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BIOMEDICAL APPLICATIONS OF SNAKE VENOME CONJUGATED NANOPARTICLES

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ABSTRACT

The aim of generating NPs conjugates that increase the effectiveness of potential biomolecules has generated attention in a number of disciplines, with the goal of establishing nanomedical approaches to medicine creation. One group of possible possibilities in this field is VT of animal origin with potential therapeutic value. Medical systems that are based on tradition and folklore both suggest the use of VT for the cure of numerous illnesses. The therapeutic applications of VT have been scientifically confirmed, and numerous active components derived from VT are now in clinical trials or have been approved for usage. NCs is a novel field of medicine in which NT is used to generate molecules with an NS dimension, which are more easily taken up by cells and have a better effectiveness than bigger molecules that are more likely to be eliminated. The focus of this review will be on some of the possible SVs as therapeutic clues against developing diseases, as well as NPs conjugated SVs.

Introduction

Envenomation by snakebites (SKB) is a significant and complicated worldwide health issue that affects over 2.5 million people every year kills over 100,000 people. The situation is particularly dire in impoverished rural areas of Sub-Saharan Africa, Asia, and Latin America [1–4]. Furthermore, an estimated 40 million persons who are bitten by snakes suffer long-term medical and mental health consequences, lowering their standard of living and causing a civil unrest in their communities and families [4, 5]. SKB envenoming (EVs) has been included to the WHO's list of Neglected Tropical Diseases (NTDs) because of its global effect [4]. The parenteral injection of animal-derived antivenoms (AVs), which are made of IgG taken from the plasma of big animals immunized with venoms, is the backbone in the treatment of SKB EVs.

AVs are safely and effectively medicines that can treat the clinical outcomes

symptoms of EVs, particularly those linked to systemic effects, when made utilizing suitable venom mixes for vaccination and following GMPs or CGMPs [6, 7]. Nevertheless, there are a number of disadvantages to AV treatment that make it less successful. AVs must be delivered by qualified health professionals in a timely way at health facilities, restricting their usage in rural regions with limited public health care and health personnel [8]. The fact that AVs are selective for both vaccine venoms and venoms from closely related snake species complicates therapy [7]. AVs are only partially successful in decreasing the local tissue damage associated with most viper and certain elapid snake bite EVs [9, 10], because to the fast onset of these effects and the generally delayed dispersion of AVs.

These delays might result in irreversible tissue damage (TD) and a variety of issues [11–14]. As a result, novel therapeutic treatments that may be given in the field after EVs to block or postpone the advancement of local TD, and therefore complement AV therapy for EVs, are needed. Snake venom's (SVs) biological complexity, as well as the social and economic problems involved with its manufacture, transportation, storage, and timely delivery, must all be addressed. Fast response treatment should be both safe and effective in a rural context, with the capacity to protect against venom from a variety of dangerous species [15].

Nanotechnology (NT) has added two new dimensions to SV research: I the creation of pharmacological clues against disease using NT, and (ii) the development of SV antidotes using NT (Table 1). Dr. Calmette of the Pasteur Institute in Paris created anti-snake venom serum (ASVS), which is still the only clinically utilized antidote for snake envenomation today. Patients' limits and negative effects have long been recognized. As a result, researchers from all around the world are striving to create a more powerful antidote. Herbal resources with ASVS potential have been recognized all across the world for a long time [16]. Many plants that are helpful against SV are mentioned in folk and traditional medical systems.

Knowles [17-19] conducted the first scientific assessment of herb as an SV antidote. He tried a number of traditional healer-recommended remedies and plant extracts, but none of them worked against snake envenomation. Mhaskar and Caius (1931) [18] shown that herbs and herbal components are ineffective against SV. This assertion was later debunked by several studies on the efficacy of herbal

antidotes for snake envenomation. Several plants and herbal components have been discovered to be effective antidotes for SV in contemporary laboratories. The anti-SKB properties of these plants and herbal-based synthetic nanoparticle (NPs) components were studied further.

An important use of NT and nanomedicine (NC) is the development of new substances with nanoscale (NS) dimensions for medicinal reasons [70]. NPs allow biological interaction between bulk materials and atomic or molecular structures. Because of the unique physicochemical properties of NPs, such as their ultra-small size, large surface area-to-mass ratio, high reactivity, and efficient contact with cells, as well as their high stability, catalytic power, and solubility, this technology holds tremendous promise in medical science [71]. These NS materials may be feasible options for future medicine due to their effective routes of administration, greater penetration capacity, reduced therapeutic toxicity, efficient and accurate target oriented drug delivery (DD) system, and enhanced cellular contact. Bio imaging (BI), drug discovery (DD), bio-detection of microbes, diagnostics, tissue engineering (TE), separation of biological molecules and cells, disease combating, and, most importantly, tumour (TR) destruction and cancer (CA) treatment are just a few of the applications for NPs in medicine [72].

