



Therapeutic Antidotes to Spider Toxins: Brown Recluse, Widow and Other Spiders

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Abstract

There are about 40,000 spider species known till date. Spider bite is the most wide spreadlitch among people. Even though only sozme of them are toxin one the less delay in the treatment may lead to death. Particularly in endemic regions, the spider bites may pose hazard to the humans. Our objective in this review is to learn about most common poisonous spiders and to know the possible treatment. We here describe some of the venomous spiders depending on their morphology, post-bite symptoms and existing treatment options. Antidotes play a very crucial role in the management of certain spider venoms. This review is designed to focus on the role of antidotes, categories and its role in curing spider toxins. Spider venom toxins interact with the ion gated channels and biological activities in our body and show multiple effects. The severity of spider toxins gives rise to serious symptoms like cardiovascular disorders, chronic pain, inflammation and reproductive dysfunction. Thus a potential strategy has to be adopted for these toxins to act as therapeutics. Thus, treatment of spider venom should also involve providing supportive care to the patients and a number of synthetic antidotes available from various sources which should be readily accessible that provides immediate care to the patients.

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1 Introduction

According to World Health Organization (WHO), "Antidote is defined as the therapeutic substance which generally counteracts or minimizes effect and action of xenobiotics. Antidote reduces the overall burden of health service in managing and reducing the poisoning cases. The term antidote is a Greek word "Antididonaí" means "given against"[1].

According to the Cambridge Dictionary, an antidote is a chemical substance, particularly a medicine, that reduces the effects of poison or

a method of preventing or acting against anything terrible or damaging to the body. The risk-benefit analysis is used to determine whether or not to deliver an antidote to a specific patient. When the possible therapeutic benefit is assessed to outweigh the potential adverse effects, cost, and resource requirements, an antidote is often delivered. Clinical decision making requires precise risk assessment as well as pharmaceutical knowledge of the antidote [2] (Figure 1).





Figure 1: Identification of antidote for the therapeutic approach

These antidotes are also called as neutralizers or toxin free substances having properties which can be reversed, combat, administered to manage the effect of poisoned condition [3]. Antidote can be considered as therapeutic agent used against the toxic things which affect the person as a xenobiotic species during the specific time [4]. These are common remedy with the toxins or poisons and used as classical approach for the treatment from the ancient days. Antidote role is vital in emergency condition, supportive therapy to act as first aid also before start up for the complete course of treatments. Antidotes are useful tool to mitigate horrible consequences from the poison effect to reduce mortality cases and morbidity situation with the help of medical and non-medical support as complete care of patients [3]. Some antidotes are used as universal chemical or biological agents with their remedial measure and novel functions against poisons or toxins. The antidotes should be cost effective, potential, without any side effects can be expected to utilize it in poisoned time. It must be with standard dose, proven effects and test it diagnostically simple as well as rapid to identify the causative agents also level of poisoning [2]. A high-quality antidote dose may use it very little when require or without expertise to treat the poisoning, with the sub-standardized healthcare facilities and more

importantly must be use lower dose to avoid adverse effects by the treatment with required conditions. These applications are very useful to remote or disadvantaged areas where healthcare access is not reachable on timely or very limited facilities available [2]. Use of antidotes and storage for emergency condition are subjected to guidelines of national and international authorities.

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Studies on antidote effectiveness, detailed information of the application, storage procedure and administration methods are not yet addressed for the various poisoning issues [5]. Currently, the antidote drug delivery systems on target specific are very base level, yet to identify ideal and novel investigations to incorporate systematically by more research studies. Moreover, available antidote's application to use it within duration, time, should be mention it to claim by the researchers with all the supportive data. Some reports also found on the poor management of antidote's, their approach and without scientific investigation [6, 7]. Additionally, unscientific development also been suggested to check useful scientific output by the findings, research, safety measurements and clinical trials to sequential approach to make it use as another route. Such change in the use of antidote and their process can be use it as

translational research which start in lab and end it as product for the field should not be entertained [5, 8]. Hence, the timely review, update of innovation and research information on all type of antidotes are very essential. Till date various natural products, synthetic compounds have been identified as antidotes for different origin of poison effects to treat as indigenous approach as well as modern therapeutics even in poisoning of snake venom. In various reviews and research reported on the application of herbal traditional remedies of snake [9, 10], scorpion, spider and other poisons [11], there is noextensive report and

remarkable reviews on antidotes' effectiveness for the treatment of all type of poisoning cases as well as advanced developments. In this context, this review appraises the status of available antidotes application in *in vivo* as well as *asin vitro* studies. It similarly focusses on antidote types, modes of action, classes, sources, available treatments and the translational study application to identify novel drugs as antidotes in the form natural or synthetic molecule, and also relevant issues to combat with biotechnological tools in antidote investigation for the future projections.

Constituents	Quantity	Purpose
Powdered charcoal	2 parts	Adsorbs alkaloids
Magnesium oxide	1 part	Neutralize acids
Tannic acid	1 part	Precipitates alkaloids, certain glucosides and many metals

2Classes of antidotes

Classes of antidotes specifically developed to combat the harmful effects of toxins and specific poisons; it is classified again depends upon the types of antidotes as well as toxins/poisons. There are no systematic classifications of antidotes, till now by the researchers' identified types and different antidotes as per the need and poison specific classifications. In this scenario, classification of antidotes documented with experimental evidences depends on the efficacy [12], mechanisms of action [11, 13], the identified components of poison groups [14] and requirement of clinical emergency and complication at the poisoned time [10]. Antidotes have their own significance in clinical toxicology. Many poison information centers

help in recommending the antidotes for the specific type of poisons.

