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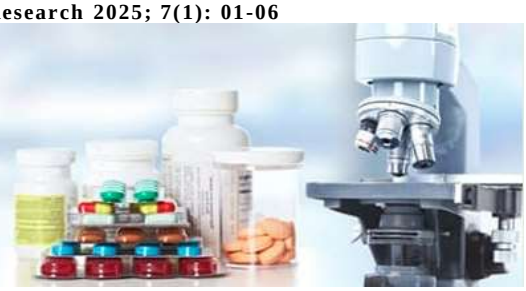

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Nanoparticle-based Antivenoms

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Abstract
Snakebite envenomation is a crucial matter regarding public health accountable for death and significant morbidity. This is classified as category A neglected disease by WHO. Snakebite envenomation is a major public health threat, particularly in rural India, where big four venomous species-the common cobra (*Naja naja*), common krait (*Bungarus caeruleus*), Russell's viper (*Daboia russelii*), and saw-scaled viper (*Echis carinatus*) are responsible for most poisoning cases. Annually, snakebites affect 2.5 million people and cause around 100,000 deaths worldwide, with India accounting for 15,000 reported fatalities. The traditional treatment, intravenous anti-snake venom (ASV), derived from the plasma of venom-immunized animals, is expensive and has limitations, including hypersensitivity reactions, species-specificity, and lack of local venom damage control. Given these constraints, research is increasingly focused on nanotechnology for snakebite treatment. This review discusses the use of various nanoparticles (NPs) in neutralizing snake venom. These nanoparticles have shown promising results in preventing local tissue damage, systemic distribution of toxins, and organ toxicity. These NP-based treatments offer a promising alternative, especially in cases where conventional ASV is not immediately available. Further research is needed to fully explore the potential of nanoparticles in treating snakebite and to address the limitations of current antivenom therapy. If successful, nanoparticles could offer a new and innovative approach to treating snakebite, particularly in resource-poor settings where access to traditional antivenom treatment may be limited.

Keywords: Nanoparticles, anti-snake venom, venom neutralizing nanoparticles, snakebite envenomation, big four snakes

Introduction
In India, there are over 236 different species of snakes, the majority of which are non-venomous. Their bites don't kill or even hurt the patient, except than producing a panic attack and localized injuries. However, of the 13 known species, four are known to be extremely venomous and are thought to be accountable for the majority of poisoning bites in India. These four species or the big four snakes are the common cobra (*Naja naja*), common krait (*Bungarus caeruleus*), Russell's viper (Dabiola russelii), and saw-scaled viper (*Echis carinatus*) [1]. Particularly in rural regions, snakebite is a serious public health risk and a potentially fatal medical emergency with little time for treatment [2].
Snake envenomation, a Neglected Tropical Disease, kills 100,000 people annually and affects 2.5 million, with therapy using animal-derived antivenoms derived from venom-immunized mammals plasma [3]. Snake venom-related deaths in India result in 15,000 deaths annually, with unreported cases being significantly higher than reported cases [4]. In Gujarat, June to October, which is monsoon season, is when the majority of snake bite instances were reported [5]. People who obtained first aid prior to hospital admission had a decreased fatality rate. When therapy was not received within six hours following the bite the morbidity was higher [6]. Cobra and krait are the most common types of venomous snake bites, and neuroparalytic manifestation of snake bite is more common [7]. The primary cause of morbidity was hemotoxic snake bite [8]. All over India, mortality from viper envenomation is primarily attributed to circulatory shock [9].
Snake venom, a complex blend of enzymatic and hazardous proteins, varies among species, habitat, age, and environment, and can be classified as hemotoxic, cytotoxic, or neurotoxic [10]. Poisonous snakes are categorized into solenoglypha and proteroglypha, with proteroglypha having neurotoxic venoms and solenoglypha having hemotoxic venoms.

Most poisonous snakes have both, with cobra, krait, and vipers belonging to the proteroglypha subfamily [4].

The two types of venom-induced tissue damage these numbers correlate to are (1) direct cytotoxic effects by "true" cytotoxins and (2) extracellular matrix disintegration, which can lead to an indirect cytotoxic effect. Classes of toxins: KUN: Kunitz-type peptides; PLA2: Phospholipase A2s; CT-3FTxs: Cytotoxic three-finger toxins; N-3FTxs: Neurotoxic three-finger toxins; Snake venom serine proteinases (SVSP) are also known as hyaluronidases, CTL (C-type lectins), CLP (C-type lectin-related proteins), Dis (Disintegrins), and Hyal (Hyaluronidases) [11].

