Which snake venom would be the deadliest?

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Abstract. Snakebites constitutes a public health problem worldwide and is a neglected tropical disease. It causes at least 120000 death each year and amputations account for about three times as many deaths. This paper explores the toxicity of three types of snake venom including hemotoxic venom, neurotoxic venom, and cytotoxic venom in the aspects of toxins contained, mechanism consequents as well as their future prospect as anticancer agents.

Keywords: Snake venoms; proteins; mechanism of toxins.

1. Introduction

An estimated 5 million people are mouthed by snakes each year, with up to nearly 3 million being envenomated. More than approximately 138,000 people die annually from snakebites, and three times as many amputations and other lifelong impairments are inflicted every year [1].

Snake venoms are intricate combinations of enzymatic and nonenzymatic proteins. In addition, snake venoms may also consist of lipids, carbohydrates, and biogenic amines. Snake venoms, that are derived from modified salivary glands, paralyze and predigest preys [2]. Despite their limited mobility, they are among the most dangerous creatures on the planet. In fact, the black mamba, which is a species which belongs to the family of Elapidae, has a fatality of 100% if antivenom treatments are not applied [3].

Even within closely related species, snake venoms are extraordinarily complex and varied mixtures of toxins. Not all of the harmful components of snake venom have been clearly addressed. Proteolytic venom, hemotoxic venom, neurotoxic venom, and cytotoxic venom are the four forms of snake venom. Proteolytic enzymes are frequently involved in the mechanism of other toxins, such as cytotoxin, and is present in all snake bites. Thus, in this paper, the other three have been thoroughly studied and compared [2].

2. Hemotoxic venom

Hemotoxic venom destroys red blood cells while also damaging tissues and organs in the affected individual. The venom destroys cells and tissue around the injection site, causing excruciating agony. This venom can also induce or inhibit blood coagulation, both of which are potentially fatal. This venom causes circulatory failure, as well as extensive internal bleeding [2].

2.1. Major components

The four main hemotoxic enzymes are serine proteases (SVSP), phospholipases A2 (PLA2), metalloproteases (SVMP), and hyaluronidases (SVH). The experiment on the SDS-PAGE protein banding pattern used a mixture of 10 or 12 percent SDS-PAGE gel and 20 mg of lyophilized venom protein. The mixture was then subjected to electrophoresis using a Mini Protean II machine or Hoefer MiniVE system. The experimental finding shows the venom's enzymes individually in reducing and non-reducing environments. Ca, Cp, and Cmn these three hemotoxic venoms were employed in the test for comparisons, with the primary differences occurring between 50 and 15 kDa. A specific

enzyme called LAAO has also been found, and it has been determined that this enzyme corresponds to the yellow hue of venom in addition to employing the test to distinguish between different venoms [4].

The quantities and activity of the enzymes vary amongst different snake species. A variety of assays could be used to verify the enzyme activity. Two enzymes that are listed among the four primary hemotoxic enzymes have been proven to function. First, the amidolytic activity of 50 micrograms of venom protein was measured for serine protease, and the trypsin-, chymotrypsin-, and elastase-like activities of serine protease were measured independently using a variety of substrates including BapNA and SAAPFpNA. The reaction then happens. The mixture was diluted with a 0.1 molar solution of Tris to a final volume of 120 microliters before 10 microliters of substrate were added. The buffer solution of Tris used has a pH value of 8. The amount of p-nitroanilide released, which absorbs at a wavelength of 405 nm and reports as a venom protein with activity units (AU)/min/μg, was used for measuring activity [4].

The subsequent enzyme to be mentioned in court was phospholipase A2. Firstly, the Cayman Chemical kit was utilized to measure the phospholipase activity in 100 ng venom protein (Ann Arbor, MI, USA, catalogue number 765001). The 1,2-dithio diheptanoyl phosphatidylcholine equivalent was used as a substrate binding with the phospholipase to form enzyme-substrate complexes. The free thiols were created by hydrolyzing the thioester linkages and could be recognized by DTNB [(5,5′-dithio-bis- (2-nitrobenzoic acid)]. A growing absorbance is detected by using a spectrophotometer (Benchmark Plus, Bio-Rad, USA) at a wavelength of 414 nm. This process would take about 10 minutes, and results were recorded every minute. The results concluded the enzymes distribution in each venom. The highest SVMP activity is found in Ca venom; SVSP and SVH proteases were the most active in Cp venom, followed by Cmn venom with a similar level of SVSP protease activity. Finally, all of the venoms had highly active PLA2 enzymatic activity [4].

