade like prothrombin and factor X, resulting in procoagulant effects leading to systemic haemostatic disruptions and intravascular thrombosis (48). PLA_2 can also cause damage to muscles by inducing calcium influx into the muscle cells resulting in the rupture of sarcolemma membranes leading to pain, weakness and muscle necrosis aiding in the immobilization of the prey (49).

Three-Finger Toxins (3FTx). Three-finger toxins are typically small and highly stable proteins which are characterized by their unique three-finger fold consisting of loops stabilized by disulfide bonds involved in specific target binding and are commonly present in cobras and kraits (50). These proteins are primarily neurotoxic interfering with neurotransmission by binding to various types of receptors of the nervous system, such as nicotinic acetylcholine receptors (nAChRs) and muscarinic acetylcholine receptors (mAChRs). By binding to these receptors, they can block nerve impulse leading to paralysis, respiratory failure and ultimately the prey gets immobilized (51). Some 3FTxs interfere with blood coagulation by inhibiting factors involved in the coagulation cascade leading to systemic haemorrhage and facilitating prey capture and digestion (52).

Table 1. Group of snake venom protein families

S.No.	Groups	No. of Families	Family names	References
1.	Dominant protein family	4	Phospholipase A_2 (PLA_2), Three-finger toxins (3FTx), Snake venom metalloproteases (SVMP) and Snake venom serine proteases (SVSP)	(101, 102)
2.	Secondary protein family	6	Kunitz peptides (KUN), L-amino acid oxidases (LAAO), Cysteine-rich secretory proteins (CRiSP), C-type lectins (CTL), Disintegrins (DIS) and Natriuretic peptides (NP)	
3.	Minor protein family	9	Acetylcholinesterase, Hyaluronidase, 5'nucleotidase, Phosphodiesterase, Phospholipase B, Nerve growth factor, Vascular endothelial growth factor, Vespryn/Ohanin and Snake venom metalloprotease inhibitor	
4.	Rare protein family	36	Glutaminyl cyclase, Aminopeptidase, Endonuclease, Cobra venom factor, Transferrin, Waprin, Endopeptidase, Glutothione peroxidase, Kazal-type inhibitor, Galactose-binding protein, Trypsinogen, Albumin, Prokineticin, Selectin, Peroxiredoxin, Protein C activator, Cholinesterase, Polyglycine peptides, Glycine-histidine rich peptide, Flavine monoamine oxidase, Lysosomal acid lipase A, Fibrinogenases, Haemoglobins, Neurotrophin, Aspartic protease, Type-B carbyoxylesterase, Cytotoxin, Neuronal membrane glycoprotein, Insulin-like growth factor, Sulfhydryl oxidase, Aminotransferase, Complement decay accelerating factor, Kinesin-like protein, Ribosomal protein, Multiple inositol polyphosphate phosphatase and Phospholipase A_2 inhibitor	
5.	Unique protein family	4	Defensins, Waglerin, Maticotoxin and Cystatins	

Snake Venom Metalloproteases (SVMP). Snake venom metalloproteases are zinc-dependent enzymes characterized by a catalytic domain containing a zinc ion coordinated by histidine residues (53). SVMPs are commonly present in viperid snakes where these proteins target the extracellular proteins like collagen, elastin and fibronectin leading to local tissue destruction, haemorrhage and inflammation which can even cause organ damage to the envenomed organism (54, 55). SVMPs can have various structural domains like metalloproteinase, disintegrin, cysteine-rich and lectin-like domains which aid in diverse biological activities. SVMPs with disintegrin-like domains can attach to integrin receptors on platelet surfaces limiting platelet aggregation which contributes to coagulopathic effects and produces antiplatelet activity (54).

Snake Venom Serine Proteases (SVSP). Snake venom serine proteases are enzymes that belong to the serine protease family typically consisting of one or more catalytic domains containing the conserved catalytic triad (histidine, aspartate and serine). These proteins often contain additional domains such as exosites or disulfide-rich loops that contribute to substrate specificity and inhibitor binding (56). They modulate haemostasis either by activating or inhibiting the components of the blood clotting cascade mechanism ultimately resulting in blood coagulation and fibrinolysis (57). Some SVSPs cause intravascular thrombosis and consumption coagulopathy by activating the clotting factors such as factor X and prothrombin. While others inhibit platelet aggregation or fibrin formation, resulting in bleeding disorders. SVSPs also play a crucial role in degrading the components of the extracellular matrix and disrupt cell to cell adhesion facilitating the easy digestion of prey (56).

Production of antivenom for curing snakebites

In India, antivenom for snakebite commercially produced as Anti Snake Venom (ASV) is a life-saving medication used to treat patients with snakebite envenomation. ASVs are mostly polyvalent antibodies that try to neutralize the toxic effects of any venomous snakebite, therefore preventing serious medical complications and death (58). The production of ASV involves a serotherapy process of immunizing the animals mainly equines and ovines by injecting the mixture of venom collected from venomous snakes. Through repeated exposure to venom, these animals develop prominent IgG antibodies in their blood, which are harvested and purified to create ASVs. The purified antibodies are then tested to ensure their quality, efficiency and safety for human use (59). Once a person is bitten by a venomous snake, upon severity of the symptoms the ASV is continuously administered intravenously with complete medical surveillance. The antibodies in ASV bind to the venom toxins in the bloodstream and neutralize their effects by reducing symptoms such as tissue damage, bleeding, paralysis and organ failure (60). However, antivenom does not reverse damage that has already occurred but can stop the progression of envenomation. Despites its life saving capacity, ASVs may also cause some allergic reactions ranging from local itching to severe anaphylaxis (61). The major challenge in the production of ASVs is the variability in venom composition between the species which is highly specific (62, 63). ASVs may not be readily available in the regions of envenomation, even the limited availability has been reported previously in India. Currently there are eight authorized manufacturers of polyvalent antibodies in India raised against the big four venomous snake species with a total installed capacity of 6.75 million vials per annum. However, only 1.5 - 2 million vials are produced in India every year (64). Considering these constraints, various other studies with designing unique aptamers, employing phage display techniques, using small molecule inhibitors and isolating natural phytochemicals in neutralizing the snake venom were undergone previously (65). But when numerous clinical trials report the failure of ASVs even against the Indian geographical snakes due to the complex variable nature of venom proteins, it is an alarming threat to each citizen of India (66). Hence the need for next generation antivenom is the spotlight area for researchers to develop a sustainable system to treat snakebite envenoming.