Elapid snake venom causes neuromuscular block, respiratory failure, and hemotoxicity in viperine bites. Russell's viper bite mortality is due to fibrinolysis, intravascular coagulopathy, or renal failure, with saw-scaled bites causing coagulation dysfunction [12]. Table 1 Effects and toxins of big four snake venoms explains the pathophysiological effects of envenomation of different snakes.

Table 1: Effects and toxins of big four snake venoms

S. No	Species of Snakes	Local effects	Systemic effects	Toxins
1	Cobra (*Naja naja*)	Pain Swelling Bruising Blistering Necrosis (in severe cases)	Respiratory failure Cardiac arrest Renal failure Neurotoxicity: - Tremors - Convulsions - Muscle weakness - Paralysis	Neurotoxins & Cardiotoxins
2	Krait (*Bungarus caeruleus*)	Minimal local reaction Pain Swelling (mild)	Respiratory failure Cardiac arrest Renal failure Neurotoxicity: - Muscle weakness - Paralysis - Ptosis - Bulbar paralysis	Neurotoxins
3	Russell's viper (*Daboia russelii*)	Severe pain Swelling Bruising Blistering Necrosis Bleeding	Haemostatic disorders: - Haemorrhaging - Coagulopathy Renal failure Cardiovascular collapse	Hemotoxins
4	Saw-scaled viper (*Echis carinatus*)	Severe pain Swelling Bruising Blistering Necrosis Bleeding	Haemostatic disorders: - Haemorrhaging - Coagulopathy Renal failure Cardiovascular collapse	Hemotoxins

Patients receiving ASV and supportive treatments require ventilator assistance due to multiple factors determining the severity of envenomation and its eventual development to respiratory failure (Shown in Table 2) as well as the type and timing of medical attention and first aid [13].

Table 2 factors effecting envenomation [13]

Snake based factors	Victim based factors
The effectiveness of a snake's bite relies on its type, size, health, and condition of its fangs, as well as factors like whether it has eaten recently or is injured.	Anatomical position of bite (Proximal or distal), victim's age, health, size, and possibly immune status, as well as the kind and timing of medical attention and first aid.

India uses polyvalent ASV, created by hyper immunizing horses against the venoms of four common snake species, the "Big Four," to combat snake species that cause most deaths [2]. Anti-Snake Venom (ASV) is crucial for treating neurotoxicity or Coagulopathy, but in India, monovalent ASVs are available against Russell's viper, common cobra, common Krait, and saw-scaled viper [14]. Table 3 shows the dose of inoculation and vials of ASV required for different snake species.

ASV comes in lyophilized and liquid forms, with liquid having a two-year shelf life and powder having a five-year shelf life [14].

Table 3: Usual Dose of Envenomation by Bite of Different Species of Snakes [15]

Species of Snakes	Dose of venom inoculation	Vials ASV Required
Cobra	211.3	35
Krait	5.4	1
Russell's viper	63	15
Saw-scaled viper	13	8

Polyvalent ASV neutralizes 0.6 mg of venom, so the approximate dose for *Naja naja* bite is 330 ml/0.6, common krait dose is 5.4/0.6, Russell's viper dose is 120 ml [15].

Scientists worldwide are seeking an alternate therapy to improve snakebite treatment, as current antiserum is insufficient in preventing venom-induced pathophysiological alterations and hypersensitivity reactions [16]. Designing nanoparticles with different composition, size, shape, and surface qualities for medical uses is made possible by nanotechnology. Nanoparticles (NPs) made of synthetic or natural polymers; they are spherical & solid objects that range in size from 10 to 1000 nm [17]. The research presents a broad-spectrum antivenom using polymer nanoparticles to trap protein poisons, offering a potential cure for snakebite. This innovative approach addresses the long-standing need for effective techniques and instruments in snake venom research, utilizing nanotechnology for its potential applications [18].