Lys49-PLA2, a member of the PLA2 family, is also known as BthTX-I, and a substance called sPLA2 is found in the inflammatory exudates of mammals. Due to the fact that Lys49-PLA2 and sPLA2 share a very similar structural composition, this molecule is the primary factor driving an inflammatory response to occur. Inadvertently binding to Lys49-PLA2 by the enzymes would result in an inflammatory reaction, and functional calcium channels would enable a rapid discharge of intracellular contents till cell death [5].

2.2. Mechanism

Hemotoxic venom is one of the major snake venoms. In some extreme situations, hemolysis or muscular necrosis can directly arise from hemotoxin discharge, which can also harm the muscular tissues and circulatory system [4]. Immune cell cytosol contains a multiprotein complex called inflammasomes. These compounds can identify tissue damage or pathogen infections, and they can subsequently assist in repairing the damages. Because excessive and ongoing inflammasome activation leads to the dysfunction of inflammatory response, the toxin reaction also causes cell apoptosis. Cells inflate and break quickly, releasing their internal contents, and then they die. Pyroptosis is the name of this process [5].

Researchers conducted a number of tests to determine how the organism was impacted by the hemotoxin in order to better understand the mechanism of hemotoxic venom. Three groups of mice were prepared for the first experiment. A mouse was given PBS as a control, another was given BthTX-I, and the last group of mice received both BthTX-I and A438079 injections. The hemotoxic venom protein BthTX-I increases the release of the mediators CK and LDH. The quantity of these mediators shows how myotoxic activity is changing [5]. The number of inflammatory cytokines that are suppressed by glibenclamide depends on the activation of monocytes' P2X7 receptor, which is an antagonist of A438079 [5,6]. In other words, A438079 lessens the impact of myotoxic activity. This is further supported by the experiment's findings, which showed that the BthTX-I group had the lowest level of CK in the remaining muscle tissue. The alteration in the CK level is evidence that BthTX-I actually seems to have a myotoxic effect [5] (Figure 1).

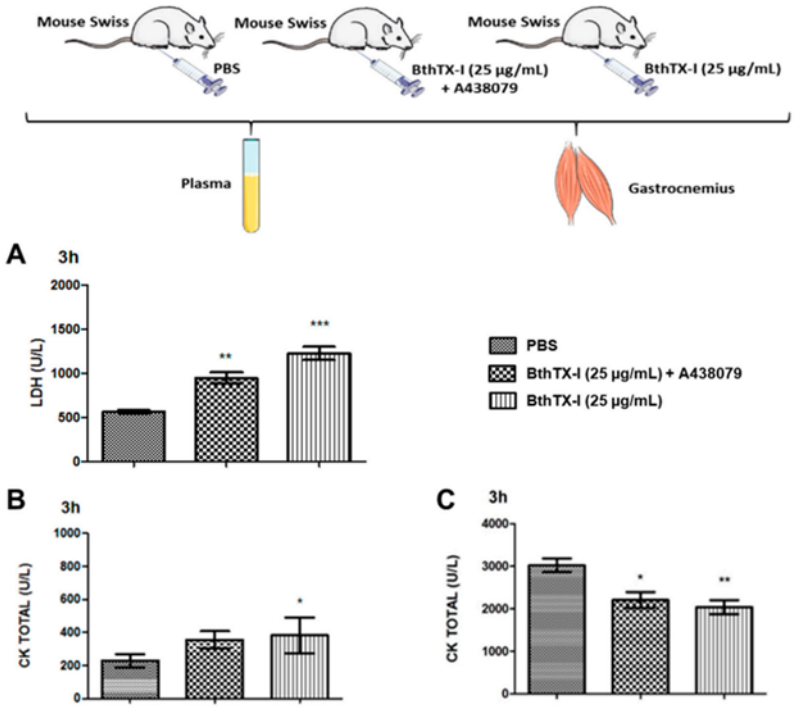

Fig. 1 The figure above the bar charts shows the three mouse groups that took part in the initial study. PBS (the control) or BthTX-I (25 ug/mL) treated with or without A438079 are injected into the animal. After 3 hours of injections, the gastrocnemius muscle's release of LDH and CK caused by BthTX-I was assessed. LDH (A), serum CK (B), residual muscle CK (C) were analyzed. The presence of the myotoxic impact is supported by the BthTX-I group's highest LDH and CK levels in bar charts A and B and lowest CK levels in chart C.