Plants with antivenom properties in traditional medicine

The utilization of plants in the Indian traditional healing medicine systems such as Ayurveda, Homoeopathy, Naturopathy, Unani and Siddha has been integral to human health and wellbeing for centuries. Medicinal plants have various therapeutic values highlighting their cultural significance along with contributions to modern health care (67). Since ancient periods, plants have been used for the treatment of snakebites traditionally by many people in remote areas all over the world. Phytochemical extracts of various parts of the plants exhibit diverse mechanisms of action against snake venom toxins (68-71). Plant families like *Fabaceae, Asteraceae, Zingiberaceae, Salicaceae, Amaranthaceae, Mimosaceae, Euphorbiaceae, Cucurbitaceae, Piperaceae, Musaceae, Rutaceae, Liliaceae, Malvaceae* and many other families were previously studied for the presence of bioactive substances with neutralizing properties of snake venom (72-79). Generally, the secondary metabolites such as phenolics, terpenoids, alkaloids and saponins present in different plants under these families were reported as natural inhibitors of snake venom proteins (80, 81). The list of these compounds studied for antivenom properties were clearly mentioned in the review written by Adrião *et al.* in 2022. Some modified glycosides like homaloside D from *Homalium ceylanicum*, itoside from *Itoa orientalis,* scoloposide from *Schisandra chinensis* and salireposide from *Symplocos racemosa* had been isolated and studied for the inhibition of venom compounds. Even proteins like *Withania somnifera* glycoprotein (WSG) and turmerin from *Curcuma longa* also showed inhibition activity of phospholipase A_2 proteins in snake venom (82). In view of these research insights and preclinical studies, plant products offer a vast opportunity to delve in snakebite envenomation. While screening the literature, there were many plants which are ethnopharmacologically reported with antivenom properties that have yet to be thoroughly investigated to identify the specific compound responsible for this effect (83). Further, by employing *silico* analysis using molecular docking and simulation to identify the potential bioactive compounds that bind to the snake venom proteins effectively with better interactions could help in designing modified natural products with high capacity to neutralize the toxicity caused by snake venom in the human body (65, 84).

(Table 2) provides a comprehensive list of 15 medicinal plants with proven antivenomous properties, detailing their scientific and common names, family classification, plant parts used, target snake species and possible modes of action. These plants exhibit diverse mechanisms against snake venom, including phospholipase A2 (PLA2) inhibition to prevent hemolysis and neurotoxicity (e.g., *Abrus precatorius*, *Mimosa pudica*), enzyme inhibition targeting acetylcholinesterase and serine proteases (*Rauvolfia serpentina*), superoxide dismutase activity reducing oxidative stress (*Ocimum sanctum*) and chelation of Zn^{2+} ions to inhibit snake venom metalloproteinases (SVMPs) (*Brownea rosademonte*). Many species, such as *Curcuma longa* and *Andrographis paniculata*, counteract venom-induced organ damage and paralysis, highlighting their therapeutic potential in snakebite management. This compilation underscores the significance of phytochemicals in neutralizing toxic venom components and suggests promising avenues for developing plant-based antivenoms.

Selection criteria for snake venom proteins and RIPs

In our study, we undertook a thorough literature search to identify both the most relevant snake venom targets and the plant-derived compounds with potential antivenom properties. First, we focused on major venom proteins from the highly venomous “Big Four” snake species-Indian cobra, Indian common krait, Russell’s viper and Saw-scaled viper-and selected only those proteins that have experimentally determined structures available in the Protein Data Bank (PDB) to ensure the accuracy and reliability of our docking analysis (Fig. 5).

Simultaneously, our literature review revealed that although many medicinal plants are traditionally reported to have antivenom properties, there is no conclusive scientific evidence pinpointing the exact compound responsible for these effects (85). Given this uncertainty, plant-derived RIPs were chosen as potential antivenom agents. RIPs are well-known for their ability to inhibit protein synthesis by inactivating ribosomes (10, 8) and have been identified in several plants that are used in traditional snakebite therapies.

Thus, our *in-silico* approach is an initial attempt to investigate whether these RIPs can effectively bind to and potentially inhibit key snake venom proteins, thereby exploring their possible role in snakebite management. After screening many plants, only those that demonstrated both antivenom properties and the presence of RIPs were selected for further investigation. The plants that have antivenom property which have also been reported for the presence of RIPs were chosen as the ligand protein for protein-protein interaction studies using molecular docking (Table 3). This integrative strategy provides a foundation for future studies aimed at developing novel, next generation antivenom therapies.

In-Silico analysis of plant derived RIPs against snake venom

The 3D structures of the snake venom proteins and plant-derived RIPs were retrieved from the PDB (86). The target proteins (*Naja naja* phospholipase A2, Alpha-delta bungarotoxin, Echistatin and Russell's viper venom serine protease) were prepared for docking analysis using BIOVIA Discovery Studio (DS4.5, Accelrys, Inc., San Diego, CA, USA). Energy minimization was performed using the CHARMm force field to ensure structural stability, with default parameters applied for accuracy and efficiency.