2.1 According to the environmental agent

Diagnosing and treating poison is entirely dependent on the environmental agents and how many attributes to select as the correct antidote for the remedial measure. On the basis of their mode of action, antidotes are divided into mechanical antidotes, physical antidotes, chemical antidotes, physiological antidotes, pharmacological antidotes, and universal antidotes. In general classification of antidotes also developed based on the environmental agents, which influence during the poisoned time with the specific incidence. As per the environment and condition antidotes are classified as [3] (Table 1 & Figure 2).

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Table 1: Types of constituents, quantity and purpose of antidote classification

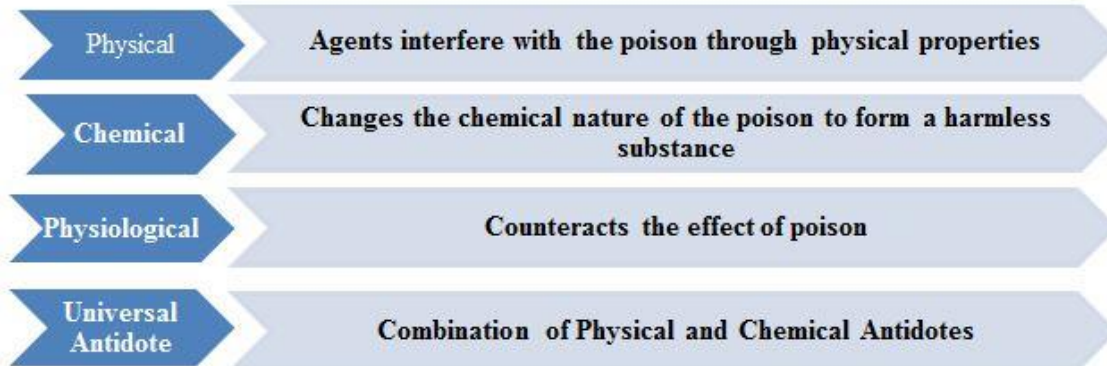


Figure 2: Classification of antidotes for spider toxins

2.1.1 Physical / Mechanical agents

These are the compounds that neutralise the poison and aid in the prevention of poison absorption in the body. They are further classified based on their functions as follows:

- a) Activated charcoal
- b) Demulcents
- c) Bulky food

a) Activated charcoal

Activated charcoal is a fine black powder with no odour. It is produced through the destructive distillation of wood pulp like organic materials, further treated at high temperatures with a variety of activating agents like steam, carbon dioxide, etc. Activating Agents increase absorptive capacity. As the particle size is small, and the surface area is very large, slurry is made by combining it with water and is suitable for treatment. Activated Charcoal works by delaying poison absorption from the stomach. Activated charcoal is especially effective at adsorbing alkaloidal poisons like strychnine and, to a lesser extent, mineral poisons. The disadvantage of activated charcoal is ineffective with hydrocarbons, corrosives, heavy metals, and alcohol poisoning.

b) Demulcents

Demulcents can protect the stomach mucous membrane by forming a protective covering. Demulcents are fatty substances such as milk, egg, albumin, oil, and so on. Fats and oils, on the other hand, should not be used to dispose of oil-soluble toxins such as DDT, organophosphorous compounds, phenol, aniline, acetone, turpentine, and so on. They have the same effect in both corrosive and irritant poisoning.

c) Bulkier food

The action of bulky food on poison is similar to that of mechanical antidotes. They allow particles to be trapped on their surface. Banana, for example, works as a mechanical antidote to glass by encasing its particles and therefore inhibiting their activity.

2.1.2 Chemical agents

When poison comes into contact with chemical antidotes, they either form harmless or insoluble compounds or oxidise the poison. Potassium permanganate, for example, has oxidizing properties. It is used as a solution for opium and its derivatives, hydrocyanic acid, phosphorous, cyanides, strychnine, barbituric acid and its derivatives, atropine and additional alkalis in a 1:5000. While reacting

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with the poison, it misplaces its pink colour in the stomach. Here are a few more examples:

1. Tannin (strong tea) forms insoluble compounds with various metals, glycosides and alkaloids. Common salt decomposes silver nitrate to form the insoluble silver chloride by direct chemical action.
2. Alkaloids like lead, silver, quinine, mercury and strychnine are precipitated by tincture iodine solution or lugol's iodine in warm water.
3. Acids are neutralised by alkalis through direct chemical action.
4. By direct chemical action, acid neutralises alkalis.
5. Acids neutralization with alkalis, and the other way around, must be evaded because the exothermic reaction of neutralisation can lead to extra damage.

2.1.3 Biological/ physiological and pharmacological agents

These agents operate on the antagonism principle. Nearly all antidotes are only partially antagonistic in their action. They act on body tissues and cause symptoms that are diametrically opposed to those caused by the poison. They are not dangerous, but their application is limited. Atropine and physostigmine are the two true physiological antidotes. They have an opposite effect on heart rate because they act on nerve endings. Examples are barbiturates and picrotoxin or amphetamine, Cyanide and amyl nitrate.

2.1.4 Universal antidote

If the nature of the poison administered is unknown and it is suspected that two or more poisons were administered. In such cases, the universal antidotes are used. They are simply a concoction of readily available substances. It is usually a combination of physical and chemical antidotes. They are ineffective, even if administered soon after the poison is administered.

In this instance, addressing the issue to understand the consequences of poison problems, their effect level and influencing

factors which involve during/ later the incidence. Hence, to diagnose and treatment of poison is completely depends upon the environmental agents how much attributes to select as correct antidote for the remedial measure.

2.2 According to their site of action (Figure 3)

2.2.1 Chelating agents

Certain chelating agents are extensively practiced as an antidote for the heavy metal poisoning. They function by forming a firm non-ionized cyclic complex with cations. These complexes are stable, soluble, non-toxic and complexes with calcium and certain other heavy metals for high renal excretion capacity. The strongest of all the available chelating agents are EDTA, B.A.L and Penicillamine [4].

