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Review Article

SNAKE VENOM-DERIVED PEPTIDES AS PROSPECTIVE PHARMACOLOGICAL TOOLS: RECENT TRENDS

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ABSTRACT

Small peptides from snake venom are studied as exceedingly selective, specific, effective and harmless therapeutics. This review article critically analyzes with numerous examples for the use of snake venom components as a potential therapeutic tool against various illnesses. The active components from numerous venoms are isolated, purified and used in assays to identify the specific therapeutic components that were categorized based on their biological goal and mechanism of action. This has paved the ways to use peptides from venom as therapeutic drugs. Peptide toxins are usually active orally, via subcutaneous, intramuscular or intravenous administrations. These peptides are targeting a wide range of membrane-bound protein channels and receptors. Peptides are recovered from the venom of diverse animals and most of these possess the possible prospects of safety after isolation and purification and venom-obtained peptides that can become practical drugs effectively, in future.

Keywords: Peptides, Venom toxin, L-amino acid oxidases, Phospholipase A2, Therapeutic tools

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INTRODUCTION

Nature has been always an intriguing source of drug design investigations [1]. It is well known that various bioactive proteins and peptides have been reported that the venom from different species of snakes, conus, scorpions, centipedes, lizards, spiders, sea anemones, bees, and octopus [2, 3]. In this present review, snake venom components, which are of importance for the treatment of various diseases, are considered. Venomous snakes are in focus of investigations and many pharmacologically useful molecules, which have already been isolated and characterized [4]. Epidemiological data estimates that 4.5–5.4 million peoples got bitten by snakes in every year and results about 1.8-2.7 million snakebites envenomation and 81,000 to 138,000 deaths in every year [5]. Hence, snakebite is one of the major public health issues in South Asia, South-east Asia, Sub-Saharan Africa, and Latin America [6, 7]. Venomous snakes with medical importance are mainly belongs to three families: Atractaspididae, Elapidae, and Viperidae [8]. Snakes from the Viperidae family are also further divided into two subfamilies; Viperinae and Crotalinae. In these families, the venom produced in specialized glands are typically delivered to the target organism throughout the modified teeth [9]. Many victims are inflicted with permanent physical injuries due to psychological sequelae, hemorrhage, nephrotoxicity, and tissue necrosis [10].

Snake venom is composed of 90-95% of proteins, which are mostly enzymes [11]. Snake venom is extremely modified with snake's saliva [12], which containing a complex mixture of amino acids, nucleic acids, carbohydrates, lipids, proteins, and peptides [13, 14]. The composition of snake venom has been illustrated (fig. 1). Proteins and polypeptides are classified into enzymes, and non-enzymatic substances [15]. The most common enzymes of snake venom are phospholipases A2 (PLA2), serine proteases (SVSP), metalloproteases (SVMP), acetylcholinesterases (AChEs), L-amino acid oxidases (LAAO), nucleotidases (5'-nucleotidases, ATPases, phosphodiesterases, and DNases), and hyaluronidases [16]. The most common non-enzymes of snake venom are three-finger toxins (3FTx), Kunitz peptides (KUN), and disintegrins (DIS) (fig. 1). The composition of snake venoms may varies depends on the variety of factors, which includes snake family, genus and species, geographical location, typical prey type, age and size of the snakes [9].

The composition of snake venom proteins may undergo distinct qualitative and quantitative variation in populations and individuals of the same species [17]. Variations in protein expression of venom components may also be observed in the same specimen with different ontogeny [18]. Diversification of proteins present in the venom, which is directly reflects its toxicity, pathophysiologic effects, and may represent an evolutionary arms race, by the adaptation of venom composition to improve the ability of subduing different predator's preys, and also to overcome the resistance of some prey species to the venom [19]. Elapidae and Viperidae venom proteins are produced and secreted by oral exocrine glands, which present in the basal-central lumen, where the venom is stored until its delivery [20]. The production of toxins will be activated by morphological and biochemical changes in secretory epithelial cells after venom injection [21]. Many regulatory mechanisms are carried out in the snakes, to effect protein compositions in their venom, such as mutations affecting gene expression [22], duplication, and loss of toxin-related genes [23], post-transcriptional microRNAs regulation [24], and proteolytic processing [25]. Based on their compositional importance and ubiquity; there are 59 protein families that have been classified into five groups [26], including group I-dominant protein families such as PLA2, SVMP, SVSP, and 3FTx; group II-secondary protein families, which are much smaller amounts than the dominant families such as KUN, LAAO, cysteine-rich secretory protein (CRiSP), C-type lectin (CTL), disintegrin (DIS), and natriuretic peptide (NP); group III-minor protein families such as acetylcholinesterase, hyaluronidase, 5' nucleotidase, phosphodiesterase, phospholipase B, nerve growth factor (NGF), and vascular endothelial growth factor (VEGF); group IV-rare proteins including 36 families, and; group V-unique protein families such as defensins, waglerin, maticotoxin, and cystatins, which are restricted to the snake species specifically [26, 27].