The ligand proteins (Abrin, APA-1, Amaranthin, Luffaculin, Momordin, β-Momorcharin, Nicotiana tabacum RIP, Ebulin and Viscum articulatum RIP) were analyzed for toxicity prediction using the ToxinPred 2.0 web server (87). As all ligand proteins were RIPs, they were predicted to be toxic.

Molecular docking was conducted using the ZDOCK protocol in Discovery Studio with an angular step size of six, while other parameters were set to default. Each target protein was docked individually with all nine ligand proteins, generating 2000 docked poses per target-ligand pair. The best poses from the largest clusters were further refined using the Process DOCK protocol, followed by RDOCK to enhance interaction accuracy.

Table 2. List of plants with antivenom properties

S.No.	Scientific name of the plant	Common name	Family	Plant parts used for curing snakebite	active against snake species	Antivenomous property of the plant	References
1.	*Abrus precatorius*	Rosary pea	*Fabaceae*	Roots	*Bungarus caeruleus* (Indian Krait)	PLA2 Inhibition - preventing hemolysis	(70)
2.	*Amaranthus spinosus*	Spiny amaranth	*Amaranthaceae*	Whole plant	*Naja subfulva* (Brown Forest Cobra)	PLA2 Inhibition and Procoagulant Activity.	(108)
3.	*Rauvolfia serpentina*	Indian snakeroot	*Apocynaceae*	Whole plant	*Naja naja* (Indian cobra)	Acetylcholinesterase, L-aminoacid oxidase, PLA2 and Serine protease inhibition.	(70)
4.	*Momordica charantia*	Bitter gourd	*Cucurbitaceae*	Flower	*Daboia russelii* (Russell's viper)	L-amino acid oxidase enzyme inhibition	(7, 103, 104)
5.	*Ocimum sanctum L.*	Tulsi	*Lamiaceae*	Leaves	*Crotalus adamanteus* (Eastern diamondback rattlesnake Snake)	Superoxide dismutase activity and lipid peroxidation reduction.	(7, 70, 78, 104)
6.	*Eclipta prostrata*	False daisy	*Asteraceae*	Leaves	*Calloselasma rhodostoma* (Malayan pit viper)	proteolytic and haemorrhagic activity inhibition.	(7, 70, 78, 104)
7.	*Viscum articulatum*	Flat mistletoe	*Santalaceae*	Whole plant	*Naja naja* (Indian Cobra)	Mitigating venom-induced oxidative stress and inflammation through its bioactive flavonoids and lectins.	(109)
8.	*Curcuma longa*	Turmeric	*Zingiberaceae*	Rhizome	*Naja naja* (Indian Cobra)	PLA2 Inhibition - Prevent oxidative organ damage	(110)
9.	*Mimosa pudica L*	Touch-me-not	*Fabaceae*	Dried Roots	*Ophiophagus hannah* (King Cobra)	Phospholipase A2 (PLA2) Inhibition – preventing hemolysis, neurotoxicity and myonecrosis.	(111)
10.	*Tabernaemontana catharinensis*	Pinwheel-flower	*Apocynaceae*	Whole Plant	*Bothrops jararacussu* (Jararacussu)	Inhibition of myotoxic effect of bothropstoxin-I and II	(112)
11.	*Brownea rosademonte*	Rose of Venezuela	*Fabaceae*	Stem Bark	*Bothrops asper* (Terciopelo)	Direct inhibition of SVMPs by chelating Zn^{2+} ion, preventing enzymatic activity and tissue degradation.	(113)
12.	*Renealmia alpinia*	Mardi grass	*Zingiberaceae*	Rhizome	*Bothrops atrox* (Common Lancehead)	Anti-hemorrhagic and analgesic activity, by inhibition of enzymes like PLA2.	(114)
13.	*Galactia glaucescens*	-	*Fabaceae*	Leaves	*Crotalus durissus terrificus* (South American Rattle Snake)	Prevents neuromuscular paralysis by interfering with the binding of venom neurotoxins like PLA_2 at the neuromuscular junction.	(115)
14.	*Andrographis paniculata*	Green chiretta	*Acanthaceae*	Whole Plant	*Naja naja* (Indian Cobra)	Inhibition of α-neurotoxin, blocking it from binding to the acetylcholine receptor, preventing paralysis and respiratory failure.	(71)
15.	*Crinum jagus*	St. Christopher lily	*Amaryllidaceae*	Bulb	*Echis ocellatus* (West African carpet viper)	Inhibiting hemorrhage and reducing tissue damage, by binding to SVMPs.	(116)