A Novel Approach to Venom Neutralization

Snakebite is a significant medical, economic, and societal issue in India's rural and tribal areas. Parenterally administered polyclonal antivenom (ASV) are effective but have limitations [19]. Consequently, in cases when antivenom immunotherapy is not administered promptly, medicinal plant extracts can be used either alone or as a helpful supplement to provide an effective alternative treatment [20]. Additionally, it was claimed that the addition of metal to whole-plant extracts would enhance and increase the phytoconstituents' action [21]. Currently used in the field of biomedicine, metal nanoparticles and nano-based bio products have also demonstrated effective therapeutic molecules against snakebites [22].

Potential of nanoparticles in detoxifying venom toxins

Nanoparticles engage toxins through a lock-and-key mechanism, ensuring specificity and focused interactions, particularly useful for charged poison patches in high concentration situations.

Toxins' kinetic characteristics optimize their effect, and multivalent interactions with toxins enhance NP-toxin binding strength, reducing toxic escape and facilitating strong toxin capture [23]. Table 4 shows the applications of different NPs on specific toxins & venoms.

Table 4 Applications of Anti Toxin Nanoparticles

Nanoparticles	Toxin targeted	Study over view	Interpretation
Abiotic hydrogel NPs	Venom from *Naja nigricollis* and elapid snakes	PLA2 & 3FTX toxins and their isoforms can be neutralized by polymeric nanoparticles engineered to sequester the major protein toxins in elapid snakes. In order to prevent or lessen the degree of local tissue damage and the systemic distribution of toxins following envenoming, inexpensive NPs like abiotic hydrogel nanoparticles can be injected subcutaneously as soon as the bite occurs at the envenoming site. The dermonecrotic action of *Naja nigricollis* venom is dose-dependently inhibited by the nanoparticles, which are non-toxic to mice.	The work demonstrates that via binding to PLA2 and 3FTX isoforms, an abiotic synthetic polymer called NP can block the dermonecrotic activity of N. nigricollis venom, which is a clinical symptom of envenomation. this NP succeeded in mitigating the local tissue damage by venom
TiO2-NPs on p-type Silicon Si h100i substrates	Venoms from *Daboia russelii* (Viper) and Naja kaouthia (Cobra)	Viper and cobra venom-induced lethal activity were effectively neutralised by the TiO2-Nps.Both *in vitro* and *in vivo* investigations successfully eliminated the haemorrhagic, coagulant, and anticoagulant effects of viper venom. In experimental animals, the sterile inflammatory molecules induced by viper and cobra venoms were effectively neutralised by TiO2-Nps.	TiO2-NPs have demonstrated efficacy in combating venom-induced pathophysiological conditions and hold promise as a potential counteragent.
Gold NPs with 2 hydroxy 4 methoxy benzoic acid	Venom from *Daboia russelii* (Viper)	Nephrotoxicity is one of the major causes of death following Russell's viper bite Viper venom cause increase in serum creatinine, urea, urinary calcium, phosphate levels High concentrations lead to acute renal failure Treatment with ASVS could not protect renal induced nephrotoxicity Treatment with GNP- HMBA significantly antagonise RVV induced renal changes	GNP-HMBA significantly prevented RVV induced Nephrotoxicity, Myotoxicity, Hepatotoxicity in Male Albino Mice. In conclusion, NPs conjugation with Herbal compound is a supportive therapy for future ASVS treatment against snake venom.
Alginic acid-based silver nanoparticles	Venom from *Daboia russelii* (Viper)	Synthesized and characterized using UV-Visible spectroscopy, Dynamic Light Scattering (DLS), Scanning electron microscope (SEM), and X-ray diffraction analysis (XRD).	Concluded that AgNP-ALG may provide supplementary strategy against snake venom in the near future.
Vitex negundo with Gold NPs	Venom from Naja kaouthia (Cobra)	Swiss male albino mice that were treated with sham control, NKV control, ASVS treatment, GNP treatment, VN treatment, and VN-GNP treatment.VN-GNP significantly antagonized toxicity, acute stress, pro inflammatory cytokines response, increased anti-inflammatory cytokine response induced by cobra venom in Swiss male albino mice model.	VN-GNP may provide supplementary strategy in attenuating toxicity, cellular stress response in addition to standard antivenom against snake venom in the near future
Curcumin conjugated with AuNP	Venom from viper snakes	Curcumin, an active ingredient in turmeric, has anti-inflammatory and antioxidant properties. It was conjugated with gold nanoparticles to counteract viper venom by adsorption method. These nanoparticles are a convenient substitute for antivenom. C-GNP was physicochemical characterized using XRD, FESEM, UV-visible spectra, and DLS (size + zeta potential). Curcumin/C-GNP's ability to neutralize snake venom was tested *in vitro* and *in vivo* utilizing these models. The study evaluated the efficacy of Curcumin, a compound found in Curcuma longa, against viper venom-induced toxicity in animal models.	Gold nanoparticles coupled with curcumin may mitigate localized harm caused by viper venom. The synthesis of C-GNP and its effectiveness against toxicity generated by RVV were validated by the investigation. For victims of snake bites, it might serve as a supportive treatment.
AgNPs synthesized using Dryopteris cochleata rhizomes	Venom from *Naja naja*	Used ecofriendly synthesis method for AgNPs, characterized by UV-Visible spectroscopy, FTIR, XRD, and AFM, yielding particles with average size of 35 nm conducted studies to optimize yield, size, and stability of AgNPs Evaluated neutralization effects on N. naja venom in concentration-dependent assays	AgNPs have been shown to have strong neutralising effects on *Naja naja* venom, improving local tissue protection. Biosynthesised AgNPs had better PLA2-neutralizing activity than whole-plant extracts.