Snake venom proteins

Snake venom proteins are classified into numerous families, which is based on the structural and functional similarities in the organization of these molecules.

Enzymatic proteins in venoms

Phospholipases A2

Phospholipase A2 (PLA2) plays an important role in the neurotoxic and myotoxic effects of snakebites [28]. These proteins have molecular masses of 13–15 kDa, classified into groups I and II, which

are found as major components in the venoms of Elapidae and Viperidae, respectively [12, 28]. There is a third group of PLA2s, which is termed as IIE, has been predominately recovered from the venom of non-front fanged snakes, although their importance in the venom arsenal is still remains unclear [29]. Studies reconstructing the evolutionary history of the multi-locus gene family and after translocation, each of these PLA2s types (I, II, and IIE) has been independently recruited into snake venom systems [30, 31]. Inflammation is induced by non-neurogenic and neurogenic components of PLAs [32]. The non-neurogenic components are especially mediate hydrolysis of membrane lipids, which generates potent pro-inflammatory lipid mediators [33].

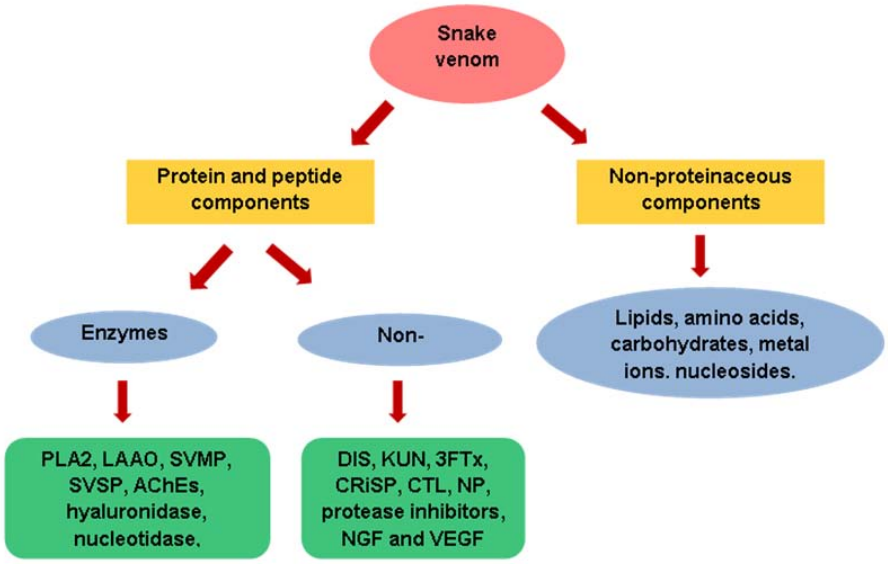

Fig. 1: Generalized composition of snake venom

L-amino acid oxidases

L-amino acid oxidases (LAAO) catalyze the stereospecific oxidative deamination of L-amino acid into the corresponding α-keto acid, hydrogen peroxide, and ammonia, which are flavin adenine dinucleotide (FAD) enzymes containing homo-dimeric proteins [34]. LAAOs are produced by different organisms, which ranging from bacteria, algae, and fungi to insects, mammals, mollusks, and certain snake species [35]. Venoms from Viperidae, Crotalinae, and Elapidae species contains relatively high levels of LAAOs, which represent up to ~25% of total protein in the venom; especially in *B. caerulus* (common krait) [36, 37]. LAAOs along with hyaluronidase and phosphodiesterase enzymes originate in snake venoms are not well studied as other snake venom proteins such as snake venom proteases [38]. LAAOs exhibit a conserved dinucleotide binding fold with other enzymes, which requires FAD as a cofactor, including monoamine oxidase and tryptophan 2-monooxygenase, although phylogenetic comparisons have been revealed a distant relationship with these enzymes [39]. LAAOs usually exist as homodimers, which contribute, in part, to the cytotoxic effects of snake venom [40]. A wide range of biological effects have been attributed to the activity of LAAO, which could activate and/or inhibit platelet aggregation [41], hemorrhage, myonecrosis, and edema [42].