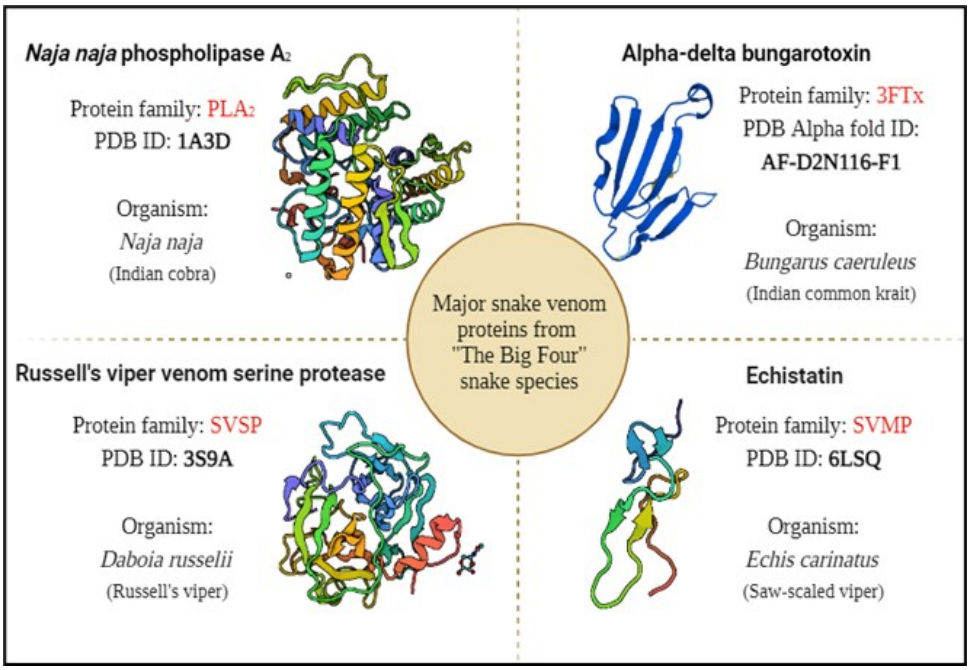


Fig. 5. Selected snake venom protein targets for molecular docking.

Table 3. List of plants with antivenom properties that express RIPs

S.No.	Scientific name of the plant	Name of the RIPs isolated	Type	Source of RIPs	PDB/ AlphaFold ID	Molecular weight (kDa)	References
1.	*Abrus precatorius*	Abrin	Type II	Seeds	1ABR	60.06	(7, 79, 103, 104)
		APA-1 (*Abrus precatorius* Agglutinin 1)	Type II	Seeds	2ZR1	118.01	
2.	*Amaranthus viridis*	Amaranthin	Type I	Leaves	AF-Q9SAQ5-F1	30.4	(7, 103-105)
3.	*Luffa acutangula*	Luffaculin	Type I	Seeds	2OQA	53.11	(7, 104, 106)
4.	*Momordica charantia*	Momordin	Type I	Seeds	1AHA	27.53	(7, 103, 104)
		β-momorcharin	Type I	Seeds	1CF5	58.3	
5.	*Nicotiana tabacum*	*Nicotiana tabacum* RIP	Type I	Leaves	AF-B0EVM3-F1	14.48	(7, 70, 78, 104)
6.	*Sambucus ebulus*	Ebulin	Type II	Leaves, green fruits, rhizomes, barks	1HWM	58.95	(7, 103, 104, 107)
7.	*Viscum articulatum*	*Viscum articulatum* RIP	Type II	Whole plant	AF-B3F5I6-F1	61.96	(7, 79, 104)

The highest-scoring pose, based on ZDOCK and ZRANK scores, was selected for detailed protein-protein interaction analysis. The binding interface and key interacting residues were identified (Tables 4, 5). The step-by-step docking workflow is illustrated in Fig. 6 (86, 87).

The protein-protein docking analysis conducted using Discovery Studio provides insights into the potential interactions between plant-derived RIPs and key venom proteins from highly venomous snake species. The docking scores and interaction profiles suggest that plant RIPs exhibit strong binding affinities toward several snake venom proteins, indicating a possible neutralization mechanism through direct protein-protein interactions.

The ZDOCK and ZRANK scores presented in the (Table 4) indicate the binding affinities and docking interactions of various proteins with venom-related targets, including PLA2, 3FTx, SVMP and SVSP. Higher ZDOCK scores suggest stronger predicted binding interactions, while lower (more negative) ZRANK scores indicate more favorable binding energies, reflecting better binding stability. Among the listed proteins, *Viscum articulatum* RIP exhibits the highest ZDOCK scores across all venom targets, suggesting strong initial docking interactions. Conversely, *Nicotiana tabacum* RIP and *Momordin* demonstrate the most favorable ZRANK scores, implying strong binding stability and affinity after refinement. Proteins like *Amaranthin* and *Luffaculin* show moderate binding interactions, with varied rankings across targets. These results highlight potential inhibitory candidates for venom components, with *Viscum articulatum* RIP emerging as a promising binder due to its high docking scores, while *Nicotiana tabacum* RIP and *Momordin* exhibit stable interactions.

Interaction between *Nicotiana tabacum* RIP and phospholipase A2 (PLA2)

The docking analysis revealed a high ZRANK score of 125.688, for the interaction between Nicotiana tabacum RIP and PLA2, indicating a strong binding affinity.

Key residues involved

The interaction involves critical residues such as ASP39 and ARG42 from PLA2, which are essential for its catalytic activity. Other residues are mentioned in Table 5.

Potential mechanism of inhibition

The binding of *Nicotiana tabacum* RIP to these active-site residues may block the catalytic site or cause conformational changes in PLA2, leading to structural destabilization. This

Table 4. ZDOCK and ZRANK scores of top protein poses

	ZDOCK scores				ZRANK scores			
	PLA_2	**3FTx**	**SVMP**	**SVSP**	**PLA_2**	**3FTx**	**SVMP**	**SVSP**
Abrin	55.99	58.22	52.88	61.72	-97.538	-92.226	-93.556	-95.095
APA-1	54.61	48.96	49.53	54.5	-93.592	-90.773	-96.193	-102.322
Amaranthin	60.59	48.27	51.17	55.59	-109.673	-81.871	-87.46	-89.727
Luffaculin	55.35	52.5	45.41	51.27	-118.52	-99.576	-85.885	-114.996
Momordin	62.84	58.19	46.26	52.51	-123.173	-94.896	-98.891	-96.195
β-momorcharin	58.19	62.33	50.12	55.02	-118.085	-109.959	-87.866	-99.142
***Nicotiana tabacum* RIP**	56.06	62.51	46.34	54.59	-125.688	-113.133	-93.512	-127.68
Ebulin	50.89	52.49	46.42	58.09	-108.197	-102.067	-73.95	-101.827
***Viscum articulatum* RIP**	74.06	64.39	66.08	69.31	-105.068	-98.496	-97.277	-113.711

could reduce the enzyme's ability to hydrolyze phospholipids, thereby mitigating its toxic effects. Similar mechanisms have been observed in studies where PLA2 activity leads to acetylcholine secretion inhibition, contributing to neurotoxic effects (88).