The A438079-containing group is absent from the experiment that follows, which only has two other mouse groups. In order to determine whether or not inflammation occurs under the impact of BthTX-I, the expression of mRNA is monitored. The NLRP3 inflammasome complex's gene expression is found using a variety of gene primers. The results show that the BthTX-I group had a relatively high amount of mRNA expression in each gene primer at that stage. In other words, BthTX-I encourages the formation of many inflammasome complexes, which leads to inflammation or myonecrosis [5]. Myotoxic activity and inflammation can both result in bleeding, tissue degradation, and necrosis [4] (Figure 2).

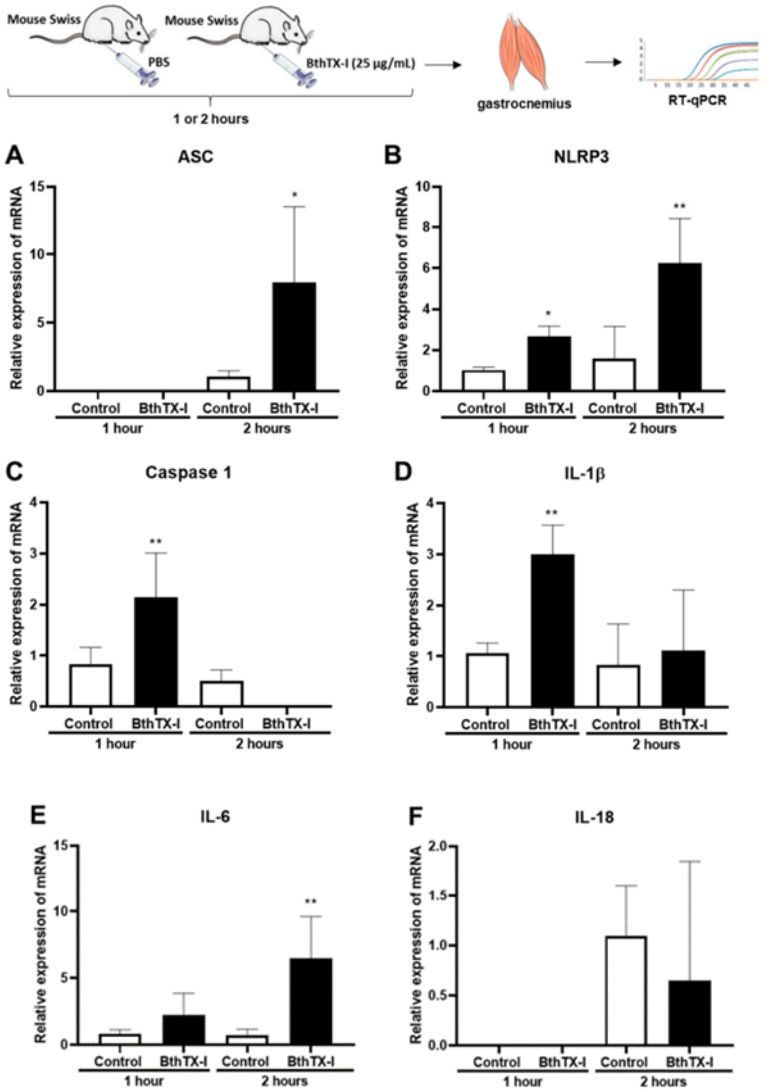

Fig. 2 Expressions of the NLRP3 inflammasome complex's genes were shown. PBS or BthTX-I were injected into the gastrocnemius muscle of Swiss mice. The muscles were taken out after 1 or 2 hours and processed for RNA extraction and the gene expression of inflammasome NLRP3 components. Gene expression of ASC protein (A), NLRP3 (B), Caspase 1 Effector Protein (C), pro-inflammatory cytokines IL-1B (D), IL-6 (E), and IL-18 (F). The majority of inflammasome complexes favouring the development of inflammation or myonecrosis were found in higher concentrations in the BthTX-I group.