2.2.2 Ethylenediaminetetraacetic acid

It is a precipitating agent and used in iron, mercury, cadmium, cobalt and nickel poisoning. It is frequently managed by sluggish intravenous infusion in isotonic glucose saline. There are some chelating agents, which forms a non-ionized cyclic complex with cations. The complex of chelates is formed with lead are non-toxic, water-soluble, non-metabolized, non-ionised, and excreted as such in the urine.

2.2.3 British anti-Lewisite

In 1941, anti-Lewisite was established as an antidote to lewisite, an arsenic-based warfare compound by the Britishers. This British anti-Lewisite can treat poisoning from soluble inorganic compounds such as arsenic, gold, and mercury. Acute heavy metal intoxication and also Wilson disease are treated with British anti-Lewisite occasionally. Dimercaprol compound is beneficial in the cure of potentially fatal acute arsenic poisoning. Dimercaprol has also been shown in vitro to have the potential to treat snakebite as being a metal ion chelator, it inhibits Zn²⁺-dependent snake venom metalloproteinases, which mediate snake venom's procoagulant property.

2.2.4 Penicillamine

Penicillamine belongs to the heavy metal antagonist class. It treats Wilson's disease by binding to excess copper in the body and allowing it to exit through the urine.

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Penicillamine can chelate heavy metals such as copper, lead, and mercury, forming a soluble compound that is expelled in the urine through kidneys. It binds to cysteine and forms disulfide bonds, allowing it to be excreted in urine more easily. This prevents the formation of cystine calculi and treats cystinuria by preventing the formation of stones. It is also used to treat rheumatoid arthritis by suppressing immune system functions.

2.2.5 Acceleration of detoxification

N-acetyl cysteine can replenish hepatic glutathione supplies needed in conjugating N-acetyl P-benzoquinone imine like toxic metabolite. Paracetamol-induced hepatic injury is prevented in this way.

In cyanide poisoning, sodium thiosulphate converts cyanide to thiocyanate, which acts as a sulfhydryl donor to the rhodanase enzyme. Here, toxic metabolites are converted to lesser toxic compounds.

2.2.6 Reduced toxicity

The toxin's injurious effect is mitigated in two ways: by justifying the toxin's effect or by directly opposing the drug's action. Organophosphorus poisoning is treated with atropine. In this case, it acts as an antidote, counteracting and mitigating the poison's multiple muscarinic effects. Several vitamins, such as vitamin K in warfarin toxicity, pyridoxine in isoniazid toxicity, and folic acid in methotrexate toxicity, can directly counteract drug or toxin effects. Pyridoxine by binding to isoniazid, substitutes pyridoxine stores, and stimulates the making of γ -aminobutyric acid, which supports in seizure control.

2.2.7 Receptor site blocker

This can happen at either the enzyme or receptor level. The enzyme level action are of two types: competitive inhibition or reactivation

of enzyme action. Using ethyl alcohol in ethylene glycol or methyl alcohol poisoning is best example of competitive enzyme inhibition. These agents work by competing for alcohol dehydrogenase (ADH) with ethylene glycol and methyl alcohol, reducing the formation of toxic metabolites.

2.2.8 Cyanide binders

The prompt administration of a cyanide antidote is critical for the treatment of symptoms and mortality. At the moment, there are two widely accepted antidotes: sodium thiosulfate and hydroxocobalamin. Hydroxocobalamin is the first-line treatment for cyanide toxicity (HCO, vitamin B-12). It plays role by fixing cyanide to its cobalt ion to form cyanocobalamin, which is rather nontoxic and excreted through the kidneys. Combine HCO with sodium thiosulfate for faster detoxification. Sodium thiosulfate is given intravenously for nearly 30 minutes. Hydroxocobalamin detoxifies cyanide by binding to it and producing nontoxic vitamin B-12. This medication neutralises cyanide at a slow enough rate that it can be detoxified further in the liver by an enzyme known as rhodanese.

2.2.9 Cardiac drug antidotes

Diltiazem, verapamil, or nifedipine are calcium channel blockers. Overdose of these drugs causes cardiovascular harmfulness which can be treated through calcium chloride or calcium gluconate. These compounds work through increase in calcium concentration present in the cells. In the instance of a beta blocker overdose, such as atenolol or propranolol, the preferred antidote is glucagon, followed by an anti-emetic. Glucagon stimulates adenylate cyclase without relying on beta-receptors [16] (Table 2 & Figure 3).

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Table 2: Selected antidotes and their respective indications against to spider toxins

Class	Mechanism of action	Example	Reference
Chelating agents	Interacts with poison to form a non-toxic complex that can be excreted.	Superoxide dismutase, zinc oxide and manganese oxide	
Acceleration of detoxification	During poisoning, it speeds the detoxification of potentially harmful metabolites.	Acetyl cysteine, thiosulfate	



	Reduces toxicity of poisons by either accelerating or avoiding the change of a potentially hazardous compound to a less toxic one.	Ethanol, Methaemoglobin and fomepizole	5
Receptor site blocker	Binds to the receptor before to the toxin, hindering its site and stopping the toxin from attachment.	Atropine	
Cyanide binders	Categorized into physiological biochemical and causes detoxification by scavenging mode of action.	Chloropromazine	
Cardiac drug antidotes	They act by upregulating cellular calcium level		
Universal general antidotes	They work by blocking vitamin k reductase, which restores the active form of vitamin K.	Warfarin and phenprocoumon	