Interaction between *Nicotiana tabacum* RIP and Three-Finger Toxin (3FTx)

The docking results showed significant binding interactions, with ZRANK score of -113.133 between *Nicotiana tabacum* RIP and 3FTx, indicating potential inhibitory effects.

Key residues involved

The interaction involves aromatic residues TYR1 and TYR4, known for their role in receptor binding and toxin activity.

Potential mechanism of inhibition

The π-π interactions between *Nicotiana tabacum* RIP and 3FTx may disrupt the structural conformation of 3FTx or mask its binding sites, preventing it from effectively interacting with neuronal receptors. This could potentially neutralize its neurotoxic effects and reduce paralysis in envenomed individuals (89).

Interaction between Momordin and Snake Venom Metalloproteinase (SVMP)

Docking results revealed that *Momordin* binds effectively to SVMP, showing significant score of -98.891.

Key residues involved

The interaction involves residues like GLU1 and ARG9, which are essential for SVMP's proteolytic activity.

Potential mechanism of inhibition

The binding of Momordin to these residues may interfere with the protease activity of SVMP, preventing it from degrading extracellular matrix proteins. This could reduce venom-induced tissue damage and hemorrhagic effects, improving patient outcomes (90).

RIPs are traditionally recognized for their ribosome-inactivating activity, but our *in silico* studies suggest a potential secondary mode of action in which they may also inhibit proteolytic enzymes like snake venom metalloproteinases (SVMPs). Natural inhibitors of SVMPs (91), typically block proteolytic activity by binding to the enzyme's active site, often through coordination with the catalytic Zn^{2+} ion and the formation of hydrogen bonds with critical residues. In a similar manner, our findings indicate that RIPs might interact with key active-site residues of SVMPs, thereby preventing substrate access and disrupting the proper alignment of the catalytic apparatus. This interference reduces the enzyme's capacity to degrade extracellular matrix components and cause tissue damage, offering a promising alternative pathway for antivenom action.

Table 5. Interface residues involved in best docked protein-protein interaction

Best PPI		ZRANK scores	Interface residues of target protein involved in the interaction	Interface residues of ligand protein involved in the interaction
Target protein	**Ligand protein**			
PLA_2	*Nicotiana tabacum* RIP	-125.688	ASP39, ARG42, CYS43, GLN45, VAL46, ASN49, CYS50, GLU53, ALA54, GLU70, SER72, GLN73, GLY74, THR75, LEU76, THR77, CYS78, LYS79, GLY80, ASN82, SER88, ASP91, CYS92, ARG94, LEU95, ALA96, ILE98, CYS99, ALA101, GLY102, ALA103, PRO104	THR1, ASN2, VAL3, VAL5, MET6, GLY7, TYR8, LEU9, VAL10, ASN11, SER12, ALA25, GLN27, TYR28, VAL29, PHE30, LYS31, GLY32, SER33, THR34, PHE62, PHE65, ILE69, PHE73, ILE87, THR90, THR91, ALA92, ALA94, SER95, ILE104
3FTx	*Nicotiana tabacum* RIP	-113.133	TYR1, LEU3, SER20, GLY21, ASN23, LEU24, THR27, MET29, LYS40, ALA48, THR49, CYS50, PRO51, GLN52, PRO53, GLU58, THR60, CYS61, CYS62, SER63, THR64, ASP65, LYS66, CYS67, ASN68, PRO69, PRO71, GLN73, ARG74, PRO75, GLY76	THR1, ASN2, VAL3, TYR4, VAL5, MET6, GLY7, TYR8, LEU9, VAL10, ASN11, SER12, PHE16, ALA25, TYR28, VAL29, PHE30, LYS31, GLY32, SER33, PHE62, PHE65, ASP66, SER67, ILE69, THR70, LEU72, PHE73, ILE87, THR90, THR91, ALA92, SER95, TRP125
SVMP	Momordin	-98.891	GLU1, CYS2, GLU3, SER4, GLY5, PRO6, CYS8, ARG9, ASN10, CYS11, LYS12	ILE116, ALA117, ALA118, GLY119, LYS120, LYS124, ILE125, PRO126, PRO130, ALA131, ASP133, SER134, SER137, THR138, HIS141, ASP143, THR145, ALA146, ALA147, GLY149, VAL153, ASP178
SVSP	*Nicotiana tabacum* RIP	-127.68	ALA56, HIS57, ASP59, ARG60, ARG62, LYS88, TYR89, PHE90, CYS91, LEU92, ASN93, THR94, LYS95, PRO96, ASN97, GLY98, LEU99, PRO170, LEU171, TYR172, TRP173, HIS192, SER217, GLU218, LYS224, ARG245	VAL3, TYR4, VAL5, MET6, GLY7, TYR8, ASN11, TYR28, VAL29, PHE30, LYS31, GLY32, PHE62, PHE65, ASP66, ILE69, THR70, PHE73, ILE87, ILE88, THR90, THR91, ALA94, SER95, GLU101, ILE104, VAL105, ILE108