Metalloproteases

Metalloproteases (SVMPs) are zinc-dependent proteinases, which ranges from 20 to 110 kDa in size; and are categorized into three major classes P-I, P-II, and P-III classes, according to their structural domains [43]. These toxins are the major components of viper venoms, which play an important role in the toxicity of these snake venoms [8]. Venom SVMPs have evolved from disintegrin and metalloproteinase (ADAM) proteins, specifically ADAM28, with the PIII being the most basal structural variants, including of metalloproteinase, disintegrin-like, and cysteine-rich domains [44]. The multifunctional properties of SMVPs have been well described. Class P-III SVMPs tend to display stronger hemorrhagic activity when compared to P-I, and P-II SVMPs, possibly due to the disintegrin-like and cysteine-rich domains enabling them to bind with relevant targets in the extracellular matrix of capillary vessels. The functions of these domains have been investigated in inflammation, revealing that these domains are sufficient to induce pro-inflammatory cytokines TNF-α, IL-1b, and IL-6 via leukocyte migration [45].

Serine proteases

Serine proteases (SVSP) belong to the S1 family of serine proteinases and the molecular masses ranging from 26 to 67 kDa with two distinct structural domains [46]. These venom toxins have been evolved from kallikrein-related serine proteases and, following their recruitment for use in the venom gland, which have undergone gene duplication events, ultimately giving rise to various isoforms [46]. SVSPs catalyze the cleavage of polypeptide chains on the C-terminal side, which is positively charged or hydrophobic amino acid residues [47]. Similarly, SVSPs have been described in the venom of wide varieties of snake families, although they are typically abundant in viper venoms and less in other types of venoms of elapid and colubrid snakes (colubridae) [48]. SVSPs are well known for their ability to rupture capillary vessels of SVSPs, which execute their primary toxicity by altering the hemostatic system of their victims by inducing edema and hyperalgesia [49].

Hyaluronidases

Snake venom hyaluronidases are the glycoproteins ranging from the molecular mass 28 to 70 kDa, and the optimum enzyme activity was detected around pH 5.5 [50]. Venom hyaluronidases are known to hydrolyze hyaluronan, which is the major glycosaminoglycan of the interstitial matrix specially found in the extracellular matrix of mammalian cells [51]. They have the capacity to hydrolyze glycosidic linkages β-1-4 residues of N-acetyl-β-D-glucosamine and D-glucuronate from hyaluronan producing tetra and hexasaccharides [52]. During envenomation, hyaluronidases facilitate the venom diffusion in the victim's tissue due to hydrolysis, which make the venom to spread faster in the body and enhance the toxins effect [21].

Nucleotidases

Snake venom nucleotidases comprise of 5′-nucleotidase, ATPase, and ADPase. ′5 -nucleotidase is a metalloenzyme with a high molecular mass ranging from 73 to 100 kDa [53]. Gulland and

Jackson have identified the 5′-nucleotidase activity in snake venoms, which increase the anticoagulant effect of ADPases, phospholipases A2, and disintegrins by acting synergistically with these specific toxins [54, 55]. ATPases are initially described by Zeller and are known to hydrolyze ATP, which releases adenosine and pyrophosphate. Based on the reaction conditions, ATPases could cleave ATP into AMP and pyrophosphate/phosphate [56, 57]. The only ADPase isolated from snake venom (*D. acutus*, hundred-pace viper) has a molecular mass of 94 kDa in it's purified from. This snake venom is known to inhibit platelet aggregation in platelet-rich plasma, which is induced by various molecules, but it does not inhibit thrombin-induced aggregation in platelet-poor plasma [58].