2.3. Treatment and future prospect

Statistics show that hemotoxic venom is one of the major factors causing illness and deaths. From a test, scientists found that nitric oxide or carbon monoxide may suppress the venom action, lowering the frequency of fibrinogenolysis. To put it another way, regular fibrinogenolysis lowers the incidence of inflammation so that hemotoxins do not have detrimental effects on the body. The concentration of carbon monoxide required to totally block venom function varies depending on the affinity of heme attaching to carbon monoxide and the quantity of heme binding to an enzyme [7].

Hemotoxins have the potential to be utilised as painkillers, and they function by following specific instructions. Mambalgin is a 3FTX involved in Dendroaspis polylepis, and it blocks ASIC channels to promote analgesia, whereas crotalphine which is a toxin involved in Crotalus durissus venom is a 14 residues peptide capable of generating analgesia by regulation of -opioids receptors and TRPV1 channels [8].

3. Neurotoxic venom

Snakes that deliver neurotoxic venom damage the nervous systems of animals, resulting in muscular paralysis, brain damage, and loss of consciousness [9]. In some instances, this type of venom inhibits the transmission of nerve impulses across the body, with its effects occurring relatively rapidly. In contrast to hemotoxic venom, neurotoxic types can be administered painlessly. Some individuals might not realize they have been bitten until they begin experiencing symptoms. For example, black mamba, its venom may induce unconsciousness in less than an hour and can cause obvious symptoms within 15 minutes. Without treatment, which is hard to acquire, neurotoxic venom is usually lethal [9].

3.1. Mechanism

The peripheral neuromuscular paralysis caused by a snakebite is due to neuromuscular junction (NMJ) transmission dysfunction [10]. The generator nerve axon end is in charge of metabolism, packing, delivery, and discharge of the neurotransmitter acetylcholine (ACh) at the presynaptic effect. The activation of Ca2+ channels as well as the inflow of Ca2+ ions increase the discharge of ACh regarding an approaching neuronal reaction capacity [10]. A sequence of actions are provoked by a boost of intracellular Ca2+ content resulting in the development of a SNARE(Soluble N-ethylmaleimide-sensitive-factor Attachment Receptor) protein-based merging complex, which facilitates ACh discharge and merging of ACh vesicles with nerve-end membrane [10]. Neuronal Nicotinic acetylcholine receptors (nAChRs) at nerve terminals stimulate the release of acetylcholine (ACh) via shifting ACh vesicles from a common area to an usable area in regards to elevated recurrence excitation mediated by comback effects. ACh diffuses quickly across the synaptic cleft after being released from a nerve terminal. ACh must be degraded at the synaptic level by acetyl cholinesterase (AChE) to terminate the activity [10]. ACh attaches to mature nAChRs on the post-synaptic membrane at post-synaptic level. nAChRs are trans - membrane proteins which have a pore that regulates the transport of certain ions across the plasma membrane, and their activity by ACh give rise to in the entry of Na+ and Ca+ cations, K+ ion outflow via potassium channels, and the production of a terminal potential [10] (Figure 3).

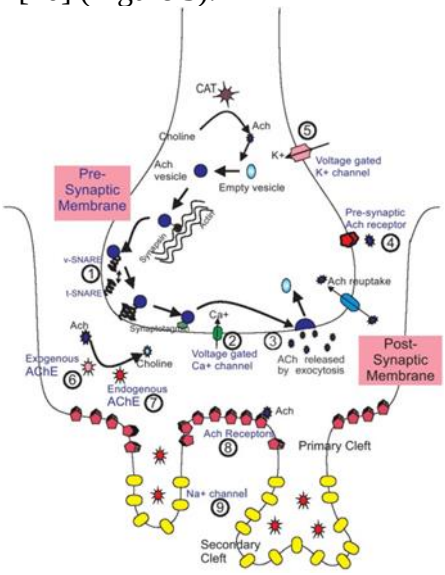

Fig. 3 Neuromuscular junction regions for interaction of snake toxicants as well as other compounds.