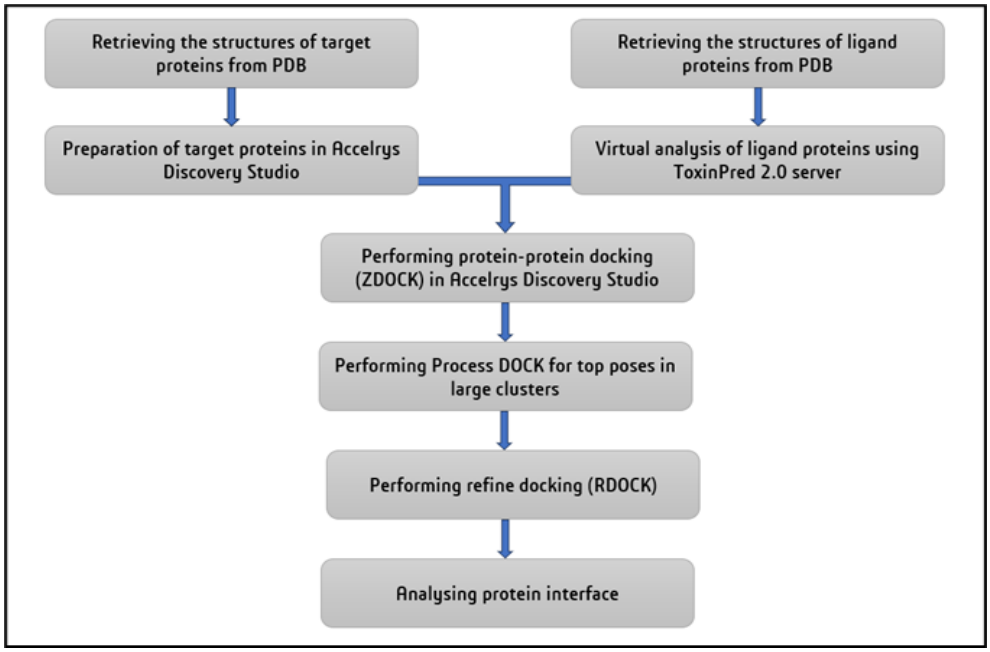


Fig. 6. Step-by-step procedure for protein-protein docking.

Interaction between *Nicotiana tabacum* RIP and Snake Venom Serine Protease (SVSP)

The docking study demonstrated strong binding, with ZRANK score of -127.68 between *Nicotiana tabacum* RIP and SVSP, indicating potential inhibition of its enzymatic function.

Key residues involved

The interaction includes residues such as HIS57 and ARG60, which are critical for the protease's catalytic activity.

Potential mechanism of inhibition

The binding of *Nicotiana tabacum* RIP to SVSP may block its active site, preventing it from interfering with the blood coagulation cascade. This could help stabilize clotting mechanisms and reduce venom-induced coagulopathy (92).

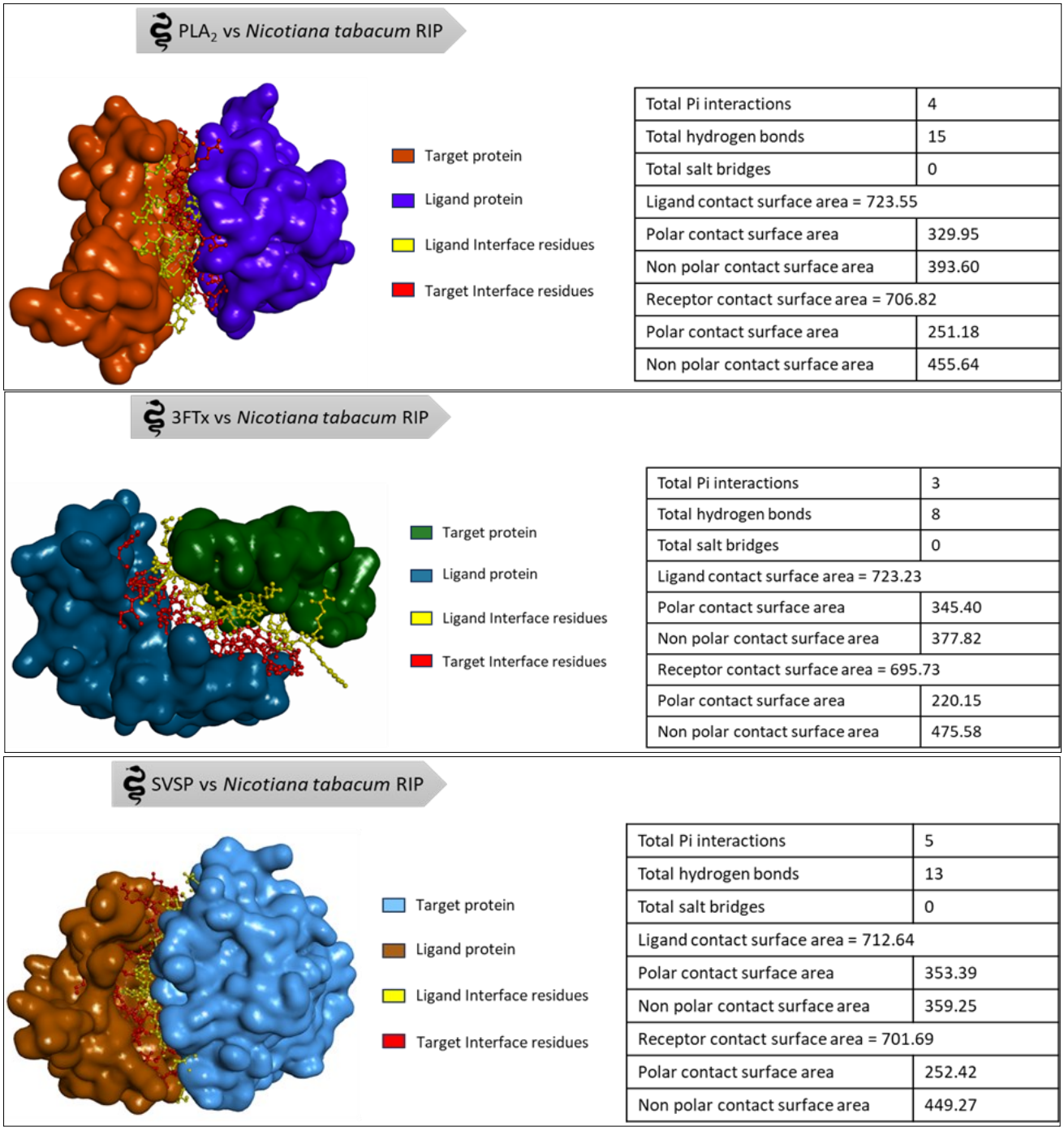
The docking results provide compelling computational evidence that plant-derived RIPs can effectively bind to and potentially inhibit key venom proteins through direct protein-protein interactions. The strong ZRANK scores observed for *Nicotiana tabacum* RIP and Momordin suggest that these molecules could serve as promising leads for developing novel therapeutic interventions against snakebite envenomation.