Acetylcholinesterase

Acetylcholinesterase (AChE) plays a crucial role in cholinergic transmission by rapidly inactivating the neurotransmitter and acetylcholine. AChE belongs to the family cholinesterase, which includes butyrylcholinesterase (BuChE) [59]. Both the enzymes hydrolyze choline esters faster than any other substrates, which inhibit physostigmine. AChE is differing from BuChE, it is more active on acetylcholine than propionyl or butyrylcholine. It is also characterized by excess substrate inhibition, which is not observed by BuChE [59]. In addition, these two enzymes may be distinguished by their sensitivity to reversible inhibitors, specifically either AChE or BuChE. The catalytic center of AChE is traditionally considered as a composition of an esterase subsite and an anionic subsite [59]. Earlier study has been suggested that amino acid residues present in the first and second loop of the toxins are involved in the inhibition of enzyme activity [60]. In all Elapidae venoms, AChE is known to be present [2].

Phosphodiesterase

Phosphodiesterase hydrolyzes phosphodiester bonds consecutively from the 30 termini of polynucleotides to produce 5-mononucleotides in the venom of *P. flavoviridis* (pit viper). In addition, phosphodiesterase activity has been found virtually in all snake venoms, although in general, there is a greater activity associated with Viperidae venoms [38]. Several transcriptome studies from snake venoms indicated that typically less than a few percent of the transcriptomes are comprised of transcripts for phosophodiesterases [61].

Non-enzymatic proteins in venoms

Three-finger toxins

The non-enzymatic proteins, such as 3FTxs family of polypeptides, comprised of 60–74 amino acid residues. These peptides showed diverse functionalities, which possesses a conserved structure [62]. Distinct structural features of 3FTxs are unique fold, including three loops, which emerge from a hydrophobic globular core [62]. Proteomic and transcriptomic analyses have shown that the ratio of 3FTxs might be higher relative to other toxins in the Elapidae venoms, for example, venom of *N. ashei* (spitting cobra), *M. pyrrhocryptus* (coral snake), and *M. tschudii* (desert coral snake) [63]. 3FTxs constitute more than 60% of the venom compositions of cobra snakes [64, 65], while there has been a wide range of distributions of relative abundance of 3FTxs among different krait species, ranging from 1.3% in *B. fasciatus* [66,67] and 60% in *L. colubrina* (a sea krait) [68, 69].

Cysteine-rich secretory proteins

Cysteine-rich secretory proteins (CRiSPs) are non-enzymatic components, which are presents in various organisms. These enzymes are also found in snake venoms, but their function in envenoming have not yet been fully understood so far [70, 71]. CRiSPs are single-chain proteins with molecular mass ranging from 20 to 30 kDa. These enzymes have been displayed sixteen highly conserved cysteine residues that can form eight disulfide bonds [72]. CRiSPs are largely distributed among Viperidae and Elapidae families from different continents [21, 72]. There are several reports suggesting the isolation and cloning of three snake venom CRiSPs from *O. hannah* (king cobra), and *C. atrox* (diamondback rattlesnake), piscivorin, ophanin, and catrin, respectively. Other CRiSPs, including triflin, ablomin, latisemin, and tigrin are isolated from the venoms of *P. flavoviridis*, *L. semifasciata* (black-banded sea krait), and *R. tigrinus* (tiger keelback) [21, 72].

Disintegrins

Disintegrins (DIS) are cysteine-rich peptides that result from the post-translational cleavage of SVMPs, which are phylogenetically related to ADAMs. The possible function and activity of disintegrins in snake venoms are assigned to support the distribution of other toxins throughout the prey tissues by binding integrins and inhibiting platelet aggregation direct upon envenomation [73]. Disintegrins are found in the venoms of Crotalidae and Viperidae snakes, which constitute approximately 17% and 18% of total venom proteins [8]. Disintegrins might exist as monomers, homodimers, and/or heterodimers. The monomers include short (49–51 amino acid residues and four disulfide bonds), medium (70 amino acids and six disulfide bonds), and long disintegrins (84 amino acids and seven disulfide bonds). Most of the disintegrins belong to the monomeric type [74].