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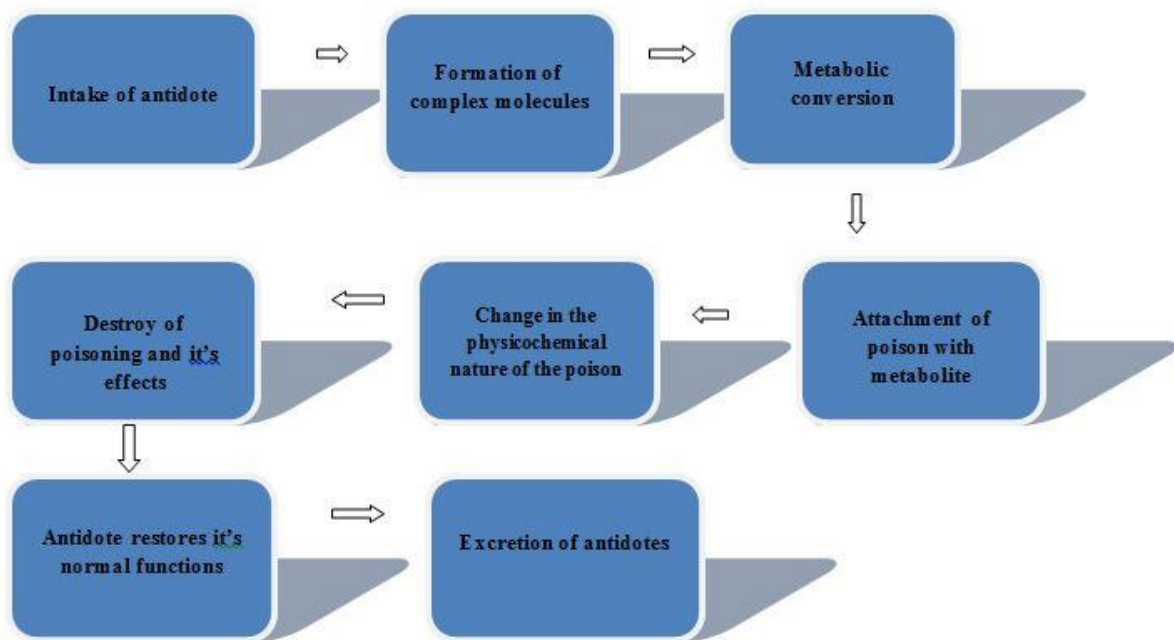


Figure 3: Flowchart representing the mechanism of action of antidotes

3. Mechanism of action

3.1 Antidotes and their indications (Table 2 & Figure 4)

3.1.1 Succimer

Succimer is a mercaptodicarboxylic acid heavy metal chelator. It is used as an antidote to heavy metal toxicity because it forms strong

chelates with them. It is oral chelating agent for treating heavy metal and lead poisoning.

3.1.2 Dimercaprol

Dimercaprol (British anti-Lewisite) is a parenterally accomplished heavy metal chelating mediator that is used to treat copper, arsenic, mercury and gold poisoning.

3.1.3 Flumazenil



Flumazenil is a benzodiazepine antagonist. It is used to reverse the effects of a benzodiazepine sedative. Flumazenil has FDA-approved clinical uses such as benzodiazepine overdose reversal and postoperative sedation from benzodiazepine anaesthetics. Flumazenil is used to wake up after a surgery or medical procedure in which a benzodiazepine was used as a sedative.

3.1.4 Zwitterionic hydroxy imino acetamido alkylamines

In humans, ionising zwitterionic aldoximes may be appropriate antidotes as viable alternatives to existing antidotes for prophylaxis and treatment of individuals affected by nerve agents organophosphates such as sarin, in pesticide exposure or in terrorist-led events.

3.1.5 Activated charcoal

Activated charcoal is used to treat certain types of poisoning as an alternative treatment. It prevents poison from being absorbed from the stomach. To treat severe poisoning, several doses of activated charcoal may be required. Normally, this medicine is ineffective and should not be used to treat poisoning caused by corrosive agents or alcohols because it does not prevent these poisons from being absorbed into the body.

3.1.6 Sodium bicarbonate

Intravenous sodium bicarbonate treatment balances acids in the blood. It treats acidosis caused by bicarbonate (base) injury, which occurs in some kidney, diarrhoea, and vomiting conditions.

Veratridine, batrachotoxin, grayanotoxin, and aconitine all modulate sodium channels. These fix to the activated sodium channel, preventing it from inactivating. Toxin-induced sodium channel barrier is treated with sodium bicarbonate, as shown by QRS widening on an electrocardiogram [17].

3.1.7 Heparin

Higher concentrations of heparin can prevent further coagulation after the onset of active thrombosis by deactivating thrombin and stopping the alteration of fibrinogen to fibrin. Also, heparin averts the activation of fibrin stabilising factor that inhibits the formation of a steady fibrin clot.

3.1.8 Lidocaine

Lidocaine is an antiarrhythmic drug of class IB that is used to treat ventricular arrhythmias such as ventricular tachycardia and ventricular fibrillation. Lidocaine is only given intravenously to treat arrhythmias. It inhibits cardiac sodium channels, causing the action potential to shorten.

3.1.9 Copper sulfate

Copper sulphate reacts with phosphorus forming cupric phosphate that is a black compound which makes visualisation of phosphorus easier. On the other hand Copper is extremely toxic which can cause death by immense hemolysis intravascularly.

3.1.10 Levallorphan and Nalorphine

Nalorphine and levallorphan are antinarcotics that work by reversing morphine's miotic action. These are opioid receptor antagonist that is used in the management of alcohol and other addictions.