Snake toxicants induce 2 forms of nerve and muscle inhibition, pre-synaptic and post-synaptic neuromuscular inhibition.

The post-synaptically active neurotoxins, or other known as α-neurotoxins, is a type of 3-finger toxins (3FTx) and attaches to the post-synaptic nAChRs [10]. Neuromuscular inhibition at the post-synaptic phase is categorised as being either non-depolarizing or depolarizing. Depolarizing

neuromuscular blocking agents (NMBAs) engage permanently to post-synaptic nAChRs. They are non-competitive inhibitors that cannot be restored by acetyl cholinesterase inhibitors (AChEIs) [10]. In contrast, non-depolarizing NMBAs suppress ACh attachment to postsynaptic muscle nAChRs by competitive inhibition. They frequently bind to and detach from ACh-binding sites, thus they may be substituted by Ach Blockade and therefore be restored by AchEIs [11]. The nAChR contains 2 ligand binding sites: for the receptor to be active, both must be concurrently occupied by ACh. Therefore, the inhibition of one binding site would restrict the activation of the receptor.

The neurotoxins that operate on pre-synaptical effect (β-neurotoxins) attach to generator nerve ends, and synaptic ACh vesicles are depleted as a result, as well as reduced outflow of ACh, and the subsequent degradation of the generator nerve terminals [10].

The typical symptoms associated with neurotoxic snakebites are ptosis, foamy saliva, slurred speech, respiratory failure, and skeletal muscular dysfunction. In 94% of the occurrences, these symptoms occurred within 8 hours, and at the latest, 19 hours after the envenomation. In certain instances, respiratory failure was accompanied by unconsciousness [12]. Although neurotoxicity cannot be fully reversed wholly, however, by administering antivenom in a short time window may reduce lethality.

Clinical evidence from snakebites containing presynaptic neurotoxins also reveals that antivenom cannot repair neurotoxicity. However, early use of antivenom may reduce severity or avoid neurotoxicity [13].

3FTxs are toxin proteins that can induce immediate paralysis in the snakebites by inhibiting postsynaptic transmission via nAChRs. 3FTxs that dominates elapid venom proteomes competitively binds to nAChRs to limit the attachment of ACh. Two types of 3FTxs are short chain 3FTxs and long chain 3FTxs, with 4 and 5 disulfide bridges respectively. Acetylcholine-binding proteins (AChBP) act as imitators of the ligand-binding area for nAChRs. Long-chain 3FTxs are likely to be neutralised by nAChR analogues, according to the *in vivo* evidence [14]. These AChBP analogues would attach rapidly and stronly to these chemicals, therefore delaying their binding to nAChRs in the victim, a desired property for novel therapies. Using a microfluidic device, AChBPs have been utilised to profile venom toxicity, hence contributing to the emergence of low-affinity binders like PLA2 [14].

The MS/MS identifications reveal AChBPs significantly retrieved long-chain 3FTxs when incubated with the cobra venom samples. These long chain 3FTxs interact with ligand-fishing due to their high degree of preservation and the existence of 2 extra cysteine remnants found within the fifth disulfide bond, thus interacts with the ligand-fishing. It may be revealed that Trp25, Asp27, and Arg33 are essential components towards the attachment of 3FTxs to neuromuscular receptors according to mutagenesis experiments. The fifth disulfide bond contains Ala28, Lys35, and Cys26 and Cys30, which bind to the 7-nAChR preferentially. It can be concluded that fifth disulfide bond is essential in the binding to 7-nAChR [14].

Also, by examining additional weak neurotoxins (haditoxin which lacks a fifth disulfide bridge) that interact weakly to 7-nAChR, it has been proposed that residues other than the fifth disulfide bond signal the ability of these toxins to attach to the neuronal receptor [14].

It may be inferred that, although the fifth disulfide bond and key residues can signify strong binding, alternative contacts may also occur in the interaction.