However, the cytotoxic nature of RIPs must be carefully considered, as their toxic effects could pose risks to human cells. Experimental validation is necessary to confirm these computational predictions and assess the feasibility of using RIPs as antivenom agents. While RIPs present an interesting avenue for antivenom research, further studies involving structural flexibility, specificity and toxicity are required to fully understand their therapeutic potential. The computational evidence provided here lays the groundwork for future experimental efforts in exploring RIPs as part of a novel approach to snakebite management. The three-dimensional representation is shown in Fig. 7 to visualize the interaction between the proteins.

Challenges in designing RIPs as an antivenom agents

Designing the plant derived RIPs as a potential antivenom agent has several significant challenges that must be addressed before their application can be realized in clinical settings. These challenges cover the issues of specificity, cytotoxicity, stability and immunogenicity, which require thorough investigation and optimization. One of the main challenges in using RIPs as antivenom agents is their lack of target specificity. RIPs are primarily known for their broad ability to inhibit ribosomal function, which is beneficial when targeting venom proteins but can also result in unintended interactions with host cells. For instance, as evidenced in our study, RIPs interact with multiple snake venom proteins, such as phospholipases, serine proteases and three-finger toxins. However, their ability to interact with a variety of protein targets raises concerns about off-target effects, particularly in human tissues. RIP's enzymatic action could potentially damage human cells, leading to adverse effects such as cytotoxicity, especially in non-target organs. RIPs, particularly those from plants like *Abrus precatorius*, are inherently toxic due to their ability to irreversibly inactivate ribosomes with known evidence in previous research. This intrinsic cytotoxic property, while useful for neutralizing venom proteins, poses a significant challenge for therapeutic use (93). The therapeutic window of RIPs must be carefully controlled to avoid damage to healthy human cells. Toxicity predictions from servers like ToxinPred, used in this study, confirmed the inherent toxicity of the RIPs analyzed, which underscores the need for engineered or modified versions of RIPs with reduced cytotoxic effects on non-target cells.

Another challenge lies in the stability and bioavailability of RIPs in the human body. Proteins, especially large ones like RIPs, are prone to degradation by proteases in the bloodstream and within tissues, potentially reducing their efficacy as antivenom agents. *In-vivo*, snake venom spreads rapidly and any therapeutic protein would need to remain stable long enough to neutralize the venom before being degraded or eliminated by the body's immune system. This may require chemical modifications or encapsulation in drug delivery systems to increase the half-life and bioavailability of RIPs in the bloodstream. The delivery of RIPs to the site of envenomation represents another significant hurdle. Venom



Total Pi interactions	4
Total hydrogen bonds	15
Total salt bridges	0
Ligand contact surface area = 723.55	
Polar contact surface area	329.95
Non polar contact surface area	393.60
Receptor contact surface area = 706.82	
Polar contact surface area	251.18
Non polar contact surface area	455.64

Total Pi interactions	3
Total hydrogen bonds	8
Total salt bridges	0
Ligand contact surface area = 723.23	
Polar contact surface area	345.40
Non polar contact surface area	377.82
Receptor contact surface area = 695.73	
Polar contact surface area	220.15
Non polar contact surface area	475.58

Total Pi interactions	5
Total hydrogen bonds	13
Total salt bridges	0
Ligand contact surface area = 712.64	
Polar contact surface area	353.39
Non polar contact surface area	359.25
Receptor contact surface area = 701.69	
Polar contact surface area	252.42
Non polar contact surface area	449.27

Fig. 7. Three-dimensional representation of best docked poses.

components rapidly disseminate through the bloodstream and into tissues, requiring the antivenom agent to reach these locations quickly and in sufficient concentrations. Currently, the most common delivery method for antivenoms is intravenous infusion. Plant RIPs can induce strong immune responses when introduced into the human body. As foreign proteins, they are recognized by the immune system, which can lead to the production of neutralizing antibodies. This immunogenicity poses a risk of allergic reactions or even anaphylaxis in some individuals. Moreover, repeated administration of RIPs as antivenom could lead to the development of immune tolerance or hypersensitivity, rendering them ineffective or dangerous over time. Reducing the immunogenicity of RIPs through protein engineering or humanization approaches is an area that needs exploration to make these proteins safer for clinical use.