Abiotic hydrogel nanoparticles

This study presents a promising treatment option for snakebite using polymer nanoparticles (NPs) designed to sequester major protein toxins in elapid snakes. The low-cost NPs can be administered subcutaneously after the bite to prevent tissue damage and mitigate toxins' distribution. The NPs bind to PLA2 and 3FTX isoforms in elapid snake venoms, controlling their expression and inhibiting the dermonecrotic action of *Naja nigricollis* venom [3].

Titanium dioxide NPs (TiO2-NPs)

Major components of metalloproteinase and phospholipase A2 (PLA2) are found in the venom of vipers and cobras. The PLA2 enzyme, which is abundant in viper venom, causes numerous pathophysiological abnormalities in its victims. These substances cause direct harm to the micro vessels, which exacerbates oedema and bleeding. The PLA2 enzyme in viper venom is what causes the inflammatory response that is brought on by envenomation. The primary mechanism of PLA2's inflammatory effects in response to cobra and viper venoms is its interaction with membrane phospholipids and the subsequent release of precursors of eicosanoid compounds. In this study they assessed for the antisnake venom activity of TiO2-NPs (Titanium dioxide) and their potential as an antidote have been evaluated. It shows how to synthesize TiO2-NPs arrays on p-type Silicon Si < 100 > substrate (about 30 ohm-cm), and uses field-emission scanning electron microscopy (FESEM) to identify the surface topography. The fatal activity generated by *Daboia russelii* venom (DRV) and Naja kaouthia venom (NKV) was effectively mitigated by the TiO2-NPs. In both *in vitro* and *in vivo* experiments, viper venom-induced hemorrhagic, coagulant, and anticoagulant activities were successfully neutralized. In experimental animals, the TiO2-NPs efficiently neutralized the sterile inflammatory molecules generated by the venoms of cobras and vipers [16].

Vitex negundo conjugated with gold NPs (VN-AuNP)

Vitex negundo is a woody, aromatic. The anti-viper and anti-Naja kaouthia venom activity of VN leaf extract. It has been noted that adding metal ashes, like gold ash or swarnabhasma, to herbal extracts can boost the strength of the herbs used in Ayurvedic formulations. The gold nanoparticles in this study were created using Vitex negundo aqueous root extract, which was then physico-chemically characterized and tested for anti-Naja kaouthia venom action in an animal model. In Swiss male albino mice, the study examines the myotoxicity, hepatotoxicity, nephrotoxicity, acute stress response, and proinflammatory activity of NKV. VN-GNP treatment led to a considerable reduction in serum creatine kinase and LDH levels, whereas ASVS treatment was unable to counteract the myotoxicity caused by venom. While ASVS did not provide any protection against hepatocellular injury, treatment with VN-GNP greatly prevented NKV-induced hepatotoxicity. Studies on the histology revealed necrotic lesions, hepatocyte loss, and hepatic bleeding [25].