Table 1: Biomedical applications of SV/NPs

SV/NPs	Biomedical applications	Activity	References
Cobra SV	Cell proliferation (CP) against L6 cells	In the control of local TD, AVS are only partially successful.	15
Naja kaouthia SV conjugated AuNPs	*In vitro* cellular toxicity	After AuNPs conjugation, the harmful impact of *N. kaouthia* on kidney tissue was reduced, according to histopathology..	20
Philodryas olfersii SV conjugated AgNPs	*In vivo* toxicity	AgNPs bind to SV components that produce edema and neuromuscular inhibition, but not those that affect the sarcolemma membrane. The protective effect of the studied AgNPs on avian preparation led to the identification of molecular targets such as intrinsic and extrinsic nicotinic receptors.	21
Naja naja SV conjugated AuNPs	Cytotoxicity (CYT)	Anticancer (ANC) potential of SV conjugated AuNPs against CA cells lines was demonstrated.	22
Walterinnesia aegyptia conjugated SiNPs	ANC activity	Cell growth was inhibited by SV conjugated SiNPs	23
Naja kaouthia conjugated AuNPs	ANC against U937 and K562 cell line	The ANC activity of SV conjugated AuNPs is induced by programmed cell death (PCD) via the mitochondrial route.	24
Macrovipera lebetina turanica (Blunt nose viper) SV	ANC activity of A549 and NCI-H460	Treatment with SV enhanced the expression of proapoptotic proteins such as cleaved caspase-3 and Bax, as well as APA protein, but it lowered the expression of Bcl_2.	25
Cobra SV	ANC activity	The CYT of venoms with mainly hemotoxic components was discovered in Vero and MDCK cell lines.	26
Alginate coated *Naja naja* and *Daboia russelii*) SV	Mucoadhesion study	Alginate might be utilized to create a regulated oral administration system for alginate beads, however animal studies and clinical trials would necessitate polymer modification.	27
Naja Atra (Chinese cobra) SV conjugated AuNPs	Antigen and antibody interaction	IgG antibodies can be utilized to detect SV antigen early and quickly.	28
Naja naja and *Bungarus caeruleus* SV	venom neutralization potential	NCS can be used for development of AV drugs	29

conjugated with nanocomposites (NCS)			
Naja nigricollis (Black-necked spitting cobra) SV	AV activity	When compared to the untreated group, the *M. oleifera* extract and AV groups had a longer clotting time.	30
Ophiophagus hannah (King cobra) SV	ANC activity against Patu 8988t cell line	CYT activity on pancreatic CA cells, reduced migration activity and induction of APA	31
Ophiophagus hannah (King cobra) SV	Antitumor (ATR) activity using Zebrafish embryos	Reduced tumor-cell-induced angiogenesis	31
Ophiophagus hannah SV	Antiproliferative activity on B16/F10, HT1080, and Balb/3T3 cell lines	Reduced migration activity and induction of APA	32
Ophiophagus hannah SV	ANC activity	Reduced migration activity and induction of APA	33
Naja kaouthia (Monocled cobra) SV	ANC activity against PaTu 8988t cell line	CYT activity on pancreatic cancer cells venom at a nonlethal dose	31
Naja kaouthia (Monocled cobra) SV	ATR activity against EAC, U937 and K562 cells	In human lung CA cells and leukemic cells, it inhibited CP and exhibited CYT activity and APA induction.	34
Naja kaouthia (Monocled cobra) SV	ANC activity against A549 and HL60 cell lines	CT3 treatment causes histopathological alterations in leukaemia cells.	35
Naja kaouthia (Monocled cobra) SV	Cardiotoxic–cytotoxic protein study against U947 and K562 cells	Induction of APA and antiproliferative action in human leukemic cells.	36
Naja kaouthia (Monocled cobra) and *Crotalus atrox* (Western diamondback rattle snake) SV combination	ANC activity	Elevated CYT in various human CA cells.	37
Cryptelytrops purpureomaculatus (Mangrove pit viper) SV	ANC activity	The SV showed a significant rise in caspase-3 and Bcl-2.	38
Agkistrodon acutus (Chinese moccasine) SV	ANC activity against Hela cells	Bcl-2 level got increased.	39
Trimeresurus stejnegeri (Chinese pit viper) SV	Anti-HIV activity	SV inhibited in a dose-dependent manner.	40
Bothrops alternatus (Urutu)	ATR activity (Balt LAAO-I cells)	Balt LAAO-I induces the APA of tumor cell lines through a CYT exerted by a generation of ROS intermediates	41
Naja naja naja (Indian cobra) SV	ATR activity against EAC cells	Edema was induced in mice foot pads and no direct haemolytic or ACS activity.	42