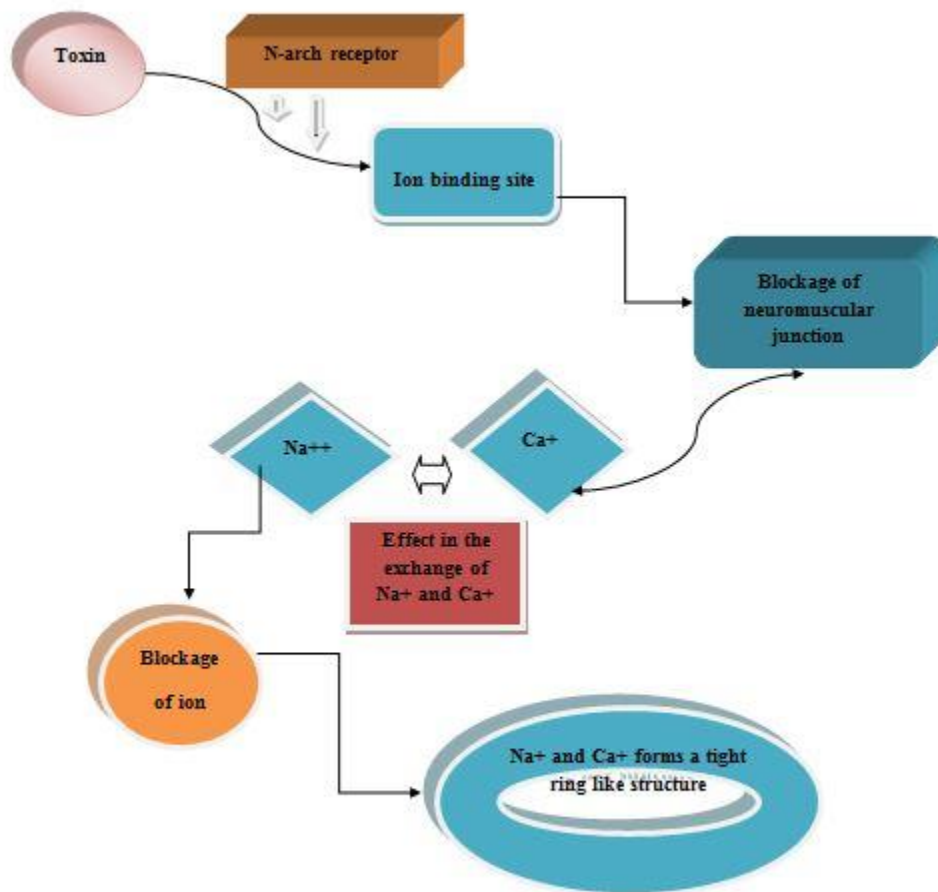
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Table 3: Antidotes and their poisoning indications

Antidote	Poisoning indication	References
Oxygen tetrachloride	Carbon monooxide, hydrogen sulfide, cyanide	6
Diethyldithiocarbamate succimer	Lead, mercury	7, 8
Dimercaprol	Arsenic, copper, mercury and gold	9
Flumazenil	Benzodiazepines	
Zwitterionic hydroxyiminoacetamido	Organophosphates	



alkylamines		10, 11
Activated charcoal	Most poisons, gastric indications	
Sodium bicarbonate	Metabolic acidosis	
Heparin	Hypercoagulability	
Lidocaine	Ventricular arrhythmias	
Copper sulfate	Phosphorous	
Levallorphan, Nalorphine	Opiates	



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Figure 4: Flowchart showing the mechanism of spider toxin peptide

3.2 Types of spider and their venom (Table 4)

Spiders seem as insects but they fit in an entirely dissimilar group called Arachnids that also contains harvestmen, ticks, mites and scorpions. A spider is different from an insect as [15].

1. A spider has eight legs, whereas an insect only has six.

2. A spider's body consists of a cephalothorax and an abdomen, but an insect's body consists of three parts: a head, a thorax, and an abdomen.

3. A spider often has six to eight eyes, whereas insects typically have two eyes.

4. While many insects have wings and antennae, spiders lack these features.



Few spiders are enormous in size. Giant Huntsman is the world's largest spider, measuring as much as a dinner plate. Most spiders are plain brown or grey in colour, but a few are a vibrant mix of yellow, red, and orange. Spiders' bodies are typically short and wide, but a few are long, narrow, and slim. Only a few species are spherical and flat, with spines, warts, and horns [18].

Spiders are tough, agile hunters with protective bites tailored to their hunting needs, however the majority of them are not dangerous to humans. According to an estimate made recently there are more than 100000 species of spiders existing worldwide. Spiders evolved around 300 million years ago during carboniferous period. During long process of evolution spiders have developed and adapted

complex venoms in their body against their enemies and predator animals[6].

The major purpose of production of venom in spider is self-defense and protection of their foods. Most of the spider species worldwide use venom as a lethal cocktail and rapidly paralyze their prey, sometimes even bigger than their own size. The venom glands of spider are present in their mouth and secrete toxins which inflict their prey and immobilize it either by respiratory paralysis or cardiac arrest and kill them. Spider venom is the source of thousands of bioactive and low molecular weight compounds which are either organic or inorganic in nature. Most of them are salts, carbohydrates, biogenic amines or amino acids [19].

Table 4: Spider toxin types and functions

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Toxin type	Function	References
Huwentoxin-IV toxin	It is found in Chinese spider <i>Orin thoctonous huwena</i> venom. The toxin is accessible from the spider venom glands having K units type toxins and are functionally voltage gated blockers. Spider venom peptide 8-amaurobitoxin –PI1a targets snow drop lectin and confer oral toxicity.	16, 17
Agritoxin	Natural agritoxin (Arg TX-636) and its two analogues Arg TX-75 and Arg TX-48 are isolated from venom of <i>Agriope lobata</i> sider. These are used as diagnostic ligand to bind with p-type Calcium++ channels. Agatoxins isolated from venom of funnel web spider <i>Agelenspis aperta</i> inhibits the glutamate receptor and prevent the traction of insect muscle cells.	18
Omega toxin	Omega conotoxin MVILA and pha 1 β induce acute and chronic pain while PhTx3-4, omega conotoxin MVIIA and MVIIIC inhibit the glutamate uptake and capsaicin induced glutamate release and Ca++ ion spinal cord synaptosomes in calcium dependent manners.	18
Guangxitoxin	They are isolated from brown spider venom which is enriched in three molecular families, the phospholipase D, metalloprotease, inhibitor cysteine knot (ICK) peptides.	19
Oxytoxin	OxyTx1 and OxyTx2 are disulfide-rich peptides extracted from the spider <i>Oxyopes lineatus</i> that inhibit voltage-sensitive ion-gated channels. OxyTx1 has been found in <i>Oxyopes kitabenesis</i> and has been shown to have increased paralytic activity against <i>Spodoptera litura</i> larvae.	20
Hainantoxin-1	HNTX-1 is an ion gated channel which shows little effect on Sodium+ and Calcium+ channels. M-TRTX-Hn1b is a short peptide extracted from the venom of the spider <i>Orin thoctonus hainana</i> that is morphine-like and thus utilised to treat inflammatory and chronic	19