These AChBP analogues would theoretically attach to venomous chemicals rapidly and with great selectivity, inhibiting their attachment to the victim's nAChRs [14]. Thus, investigating AChBPs displacement might be key to future approaches. In addition, it is demonstrated that the humanised 7-AChBP provides some defence against snake venom and is therefore probable to neutralize part of the toxicity induced by long chain 3FTxs [14]. These findings may aid future therapeutic treatments against neurotoxic snakebites.

It is also proven by the following case study that neurotoxicity in snakebites are partially irreversible.

Chinese Brait's post synaptic neurotoxins are relatively irreversible alpha-neurotoxins with long chains. By interfering with the release of acetylcholine (ACh), presynaptic neurotoxins eliminate

nerve-activated involuntary twitches. By inhibiting the interaction between transmitters, post-synaptic neurotoxins suppress the nerve-induced twitches [13].

Venom inhibited nerve-mediated twitches in proportion to their concentration. Post- and presynaptic neurotoxins present in Chinese Brait venom are recognised by both Australian elapid and Chinese Brait snakes [13].

However, neither antivenin administered at t90 following snake toxin was able to restore the absence of twitches. By administering the venom at earlier time points, feedback to the nAChRs agonist ACh were partly recovered in majority of the circumstances, implying that the post synaptic implications are partially reversible but not presynaptic activity [13]. This shows that antivenoms might be incapable of reversing the presynaptic effects of neurotoxins.

Antivenom can only block presynaptic activation if administered 5 minutes after the venom and greatly restored the suppression of ACh responses generated by venom [13].

In conclusion, neither antivenom might be capable of reversing the neurotoxicity caused by the venom. Given the irreversibility of the neurotoxic consequences of neurotoxic toxin, it appears that prompt distribution of the specified antitoxin within a set time frame will reduce mortality.

4. Cytotoxic venom

Cytotoxic venom causes toxic effect on cells [2]. Cytotoxic venom is possessed by many of the dangerous snakes in th world like cobras. This venom is known to severely harm the victim's skin and underlying tissues, frequently resulting in disability [2]. Cytotoxic venom frequently causes secondary damage such as impairment of limb mobility and other disorders [2]. Even if the individual survives the first bite, these consequences might leave them permanently handicapped [2].

4.1. L-amino acid oxidases (LAAO)

LAAO is the enzyme involved in both venoms of Elopidae and Viperidae which exhibit cytotoxicity ([15], Figure 4). It is a flavoenzyme with cofactor of non-covlently bound flavin adenine nucleotide (FAD). The oxidative deamination of L-amino acid substrate can be catalysed by it to α-keto acids. Meanwhile, ammonia and hydrogen peroxide are generated [16]. LAAO in venom induces the death of mammalian cells via hydrigen peroxid generated [17].