Naja kauthia (Monocled cobra) SV	ANC activity against B16F10 cells	Phospholipase A_2 and trypsin inhibitory activity was observed	43
Naja naja atra (Chinese cobra) SV	ANC activity against Ca9-22 cells	Cardiotoxin induces APA leading to Akt signaling pathways	44
Naja naja atra (Chinese cobra) SV	ANC activity against MDA-MB-231 cells	CTX III induces APA by Akt signaling pathways.	45
Naja naja atra (Chinese cobra) SV	ANC activity	Cardiotoxin induced cell death through mitochondrial alteration and ROS generation	46
Naja kaouthia (Monocled cobra) SV	lethality and neutralization of venome	The AVs were able to neutralise venom to varying degrees.	47
Bothrops asper (Lancehead) SV	Antiplasmodial activity	SV may be useful as a lead chemical in the quest for new antimalarials.	48
Cobra SV	CYT against K562 and HL-60 cells	Differences in CYT leading to cell death.	49
Calloselasma rhodostoma, *Daboia russelii*, *Naja mossambica*, *Naja nigricollis* and *Naja pallida* SV	Erythrocyte haemotoxicity	Haemolytic assaying revealed venom-CYT profiles and allowed the toxins responsible for haemolytic action to be identified.	50
Viper SV	Coagulopathic toxicity	Both procoagulants and anticoagulants were found in the SV studied (ACS). Phospholipases A2s (PLA2s) were found in the majority of ACS.	51
Tarantula cubensis (Cuban spider) SV	ATR activity against HEK293, MCF7 and HN5 cells	Inducing caspase-3 mediated APA	52

Crotalus (Rattle snake), *Micrurus* (American coral snake) and *Hydrophis* (Sea snake) SV	Toxicity study	Neurotoxic and cardiotoxic effect.	53
Naja kaouthia (Monocled cobra) and Daboia russelii (Vipera russelli) SV	ANA activity against EAC, U937 and K562 cells	Venoms reduced CP rate and produced morphological alterations indicative of APA induction.	54
Naja kaouthia (Monocled cobra) SV	CYT study against U937 and K562 cells	In comparison to imatinib mesylate, Venome has a mild cytotoxic impact on normal human leukocytes.	55
Naja naja oxiana (Central Asian cobra) SV conjugated chitosan nanoparticles	Synthesis of chitosan (CHS) NPs using venome	CHS reacts with tripolyphosphate to form stable cationic nanoparticles.	56
Ophiophagus hannah SV	CNS and anticonvulsant	In male albino mice, a non-protein toxin identified from SV offered substantial protection against drug-induced convulsions.	57
Protobothrops mucrosquamatus (Brown spotted pitviper), *Daboia siamensis* (Russell's viper) and *Trimeresurus stejnegeri* (Chinese pit viper) SV	Diagnostic tool for SKB	In clinical snake envenoming case samples, good detection capabilities.	58
Daboia russelii russelii (Russell's viper) SV	AVA treatment	Even in one highly envenomed patient, blood coagulability was restored and systemic bleeding stopped.	59
Agkistrodon rhodostoma, Trimeresurus gramineus and Echis carinatus SV	Platelet-aggregation (PAG) inhibitors	By interacting directly with the platelet integrin receptor GPIIb-IIIa, this compound can prevent PAG.	60
Bothrops alternatus (Urutu) SV	PAG inhibitors	SV causes platelet aggregation and has antibacterial properties.	61
Bothrops colombiensis (Lancehead) SV	PAG and CYT	ADP-induced PAG, fibronectin adhesion, and cell migration were all inhibited.	62