Natriuretic peptides

Natriuretic peptides (NPs) are mostly found in Viperidae than Elapidae [75]. NPs constitute only 3% of the venom proteome of *Dendroaspis polyepis* and 37% of *B. nigroviridis* [75]. NPs are found in vertebrates, which play an important role in natriuresis. Moreover, the homologous peptide has been reported in plants and bacteria [76]. Three mammalian NPs are well known, such as atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), and C-type natriuretic peptide (CNP). These NPs regulate the functions of cardiovascular and renal systems, which render them by forming a complex and binding to the natriuretic peptide receptor [76]. For example, ANP and BNP could act in an endocrine manner to maintain blood pressure and volume. Both ANP and BNP might be released by cardiomyocytes in response to elevated blood pressure and hypervolemia [77,78] and CNP is produced by endothelial cells [79]. Nowadays, NPs seem to be great, as they support the development of therapeutics and medical procedures for the treatment and diagnosis of unfortunate physiological conditions such as heart failure and hypertension [80].

Protease inhibitors

The first protease inhibitors are found by documenting the isolation of potent kunitz type protease inhibitors from the venom of *D. russelli* [81]. The occurrence of the protease inhibitors is reported in Elapidae and Viperidae snake venoms [82, 83]. Snake venoms are the interesting sources of protease inhibitors, although these molecules represent in a small proportion of snake venoms. Further, the chemical reactions of the body is sustained and controlled by the antagonism of: (i) proteases, which play key functions in different systems and biochemical pathways and (ii) the correspondent protease inhibitors, which is responsible for controlling protease activities [84].

Kunitz inhibitors

The first identified Kunitz inhibitor is from Australian elapid venoms *O. scutellatus* by Possani *et al.* 1992 [85]. Kunitz inhibitors are mainly found in different animals and are characterized by conserved folds consisting of approximately 60 amino acids, which are stabilized by three disulfide bonds [86]. Protease inhibitory activities are conferred by the binding of these highly specific Kunitz inhibitors to the active site of the serine protease in a substrate-like manner. A major contact is formed between a peptide bond of the inhibitors and the active site of the protease, but in contrast to the usual substrate, these peptides bond only with limited and extremely slow hydrolysis [87]. Sequence analysis of the snake venom Kunitz inhibitors has revealed that the amino acids are highly conserved at the core and in the N-terminal surface area but not at the anti-proteinase site [84]. This suggests that Kunitz inhibitors have been retained the same overall fold but evolved to have various functions [84].

Growth factors

The "growth factor" is conventionally associated with growth and cell proliferation. Later, however, other cellular responses are attributed

to these neurotrophins, including cell differentiation, transformation, synthesis, secretions, death, and motility [88]. The first identified growth factor is a nerve growth factor (NGF) from mouse sarcoma 180 in the 1950s [89]. NGF is isolated in 1956 from the venom of *A. piscivorus* (black water viper) [90]. NGFs are participated in neuronal differentiation, synaptic plasticity, and neuroprotection in peripheral and central nervous systems [91]. NGF is also acts on no neuronal cells, but especially on hematopoietic stem cells. However, most of these effects are already reported for murine NGF [92]. It has been described that the part of the sv-NGF is injected at the bite site of *N. atra* (Chinese cobra) might reach the circulation, which could lead to some physiological activities on non-neuronal cells or tissues. NGF from *N. atra* exerts important systemic effects in the envenoming, including plasma extraction and histamine release, which could result in tissue vulnerability and facilitate toxin diffusion in the prey organisms [92]. VEGF is formerly designated as vascular permeability factor, which stimulates vasculogenesis, angiogenesis, and lymphangiogenesis. The VEGF family is divided into seven groups, which is designated as VEGF-A to VEGF-F and placental growth factor (PGF) [93]. Snake venom glands are present as at least three different VEGF-Fs with unique features and with distinct receptors selectivity, designated as VEGF-F1 to VEGF-F3. Additionally, VEGF-A-like transcripts have been identified in some snake venoms [94].

Prospective pharmacological tools of snake venom

As new peptides of venom source are recognized and characterized, this can be considered as a new era of medicine. Several drugs produced in venom of various organisms, which are currently being used in the treatment of human disorders. Furthermore, as the competence and price of both commercial production and recombinant expression of peptides endure to progress, it is possible that more of these composite peptide drugs will be produced in the future [95]. Table 1 depicts the prospective pharmacological effect of snake venom peptide in various diseases.