Plant-derived RIPs, while naturally occurring, can be expensive and difficult to purify in large quantities. Scaling up production to meet the demands of treating snakebites, particularly in regions where venomous snakebites are common, may not be economically viable. Furthermore, the consistency in producing high-quality, biologically active RIPs for antivenom therapy could be a challenge, especially in regions with limited access to advanced manufacturing technologies. The development of recombinant or synthetic versions of RIPs with enhanced stability and reduced toxicity may be a more feasible approach, but this adds to the overall cost and complexity of production. Introducing a new class of biologically active compounds like RIPs for antivenom therapy would require stringent regulatory approvals and extensive clinical trials to ensure their safety and efficacy. Given the potential risks associated with cytotoxicity and immunogenicity, regulatory agencies may

impose strict guidelines for testing, which could delay the introduction of RIP-based therapies. Additionally, ethical concerns related to the use of highly toxic proteins even when modified must be addressed particularly when considering the balance between potential therapeutic benefits and risks.

Future prospects

The RIPs with high binding affinities to snake venom proteins could be involved as an innovative approach in building a successive candidate biomolecule for the inhibition of snake venom components. Not only is performing in silico studies enough to prove that RIPs are the effective candidate molecules but also *in vitro* and *in vivo* assays should be conducted for the standard results. Alternative binding scaffolds like nanobodies, affimers, adnectins, affibodies, affitins, anticalins, avimers, armadillo repeat proteins, β-hairpin mimetics, bicyclic peptides, designed ankyrin repeat proteins (DARPins) and fynomers are already underway in the progression of development of promising therapeutic modalities leading to an effective next-generation envenoming therapies (94). Entailing RIPs along with these scaffolds or any other effective ligand with advanced technologies could be a revolutionary breakthrough for snakebite treatment. Research works in designing RIP based immunotoxins for the targeted cancer therapy is an upcoming technology where the RIPs with N-glycosylation domain inducing apoptotic pathway are bound with the antibodies targeting the oncogenic cells leading to the death of cancer cells (95-97). Such methodology can be utilized in designing immunotoxins that are specific to snake venom protein complexes for the treatment of snakebite envenomation. However, the non-specific broad spectrum cytotoxic effect of RIPs is a challenging part to overcome the untargeted lethal effect on healthy cells. In order to overcome the unintended effects of RIPs, protein engineering is a prominent biotechnological approach to create an effective pharmacokinetic agent against snake venom (98). Advances in protein engineering, such as site-directed mutagenesis or CRISPR-based modifications, could help to enhance the specificity of RIPs toward venom proteins while reducing off-target interactions. Furthermore, incorporating RIPs into nanoparticle-based delivery systems could improve their stability, reduce systemic exposure and enhance targeted delivery to envenomed tissues (99, 100). And, the native immunogenicity of the host organism may mislead the immune response towards the RIP candidates developing resistance to its effect (97). Collaborative efforts between biochemists, pharmacologists and clinicians will be critical in advancing RIPs from promising *in-silico* candidates to viable therapeutic agents.

Conclusion

Time is a critical factor in managing snakebite victims due to the swift onset of pathophysiological effects. Biomolecules offer not only an alternative therapeutic avenue but also serve as an auxiliary approach to minimize preclinical effects before antivenom administration. The intricate and diverse composition of snake venoms poses a significant challenge, making it impractical for a single molecule to neutralize all venom proteins. In response to this complexity, a multifaceted strategy is proposed, encompassing the integration of ethnobotanical insights from traditional medicine.

Despite their challenges, RIPs offer several advantages over traditional antivenom approaches. One of the key benefits is broad-spectrum efficacy, as RIPs can neutralize multiple venom components such as phospholipase A2, three-finger toxins and metalloproteinases, whereas traditional antivenoms often target only specific venom proteins from a limited number of snake species. Additionally, RIPs work through direct enzymatic inhibition rather than relying on immune recognition, allowing for a potentially faster and more consistent mode of action across different venom types. Unlike conventional antivenoms, which are derived from animal immunization and can trigger severe allergic reactions or serum sickness, plant-based RIPs can be engineered for reduced immunogenicity, making them safer for repeated administration. Furthermore, RIPs are more stable at higher temperatures, which is a major advantage in regions where cold-chain storage for antivenoms is challenging. Their potential for recombinant production also allows for scalable, cost-effective synthesis without the need for maintaining venom-producing animals, making them a promising alternative for global snakebite treatment.

This multifaceted strategy involves leveraging traditional medicinal knowledge to uncover novel natural products, such as RIPs. The integration of these compounds with conventional pharmaceuticals holds promise for developing a comprehensive treatment approach that addresses the varied effects of envenomation. By exploring potential synergies between traditional remedies and modern pharmacology, it is possible to identify compounds that not only neutralize venom components but also provide a more tailored and effective response to the intricate biochemistry of snake venoms. This combined strategy, with its emphasis on diverse therapeutic treatments, presents a promising path forward in the quest to improve outcomes for snakebite victims.

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Authors' contributions

UP and PS did the molecular docking and tabulation of results. BN guided the bioinformatics data acquisition. TAU, PR, BR and SVP reviewed the work and suggested improvements in the results and subsequently the manuscript. RB conceived the idea and mentored the study and guided the writing of the manuscript.

Compliance with ethical standards

Conflict of interest: Authors do not have any conflict of interests to declare.

Ethical issues: None

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used ChatGPT in order to improve language and readability, with caution. After using the tool, PS and UP reviewed and edited the content as needed and take full responsibility for the content of the publication.

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