	neuropathic pain in animals. It also serves as a model for clinical analgesic medication development.	
Zinghaotoxin	JZTX-V, also known as B-theraphotoxin-CJ2a toxin, is a toxin that blocks Na ⁺ and K ⁺ channels. Zinghaotoxin has a TC50 inhibitory impact on TTX-S sodium current in rat DRG cells.	21
Latrotoxins	Latrotoxin venom is isolated from <i>Latrodectus hesperus</i> and inhibits cystine knot toxin CRISPs hyaluronidase, chitinase and protease and 59% of VSTs. The presence of an inhibitor cystine knot in most of the spider venom toxin provides it an extra stability.	22
Therophotoxin	This venom is isolated from <i>Tarantula grammastola rosea</i> . A tarantula venom peptide of protein-1 is isolated from the venom of the Peruvian green velvet tarantula <i>Thrixopelma pureins</i> , a well-known TRPA 1 segment. The toxic factors in most spider venom toxin are small and disulphide rich peptides.	23
Sphingo myelinase D	<i>Loxosceles</i> species spider main toxin is sphingomyelinase D, a phospholipase used in generation of antibodies. Two <i>Loxosceles lata</i> SMD isoforms LI1 and LI2 are produced in bacteria. The venom has high crude protein content and possesses cysteine knot as potent neurotoxins.	24

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4. Mode of action of spider toxin peptides (Table 5)

Spider toxins potentially interact non-specifically with cell membrane and are mostly cytolytic in nature. They bind to sodium and potassium gated channels through blood and shows various diverse biological functions. Spider toxins are very active physiologically and block various channels and allow the free movement of various molecules across the membrane. Few spider toxins are known to cause hemolysis of red blood cells and damage nerve tissues [20].

Venom toxins act on neuron, nicotinic acetylcholine receptors and neuromuscular junctions. A phospholipase toxin acts very severely on upon motor nerve and cause damage to the muscle cells and inhibits cell regeneration. An experiment conducted on laboratory animals are known to cause acute and chronic inflammatory response [20].

The bioactive compounds found in spider venom are carbohydrates, peptides, amino acids and low molecular weight proteins which results in the induction of paralysis, killing of micro-organism and other cytoplasmic effects [20, 21].

Table 5: Showing the recommended dosage of drugs

Drug	Indication	Presentation	Recommended stock	Reference
Acetylcysteine	Paracetamol	200mg/ml, 10 mL ampoule	20 ampoules	44
Activated charcoal	Oral poisons	50g pack	7 packs	
Atropine	Bradycardia, Carbamate or organophosphorous insecticides	600 mcg/mL , 1mL ampoule	10 ampoules	
Calcium chloride	Calcium channel blockers	10 mL ampoule	6 ampoules	



	Systemic effects of hydrofluoric acid		
Calcium gluconate	Location infiltration for hydrofluoric acid	10 mL ampoule	10 ampoule
Calcium gluconate gel	Hydrofluoric acid	25 g pack	1 pack
Dicobalt edetate	Cyanide	15 mg/mL,	6 ampoules
Hydroxocobalamin		20 mL ampoule 5g pack (3%)	2 packs
Sodium nitrate		10mL ampoule	5 ampoule
Sodium thiosulphate		50% mL ampoule	5 ampoule
Flumazenil	Reversal of iatrogenic over sedation with benzodiazepines.	100 mcg/mL, 5 mL ampoule	5 ampoule
Glucagon	B – adrenoreceptor blockers.	1 mg vial	50 vials (Store in fridge)
Intralipid 20%	Severe systemic local anaesthetic toxicity.	100 mL 20% solution	1.5 litres
Methylthionium Chloride	Methaemoglobinaemia	0.5%, 10 mL, 10 mL ampoules	5 ampoules
Naloxone	Opioids	400 mcg/1 mL, 1mL ampoule	30 ampoules
Procyclidine Injection	Dystonic reactions	5 mg/mL, 2 mL ampoule	5 ampoules
Vipera tab	European adder	10 mL ampoule	2 ampoules

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5. Brown recluse spider (Figure 5)

5.1 Scientific classification

Kingdom- Animalia
 Phylum- Arthropoda
 Class- Arachnida
 Order- Aranceae
 Family- Sicariidae
 Genus- *Loxosceles*
 Species- *recluse*





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Figure 5: Brown recluse spider

5.2 Characteristics

The size of brown recluse spider ranges between 5-20 mm. They are normally light to medium brown in colour and have a violin pattern on the cephalothorax back, with the violin's neck directing to spider back with names like fiddle back spider, brown fiddler, or violin spider. Although spiders have eight eyes, recluse spiders have six pairs of eyes, commonly known as dyads along with two lateral pairs and one median pair [22, 23].

5.3 Life cycle

Adult brown spiders live for 1-2 years. From May to July, each female produces multiple egg sacs with roughly 50 eggs in each sack over a two-to-three-month period. It takes around a year for spiderlings to mature. The brown recluse spider is tough and may survive up to 6 months of intense drought and food scarcity [23].