Table 1: Prospective pharmacological influences of snake venom proteins/peptides

Family	Scientific name	Venom peptides/proteins	Experimental model	Observation	Reference
Cancer					
Viperidae	*Bothrops jararaca*	Jararhagin	Human melanoma cell lines (SK-Mel-28)	Increase in the expression of cell cycle and apoptosis	[99]
Elapidae	*Naja naja atra*	Cardiotoxin III	Human breast cancer cell lines (MDA-MB-231)	Suppression of EGF-induced cell invasion and, migration	[100]
Viperidae	*Cerastes vipera*	L-amino acid oxidase	Human breast cancer cell lines (MCF-7)	Increase in H_2O_2 and TBARS levels by depletion of catalase activity	[101]
Viperidae	*Calloselasma rhodostoma*	L-amino acid oxidase	Human colon cancer cell lines (SW480, SW620)	Significant increase in the activity of caspase-3, and reduction in Bcl-2 levels	[13]
Viperidae	*Cryptelytrops purpureomaculatus*	L-amino acid oxidase	Human colon cancer cell lines (SW480, SW620)	Significant increase in the activity of caspase-3, and reduction in Bcl-2 levels	[102]
Viperidae	*Daboia russelii*	L-amino acid oxidase (Rusvinoxidase)	Human breast cancer cell lines (MCF-7)	Induction of apoptosis in both intrinsic and extrinsic pathways	[103]
Viperidae	*Crotalus durissus*	Crotoxin	Human lung squamous carcinoma cell lines (SK-MES-1)	Expression of p-JNK and p17 increased during apoptosis	[104]
Viperidae	*Macrovipera lebetina*	Snake venom toxin	Human lung cancer cell lines (A549 and NCI-H460)	Induction of caspase-3, 8, 9, Bax, p21, p53, and reduction of cIAP, Bcl2 expression	[105]
Elapidae	*Naja oxiana*	Cytotoxin I and II	Human cancer cell lines: breast cancer (MCF-7), hepatocellular carcinoma (HepG2) prostate carcinoma (DU145), and promyelocytic leukemia (HL-60)	Activation of apoptotic pathways	[106]
Viperidae	*Bothrops pauloensis*	L-amino acid oxidase (BnSP-6, a Lys-49)	Human breast cancer cell lines (MDA-MB-231)	Involved in signaling pathways of apoptosis, and autophagy	[107]
Cardiovascular disease					
Viperidae	*Bothrops marajoensis*	Phospholipase A_2	Wistar rats (WTs)	Induction of hypotension, and bradycardia while simultaneously blocking electrical conduction in the heart	[110]
Viperidae	*Bitis Arietans, Bitis gabonica, Bitis rhinoceros, Bitis nasicornis*	Crude venom	Wistar rats (WTs)	Leads to hypotensive shock, and require special attention in cases of envenoming	[111]
Viperidae	*Bothrops jararaca*	Proline-rich oligopeptide (Bj-PRO-10c)	Spontaneously hypertensive rats (SHRs)	Modulates gene expression of key enzymes in NO production	[112]
Elapidae	*Ophiophagus hannah*	Cobra venom factor	Mongrel dogs	Alteration of cardiac performance, collateral blood flow to the clotting system	[113]
Elapidae	*Ophiophagus hannah*	Cobra venom factor	Feral baboons	Reduction of PMN recruitment, and activate myocardial ischemia, and coronary reperfusion to reduce tissue injury	[114]
Viperidae	*Bothrops jararaca*	Bradykinin potentiating peptides (BPP-5a)	Spontaneously hypertensive rats (SHRs)	Antihypertensive, and vasorelaxation effects are due to an endothelium, and NO-dependent mechanism	[115]