Gold Nanoparticles (AuNP) conjugated 2-hydroxy-4-methoxy benzoic acid (HMBA)

Hemidesmus indicus roots are used to cure scorpion stings and snake bites. It has been demonstrated that the an organic acid HMBA, which was extracted and purified from the root extract of H. indicus, possesses viper venom inhibiting action. To boost the effectiveness of herbs, metal ashes (Gold, silver, iron, etc.) are combined with them in Ayurveda. Currently used in the field of biomedicine, gold nanoparticles and nano-based products have demonstrated promising advantages as therapeutic molecules. The antiviper venom activity of gold Nanoparticles conjugated with HMBA was determined. Haemorrhage, localized tissue injury, nephrotoxicity and myotoxicity, cardiovascular shock, and multiple organ failure are the hallmarks of a Russell's viper bite. Additionally, hepatotoxicity was noted. ASVS failed to neutralise the pathophisiological affects and organ toxicity caused by Viperidea phosphate lipase (PLA2). They conjugated GNP with HMBA and used on male albino mice and they succeeded in neutralizing the toxicity induced by RVV. GNPHMBA offers superior protection against RVV due to its conjugation with gold nanoparticles, increasing accessibility, cellular uptake, and repairing RVV-induced damage, thus antagonizing organ toxicity [24].

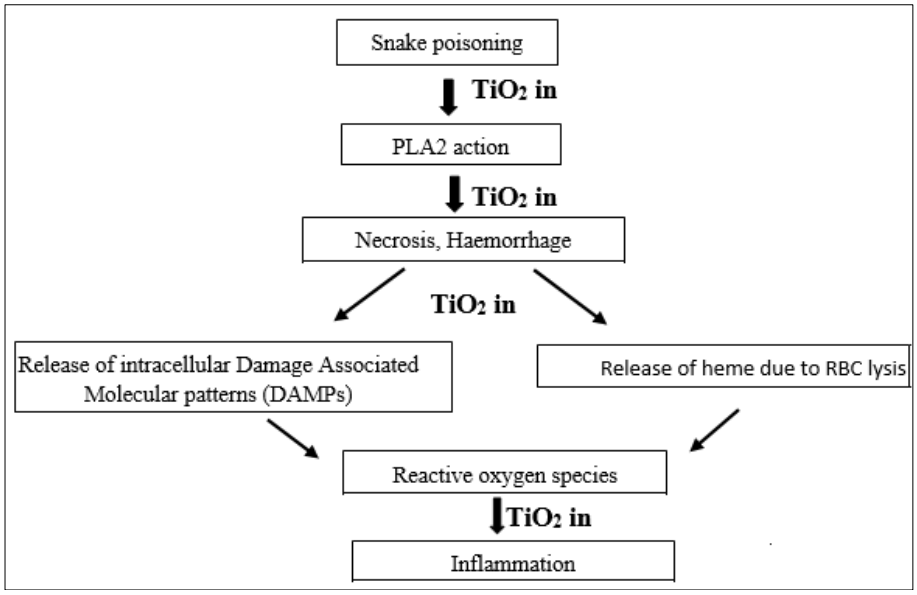

Fig 1: Possible mechanism of action of TiO2 [TiO2-in (inhibition)]. Snake venom-induced necrosis, haemorrhagic, lethal and inflammation and its neutralization by TiO2-NPs

Curcumin conjugated gold Nanoparticles (C-GNP)

Turmeric, a popular spice, contains an active ingredient called curcumin (Curcuma longa). Curcumin's anti-inflammatory and antioxidant properties are well-established. By using the adsorption method, curcumin was conjugated with gold nanoparticles, and the antiviper venom activity was evaluated in experimental animals. It was suggested that curcumin-conjugated gold nanoparticles could counteract local damages caused by viper venom at the vascular bed by blocking the venom's pro-oxidant activity, directly inhibiting the enzyme at the enzymatic level, and interfering with cellular markers such as antioxidants and inflammatory markers. Certain nanoparticles are a cheap and convenient substitute for antivenom against toxins from systemically distributed snake venom due to their pharmacokinetic and protein-binding characteristics[18,26].