5.4 Behaviour pattern

When exposed to danger, it normally flees to evade fighting. The spider rarely jumps unless it is touched, and even then, its evading through a horizontal swing. On a level surface, a brown recluse's stance is normally with all legs radially extended. When disturbed, it lowers its body,

withdraws the two front legs backwards in a defensive stance, and withdraws the rearest set of legs into a lunging forward position [22].

5.5 Habitat

They frequently build their webs in closets, cellars, garages, wood piles, shade, dry and undisturbed places. They are also found in shoes, cloth stacked or piled in the floor, inside dressers, work gloves, bed sheets of infrequently used beds, behind baseboards, near sources of warmth [22].

5.6 Location

They are mostly found in Indiana to Southwestern Ohio and southeastern Nebraska through Southern Iowa, Illinois [24].

5.7 Bite

The brown recluse venom is extremely poisonous. Its powerful necrotizing venom consists of sphingomyelinase D, the dermonecrotic agent with more potency than rattlesnake venom. The effect of recluse venom is comparatively less although it is toxic to cells and tissues. The brown recluse spider is hardly violent in nature and bites are not common. The spider generally bites only when injured or pressed against the skin or inside gloves tangled with towels, bedding, clothes,

and This species normally attacks its prey by injecting venom along with its bite. The venom is considered to be very powerful and it is used to kill other insects[25].

5.8 Effects of bite

The bite is not felt at first and may not be painful, but it can be serious. The bites caused loxoscelism, a set of symptoms shared by many members of the *Loxosceles* genus that can vary from severe dermonecrotic lesions to severe cutaneous or viscerocutaneous symptoms. The most common systemic symptoms include vomiting, rashes, fever, nausea, and muscle and joint discomfort. Rarely, such bites cause hemolysis, organ damage, thrombocytopenia, disseminated intravascular coagulation and even death. The bite causes a necrotizing ulcer, destroying soft tissues and taking months to heal, leaving lasting scars. Within 2 to 8 hours, these bites frequently become unpleasant and

irritating. Pain and many other symptoms worsen 12 - 36 hours after bite following necrosis afterwards. The wound might develop to be as large as 25 cm in size over time. Gangrene develops in the injured tissue. The majority of fatalities are reported in youngsters under eight and with weakened immune system[25].

6. Widow spiders (Figure 6)

6.1 Scientific classification

Domain- Eukaryota
Kingdom- Animalia
Phylum- Arthropoda
Subphylum- Chelicerata
Class- Arachnida
Order- Araneae
Family- Araneomorphae
Genus- *Latrodectus*
Species- *tredecimguttas*

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Figure 6: Black widow spider

Out of the 40,000 spider species, the black widow spider is deadliest among genus *Latrodectus* affiliates. The "widow" spider family members found globally are responsible for nearly all deadly spider bites. This species originated in Canada, North America, and Mexico. The name *Latrodectus mactans*, which

means "deadly biting robber," is a combination of Latin and Greek words. The dangerous female black widow spider is very poisonous to humans. The female black widow spider is called "The Hourglass Spider" due to red hourglass-shaped mark on abdomen. The widow spiders possess eight eyes, which are

organised in two rows of four with poor vision. The male spiders are roughly half of size of females and are generally harmless to vertebrates. A black widow spider's bite is poisonous. This spider is medically significant in humans because its bite leads to extreme pain and various other clinical signs. The venom of *Latrodectus* is formed by glandular cells in the spider's chelicerae. These cells dissolve and their contents are discharged into the gland's lumen in a process known as holocrine secretion. The black widow spiders are not very big but their toxin is regarded to be significantly more deadly than rattlesnake venom and far more potent than cobra and coral snake poison. The primary function of black widow venom is to paralyse or kill insects. Toxicity against vertebrates most likely evolved to defend the species against predation and accidental crushing. Even in adult females, the actual amount of venom injected is quite modest in physical volume [26, 27].

6.2 Black widow spider venom

It mainly comprises of latrotoxins i.e., smaller polypeptides toxins intermingling with cation channels that display spatial structure homology affecting potassium, sodium, calcium, channels functioning [28]. Also, adenosine, guanosine, inosine and 2,4,6-trihydroxypurine are present.

Latrotoxins being the primary active part of spider venom from the genus *Latrodectus* are actually neurotoxins causing latrodectism. The most well-studied latrotoxin is α -latrotoxin, that acts presynaptically causing acetylcholine, norepinephrine, and Gamma-aminobutyric acid like neurotransmitters release from sensory, motor neurons and endocrine cells in vertebrates. Latrotoxin is the active component of the venom that affects only vertebrates. The black spider's venom is a neurotoxin that changes the structure and function of nerve terminals without causing any major local reaction. The clinical signs of envenoming are caused by the release of these neurotransmitters. If enough venom is put into a person's body, the pain begins in a local muscle group and subsequently spreads to the

regional muscle groups. The toxin is conveyed by the lymphatic system to bloodstream where it is circulated depositing the poisons in nerve endings in connection with muscle. It works at nerve ends, where nerves enter muscle. The venom acts on nerve terminals to impede muscle relaxation, resulting in tetany (continuous, intense, painful muscle spasms) [29].

α -latrotoxin (-LTX) has a molecular weight of about 130 kDa and is a stable dimer that can be tetramerized. This toxin has three unique domains, as shown by its 3D structure using electron microscopy: head, body, and wings. Under normal conditions, the α -LTX monomer forms a dimer with additional α -LTX monomer. Dimers can spontaneously form tetramers, which necessitate conformational modifications. Divalent cations, such as magnesium or calcium, generate these conformational changes, which are also required for latrotoxin action. Toxicity is activated by tetramer formation. The dimer's wings are pointing in opposite directions, making it unlikely that it will be able to pierce the membrane. Because of its hydrophobic or lipophilic bases, the tetramer can insert itself into the membrane and these bases permeate the membrane) is around 130 kDa and is a stable dimer that can be tetramerized. The toxin's 3D structure shown by electron microscopy has three unique domains: the head, body, and wings. Under normal conditions, the α -LTX monomer forms a dimer with another α -LTX monomer. Dimers can spontaneously form tetramers, which necessitate conformational modifications. Divalent cations, such as magnesium or calcium, generate these conformational changes, which are also required for latrotoxin action. Toxicity is activated by tetramer formation. The dimer's wings are pointing in contradictory directions, creating unlikely condition to stab the membrane. Because of its hydrophobic or lipophilic bases, the tetramer can embed itself into the membrane, and these bases permeate the membrane [30].