Montivipera xanthine (Rock viper) SV	CYT and antimicrobial activity	cytotoxic and antibacterial properties, SV can be used as an alternative treatment strategy.	63
Bungarus multicinctus (Chinese krait) and *Bungarus fasciatus* (Banded krait) SV	Proteomic analysis	Both SVs showed the existence of complement depleting component.	64
Hydrophis curtus (Short sea snake) SV	Myotoxicity against HSkMC cells	SV myotoxicity was much lower in cardiac muscle cells than in skeletal muscle cells.	65
Lachesis muta (Atlantic bushmaster) SV	CYT study	Autophagic processes are most likely activated to aid in the elimination of the toxic stimuli and the repair of damaged cells.	66
Deinagkistrodon acutus (Pit viper) SV	Antiplatelet aggregation and antithrombosis efficiency	Prothrombin-A and B in the SV that are contributed to CVD prevention.	67
Bothrops leucurus (White tail lancehead) SV	Platelet aggregation and tumor growth	Anti-angiogenesis effect was observed.	68
Naja naja (Indian cobra) SV	CYT and APA study	Declining numbers of cells in the mitotic phase.	69

Liposomal (LP) NPs are ideal drug carriers because of their special ability to encapsulation effectively with diverse ligands for targeted tissue orientated treatment, longer half-life length in vivo, bio - compatibility, and customized formulation according to required specificity [73,74]. Both drug carriers and nanodevices (NDs) have been made using carbon nanotubes (CNTs) [75]. In MRI, ultrasound, and X-ray imaging, NPs have been shown to enhance contrast, opening up new BI potential [76]. In the lab, NPs such as CHS NPs, CNT, and AuNPs have proven to be potent DD agents [77].

In investigations, CNT, SiNPs, ZnONPs, CHS NPs, AgNPs, and AuNPs have all been demonstrated to have antimicrobial properties [78]. AgNPs and AuNPs have a broad range of applications in biology, clinical applications, and treatment [79]. Due to their unique structural design, dendrimers (DRs) have also been created as DD agents [80]. Magnetic detection and diagnostic tools have been utilized using superparamagnetic NPs [81]. Antibody-coated NPs have been proven to interact well with biomolecules [82-84]. NPs have had a significant impact and can play a major role in nearly every aspect of clinical research [85-90].

NPs can interact with a number of components after they reach the body and end up in various organs, where they may remain intact or undergo alteration or metabolism. NPs have the ability to traverse cell borders and gather within them. They may attach to DNA or proteins once within the cell, interrupting normal cell activities or triggering an inflammatory response. One of the primary recognized toxicity mechanisms of NPs [91] is excess ROS, including free radicals, which can cause oxidative stress, inflammatory processes, and other cell damage.

The toxicity of NPs is determined by their chemical composition, similar to that of their parent bulk materials; however, size, surface chemistry, shape, and/or surface smoothness or roughness may all enhance an NP's toxicity profile, and all of these features can be considerably altered. While considerable research has been done to identify some of the detrimental consequences of NPs, more work is needed to completely understand the physiological effects of acute and chronic NPs exposure. In terms of safety, NPs conjugated with venoms should be used with caution in vivo because the first components are dangerous.

The majority of venom composition research using analytical "omics" approaches is focused on finding novel chemicals that can be of practical use, as mentioned in the preceding section. Any advances that improve the practical characteristics and usage of these chemicals would be extremely useful from this standpoint. Combining venoms or poisons with nanomaterials is one of them (NMs). NMs have a wide range of applications, including research, technology, and medicine. They can be employed alone or in conjunction with other materials such as venoms or poisons for magnetic and fluorescent BI, as well as DD and therapies.

Pharmaceuticals can benefit from the unique characteristics of NPs, which can be used to improve their pharmacologic and therapeutic qualities. While bigger molecules may be quickly removed from

the body, nanoparticles can be successfully retained by cells. Hydrophilic NPs such as CHS NPs, AuNPs, AgNPs, and DRs, to mention a few, were coupled with strong animal poisons to test the efficacy of NPs-based medication delivery to a biological target. In this investigation, both crude venoms and isolated toxins were utilized.

Conclusion

Omics and NT, for instance, had a huge influence on the progress of several scientific fields and have contributed significantly to recent SV scientific advances. The use of omics technology has enhanced our understanding of venom composition and the role of multiple toxins in certain venom effects. The use of NPs in the manufacture of animal toxin conjugates paves the way for new and creative therapies with improved therapeutic potential and biocompatibility, as well as more complicated delivery methods. NPs, on the other hand, can cause cell death by releasing reactive oxygen species (ROS). These actions have the ability to destroy CA cells on the one hand, but they also have the capacity to damage normal cells. As a result, while evaluating their use, the potential negative effects of NPs on human health should be considered.

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