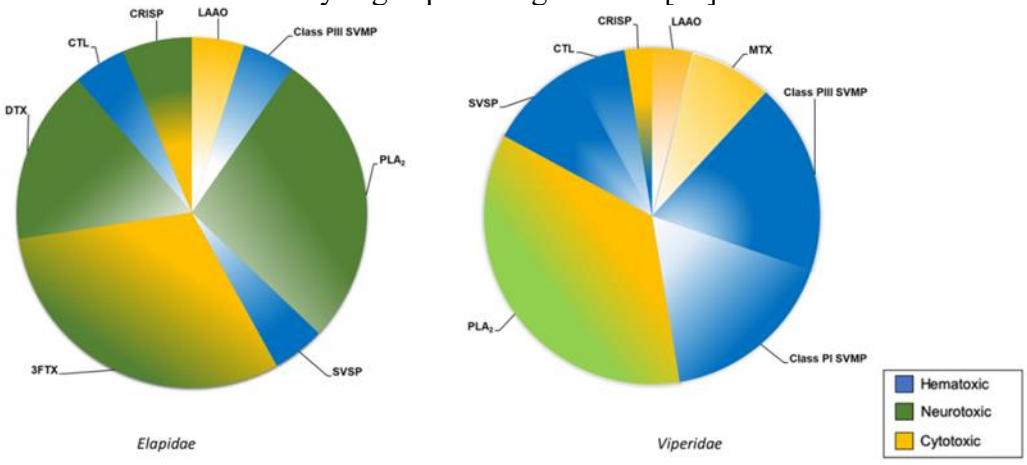

Fig. 4 Distribution of different venom toxins from *Elapidae* and *Viperidae*

4.1.1 Catalytic mechanism

The catalytic reaction of LAAO contains two reactions--a reduction reaction and an oxidative reaction ([15], Figure 3). The reductive reaction involves that His223, which is a basic residue abstracts a hydrogen ion which is contained in the amino group of the L-amino acid substrate. Simultaneously, the transference of a hydride originally at the α carbon to N5 atom of the FAD leads the formation of imino intermediate [16]. During this reaction, the cofactor FADH2 is formed. Then, the imino acid is hydrolysed to produce ammonia and α-keto acid non-enzymatically. The oxidation

reaction involves that FADH2 oxidises into FAD and generates hydrogen peroxide concomitantly. After the process, vfsC FAD cofactor is regenerated for the succeeding cycles and the LAAO catalytic cycle is completed [15].

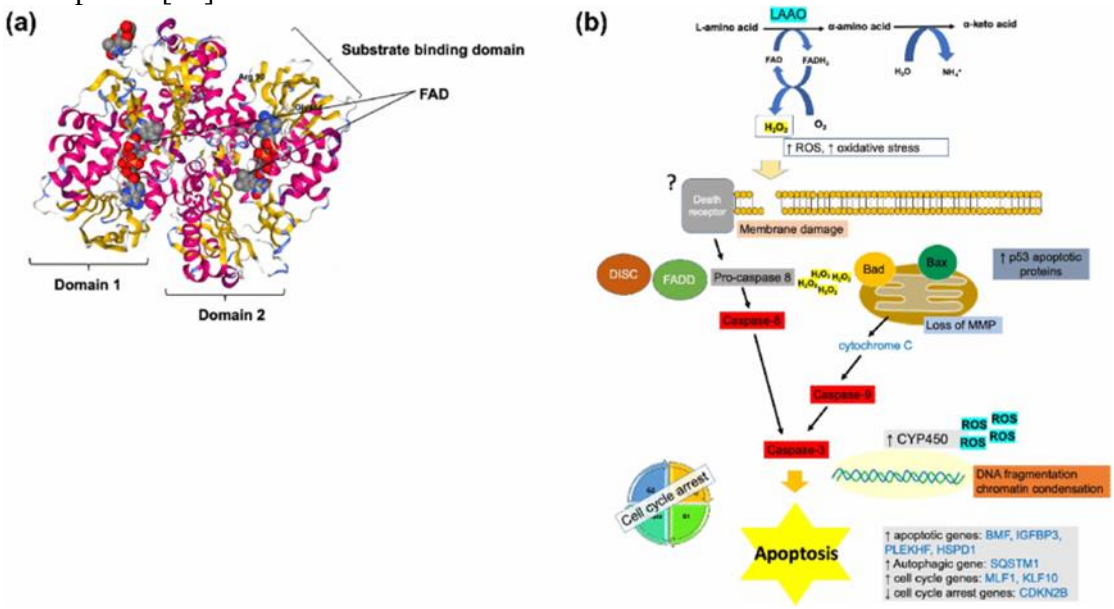

Fig. 5 The structural and cytotoxic properties of venom L-amino acid oxidase (LAAO)

4.1.2 Cytotoxicity mechanism

Oxidative stress is caused by the accumulation of hydrogen peroxide generated. It is supported by the evidence that glutathione (GSH) and catalase, which can inhibit hydrogen peroxide activity result in the reduction of cytotoxic effect caused by LAAO [15]. Hydrogen peroxide released accumulates as reactive oxygen species (ROS). The excessive accumulation of ROS causes the membrane lipid peroxidation and damage of the cell membrane [18]. In addition, the mitochondrial membrane potential (MMP) dissipating and the induction of translocation of cytochrome c to cytosol are leaded by the oxidative stress caused by hydrogen peroxide. Caspase-9 is an initiator capase which presents in the intrinsic mitochondrial- mediated apoptosis. It is then activated by cytochrome c. The p53 apoptotic proteins are expressed plentifully in the existence of LAAO. Subsequently, the cytoplasmic Bax protein activates the downstream apoptosis pathway by the translocation to mitochondrial. Moreover, it has been found that the extrinsic death receptor apoptosis which is induced by the LAAO would result in the activation of another initiator caspase-8 before the activation of caspase-3. For the sake of the formation of DISC-FADD, Ligands–death receptor interactions is required by etrinsic apoptosis. Then, the pro-caspase 8 is cleaved for the activeation of caspase-8. Neverless, it is still undetermined whether there is an interaction between LAAO and the death receptors which occur for extrinsic pathway. In addition, caspase-3 would cause some features of endpoint apoptosis like chromatin condensation (karyorrhexis) and DNA fragmentation [15].