Silver Nanoparticles (AgNPs) synthesized using Dryopteris cochleata rhizomes

The green synthesis of SNP was conducted using the rhizomes of Dryopteris cochleata, and the resulting nanoparticles were assessed for their ability to withstand the venom of snakes (ASV; N. naja). AgNPs were synthesised using an environmentally friendly process that produced particles with an average size of 35 nm, as determined by FTIR, XRD, AFM, and UV-Visible spectroscopy. investigated ways to improve AgNP stability, size, and yield. conducted concentration-dependent experiments to assess the neutralising effects on N. naja venom. Using the MIHD assay and *in vitro* tissue damage activity, the inhibition of N. naja snake venom and PLA2 activity of the biosynthesised SNP of D. cochleata was assessed. In addition to confirming the plant extract's successful association, PLA2 neutralisation demonstrated that biosynthesised SNP have stronger PLA2 neutralising activity than whole plant extracts. Nevertheless, N. naja venom neutralisation is gradually increased by increasing the quantity of D. cochleata SNP in a concentration-dependent manner. It is concluded that when administered as D. cochleata nanoparticles, the activity of the extract as antivenoms was enhanced by a factor of ten[19].

Alginic acid-based AgNPs

Macrocystis pyrifera, a common kind of brown seaweed, is the source of alginic acid, a naturally occurring hydrophilic colloidal polysaccharide. It is a linear copolymer mostly made up of 1,4-linked D-mannuronic acid and 1,4-linked L-glucuronic acid residues. Alginic acid has been shown in recent experimental research to possess antioxidant, immunomodulatory, anti-inflammatory, and anti-anaphylactic effects. The antisnake venom activity of Alginic acid-based silver nanoparticles through various *in vitro* methods such as direct haemolytic assay, proteolytic activity, blood clotting test, and ultraviolet visible spectroscopy analysis and fluorescence spectroscopic study. The direct haemolytic and proteolytic activities of *Daboia russelii* venom have been examined in this work. Alginic acid provided up to 55% protection against the proteolytic activity of venom. However, it was also found that AgNP-ALG considerably neutralized the proteolytic activity caused by VRV, offering up to 77% suppression of the proteolytic action. Alginic acid-based silver nanoparticles display antagonistic potential against the proteolytic activities of *Daboia russelii* venom, which may be regarded as noticeably strong. This may be the result of alginic acid and alginic acid-based silver nanoparticles (AgNP- ALG) neutralizing hemorrhagic toxins of *Daboia russelii* venom and metalloproteases found in snake venom[27].

This study explains about the NPs which act against toxins present in Naja species and *Daboia russelii* snake venom, further research is needed for detailed mechanism of NPs action against toxins. Other snakes in big four like common krait and saw scaled vipers' bite are also highly lethal and scientists are working to find affective NPs against their venom.

Conclusion

Snakebite envenomation poses a significant public health threat, particularly in rural India, where venomous species like cobras, kraits, Russell's vipers, and saw-scaled vipers contribute to high morbidity and mortality rates. Despite the effectiveness of traditional antivenom therapy (ASV), its limitations, including high cost, limited availability, and potential side effects, necessitate alternative solutions. Nanotechnology offers a promising approach to enhance snakebite treatment. Recent advancements have shown that nanoparticles (NPs) like TiO2, gold nanoparticles conjugated with HMBA, VN-AuNP, C-GNP, and AgNPs synthesized from plant extracts can effectively neutralize venom-induced toxicity, providing protection against hemotoxicity, neurotoxicity, and local tissue damage. NP-based antivenoms have the potential to mitigate systemic toxicity, enable localized treatment at the bite site, and supplement ASV therapy. Further research is crucial to elucidate the mechanisms of NPs against venom toxins, especially for under-studied species like the common krait and saw-scaled viper. Urgent continued exploration of these innovations is vital to develop more efficient, accessible, and affordable treatments for snakebite victims worldwide, ultimately reducing the significant public health burden of snakebite envenomation. In order to create more specialized and effective nanoparticle formulations, future studies should concentrate on clarifying the precise molecular processes by which nanoparticles interact with and neutralize venom poisons. It will also be essential to create broad-spectrum nanoparticles that can neutralize a range of venom poisons, particularly in areas where it is difficult to quickly identify different snake species. To evaluate the long-term biocompatibility and possible adverse consequences of treatments based on nanoparticles, *in vivo* research is also required. Improving delivery techniques, including topical or injectable versions, could improve accessibility and efficacy in isolated or rural areas. To make these cutting-edge treatments accessible for broad use, it is also necessary to investigate scalable and economical synthesis techniques. In the end, controlled clinical trials will be necessary to prove the safety and effectiveness of these antivenoms based on nanoparticles, paving the way for regulatory approval and incorporation into accepted snakebite treatment procedures.

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