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In its tetrameric form, α -LTX interrelates with neuronal membrane receptors causing α -LTX to be inserted into the membrane. Then, tetramer is incorporated into cell membrane that causes extensive neurotransmitter exocytosis via two calcium-dependent pathways and a calcium-independent mechanism that has yet to be identified. The pores created by α -LTX in the membrane are holey to calcium ions, allowing calcium to enter the cell. This influx efficiently induces exocytosis. The cation influx is relative to pores created, and calcium ion substantially promotes the creation of tetramers and thus pore formation. The pore is also leaky to neurotransmitters, resulting in significant neurotransmitter pool leaking into the synaptic cleft. The channel is not highly selective, allowing sodium, potassium, barium, strontium, magnesium, lithium, and caesium to pass through as well [31].

α -LTX is capable of strongly interacting with distinct membrane proteins in neurons. Neurexin, latrophilin, and protein tyrosine phosphatase sigma are the receptors for α -latrotoxin. Latrophilin stimulates a receptor, which triggers the downstream effector phospholipase C, that meanderingly causes calcium ion release from intracellular pores. This increase in cytosolic calcium ion concentration may upsurge release and the pace of spontaneous exocytosis. So, latrophilin in combination with α -LTX causes transport vesicle exocytosis [32].

6.3 Clinical syndrome

Latrodectism is a clinical illness induced by the neurotoxic venom injected through Latrodectus spider bite.

6.4 Symptoms

During the first 24 hours after the bite, the symptoms include acute muscle pain and cramping. In a rare case, rashes, piloerection, and minor edema occur. Symptoms such as muscle spasms, tingling, anxiety, and weakness emerge in the following weeks or months, potentially leading to paralysis [33].

7. Other spiders

7.1 The funnel web spider

- Venomous.

- 1.5 to 5 centimeters in length.
- Lifespan lasts upto 20 years.
- They live along the coast, mountains, rainforests and snow country.
- Live in silk lined burrows.
- Their bites are very dangerous and might cause death in few cases [34].

7.2 The wolf spider

- Venomous.
- 1-2 inches in length.
- Lifespan upto 5 years.
- They are mostly found in woods, open grassland and along rivers or streams.
- The effect of wolf spider bite is very mild with the symptoms like pain, nausea, swelling and itching.
- They do not make webs [35].

7.3 The camel spider

- They are non-venomous.
- Size ranges around 5-6 inches in length.
- Their life span usually lasts less than a year.
- They mostly live in desert.
- The bite is very painful but it does not cause death in humans [36].

7.4 The hackled orb-weaver

- They are non-venomous.
- Their length varies from 1/16 to 3/8 of an inch in length.
- Their web measures across 10-30 inches in length [37].

7.5 The jumping spider

- They are energetic hunters who use clever camouflage to blend in with their surroundings and lie in wait for their prey.
- After spotting their target with their extraordinary vision, they pounce and deliver a poisonous bite.

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- The poison affects very quickly, practically paralyzing the prey. [38].

7.6 Trapdoor spider

- As it does not spin a web or hunt, this spider is also known as the master of disguise.
- It digs a clever hole with a trapdoor and silky spots around the burrow that serve as trip lines.
- They detect the movements of a passing insect or creature, giving the trapdoor spider the opportunity to pounce, leaping out to seize the prey with its jaw. [39].

7.7 Golden wheel spider

- This spider is only found in Namib Desert in Africa.
- The golden color helps to blend in with the environment.
- The venom of this spider is very less toxic [39].

7.8 Treatment

- Find the bite, clean with antiseptic soap and water. Apply in the area with antibiotic to prevent the infection.
- Use the cool damp cloth in the bite area to help in reducing the pain and edema.
- Physician may recommend a tetanus injection as booster dose if you haven't had one in past 5 years [40].

7.9 Future perspective

The humans are scared of some spiders due to their venomous nature. Sometimes the venom may cause fatal, and hence should be more careful about the spider bites. In India, with respect to the detection of the venomous spiders including widow spider, personnel involved in health care necessarily be aware with the symptoms caused by bite of toxic spiders. This becomes as the prerequisite in

preparation of anti-venoms. As a final point, additional domestic surveys are needed with regards to the region wise distribution of toxic spiders and immediate reporting of suspected cases of venomous spider bite at specific centers for first aid. Further, more focus should be given on the use of synthetic venom because it's non-toxic nature which is also suitable in vaccinating the people. If the individual has spider bite, the antibodies are already produced in the person's body which is efficient in reducing the ill effects caused by the venom.

7.10 Conclusion

The present review on antidote and spider toxin like brown recluse spiders, black widow spiders and other spiders highlights the venom toxin and anti-venom research mainly focused on the fact that the venom released by these spiders are known to cause clinical complications and produce symptoms like severe pain in the muscle and muscle cramping, rashes, piloerection and mild edema. Few known species of black widow spiders are known to release neuro-toxic venom which cause paralysis and even lead to death in few fatal cases. Based on the clinical studies and case reports, spider venom is not known to cause deadly effect on human beings. Moreover, the review has discussed the mechanism of venom toxicity and elaborated the mode of action of each type of toxin reported by far from 40,000 species of spiders found worldwide. The spider venom has the ability to act as potent anti-venom against other type of poisons.

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