In conclusion, LAAO induces apoptosis via two pathways--intrinsic pathway and extrinsic pathway [15].

4.1.3 Anticancer application of LAAO

LAAO presents selectivity for tumor cells. Thus, it exibitis less cytotocity to the normal cells [19]. It is supported by a few studies about the comparison with cytotoxic effects on normal cells and cancer cells respective [16, 19].

Bothrops pirajai L-amino acid oxidase (BpirLAAO-I) contained in Bothrop pirajai venom can induce apoptosis of BCR-ABL-positive cells. However, it has not responded to normal peripheral blood mononuclear cells. BpirLAAO-I is capable of reducing the BCR-ABL kinase activity and increase the cell sencitivity to apoptosis. It partially explains that the cell death induced by BpirLAAO-I potentiates when combines with imatinib mesylate (IM) which is used for Chronic

myeloid leukaumia (CML) treatment. In leukaemia cells, it is more likely to present peroxidation of lipid which is more significant and obvious and cause more serious cell damage due to the fact that there is higher lipid concentration in the tumour cell membrane than in the normal peripheral blood mononuclear cells [19]. Furthermore, another study with same authors demonstrates that BpirLAAO-I shows cytotoixcity on a tumour cell line and causes oedema of mouse paw, but there is no cytotoxic effect in mouse macrophages [20].

A study clearly determines that ROS act a pivotal part in the cytotoxicity of BaltLAAO-I resulting on the tumour cell. It is the mediater. BaltLAAO-I exhibits high cytotoxicity on the all tumor cells lines including breast adenocarcinoma cells (SK-BR-3), human leukemia T cells (JURKAT), and murine melanoma cells (B16F10) [16].

In conclusion, the cytotoxic activity of LAAO against tumour cells is preferentially compared to normal cells. The cytotoxicity on normal cells is much less than on tumour cells. Instead, it effects positively on the treatment of tumour. [16].

5. Conclusion

The investigation of three different venoms is completed from multiple angles. Validation tests have been widely carried out to identify the hemotoxin's mechanism by continuously monitoring the components' levels as they changed in the hemotoxic venom. In order to widen the search for hemotoxic venom, four major hemotoxic enzymes have been recognized. Neurotoxins function through the release of ach, and by examining the toxin protein 3FTx, it is shown that they are irreversible owing to the rapid paralysis they cause. The details of how neurotoxins operate were then explained using a case study of B. multicinctus. To determine which enzymes are accountable for cytotoxicity, an examination of enzyme distribution is employed. A mechanism of catalytic reaction of LAAO is described and a case study explains how enzyme combinations induce cytotoxicity to treat tumor cells.

According to the materials analyzed here, neurotoxic venom would be the most lethal. This is due to the fact that neurotoxins cause irreversible damage. People who have been neurotoxically envenomed will become paralyzed. Then, neurotoxins target the entire body system, whereas hemotoxins and cytotoxins target specific cells. Finally, both hemotoxins and cytotoxins have medicinal applications, whereas neurotoxins' potential applications are unknown. Hemotoxins, for example, have the potential to be used as a pain reliever, whereas cytotoxins, due to their structural uniqueness, have the potential to cure cancer. Limitations are also involved so that the definite answer of the topic question remains uncertain. This is due to the fact that snake venoms vary greatly between and within snake species and that most snake venom contains two or more types of toxins. Even the same type of toxin can go through distinct pathways, which causes the outcome to vary depending on the situation.

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