Family	Scientific name	Venom peptides/proteins	Experimental model	Observation	Reference
Elapidae	*Bungarus candidus*	Crude venom	Wistar rats (WTs)	Involved in autonomic reflex, and vascular nitric oxide mechanisms	[116]
Viperidae	*Bitis rhinoceros*	Serine protease	Human plasma	Reduction of the risk of human haemostatic disorders, such as heart attacks, and strokes	[117]
Renal disease					
Elapidae	*Dendroaspis angusticeps*	Mambaquaretin-1	pcy mice	Inhibition of dDAVP, and induction of cAMP production	[122]
Viperidae	*Trimeresurus flavoviridis*	Crude venom	Sprague dawley rats	Correlation of both ECM production, and degradation systems involved in repair process	[123]
Viperidae	*Trimeresurus flavoviridis*	Crude venom	182 sato mice (TIE2/lZ)	Glomerular endothelial cell turnover, and regeneration of glomerular microvasculature	[124]
Viperidae	*Agkistrodon acutus*	Crude venom	ddY mice	Inhibition of effect on glomerular disease	[125]
Viperidae	*Bothrops alternatus*	Crude venom	Wistar-Hannover rats	Induce morphological, and functional renal alterations with enhanced Na+/K+-ATPase expression, and activity in the early phase of renal damage	[126]
Viperidae	*Bothrops moojeni*	Crude venom	Wistar rats (WTs)	Induced intense alterations in renal physiology, including a drop in RVR associated with diuresis, natriuresis, and kaliuresis	[127]
Viperidae	*Bothrops marajoensis*	L-amino acid oxidase	MadineDarby Canine Kidney cell lines (MDCK)	Responsible for nephrotoxicity, and renal cytotoxicity	[128]
Elapidae	*Micrurus browni, Micrurus laticollaris*	Crude venom	Monkey Kidney epithelial cell lines (LLC-MK2), Wistar rats (WTs)	Alteration of renal physiological parameters, and cause nephrotoxic effects, with the involvement of oxidative stress	[129]
Pulmonary disease					
Viperidae	*Agkistrodon acutus*	Fibrinolytic enzyme	Rabbits	Reduction of thrombi, which restores blood flow in the lung, and improving cardiovascular function	[134]
Viperidae	*Bothrops jararaca*	Jararhagin	CD-1 mice	Affect lung microvessels by proteolytic activity, and also inhibits action of plasma proteinase inhibitors	[135]
Viperidae	*Agkistrodon acutus*	Recombinant fibrinogenase II	Severe acute pancreatitis rats (SAP)	Degradation of TNF-a	[136]
Viperidae	*Bothrops caribbaeus*	P-III (snake venom metalloprotease) SVMP	CD-1 mice	Induction of pulmonary hemorrhage, and thrombocytopenia, and increased FDP, without causing blood incoagulability	[137]
Neurodegenerative disease					
Viperidae	*Bothrops atrox*	Glu-Val-Trp (p-BTX-I)	PC12 cell lines	Action via trkA receptor, and PI3K-AKT and MAPK-ERK pathways by NGF	[141]
Viperidae	*Bothrops jararaca*	Crude venom (CV), Low molecular weight fractions (LMWF)	Hippocampal cell lines	Shows neuroprotective activity in cultured hippocampal cells in oxidative stress induced by H_2O_2	[142]
Elapidae, Viperidae	*Naja annulifera, Naja nivea, Dendroaspis jamesoni kaimosae, Vipera ammodytes*	Crude venom (CV)	On-line microfluidic profiling	Useful in direct post-column analysis	[143]
Elapidae	*Dendroaspis angusticeps* (Eastern green mamba)	Fasciculin 2	Acetylcholinesterase in human	Treatment of cognitive impairments associated with Alzheimer's disease	[144]
Elapidae	*Naja kaouthia*	Metalloproteinase	Human Nerve growth factor (NGF)	Regulation of platelet reactivity through inhibition of GPVI/sheddase activity	[145]
Viperidae	*Daboia russelli russelli*	β-amyloid (Aβ)	Human neuroblastoma cell lines (SH-SY5Y)	Inhibition of amyloidosis from cell viability against toxicity, and destabilization of amyloid to monomeric entities	[146]
Diabetes mellitus					
Elapidae	*Naja naja atra*	Crude venom (CV)	Wistar rats (WTs)	Reduces hyperglycemia, decreases urinary protein, improvement renal function, and prevention inflammatory factor infiltration	[149]
Viperidae	*Agkistrodon halys*	Protein C activators (PCA)	Sprague Dawley rats (SD)	Potential to anti-fibrotic activities, such as the balance between inflammatory cytokine levels and collagen content, and modulates MMP expression	[150]
Viperidae	*Trimeresurus flavoviridis*	Vascular endothelial growth factor (VEGF)	Spontaneously diabetic Torii rats (SDT)	Enhance β cell injury, microvascular failure, and diabetes	[151]
Elapidae	*Naja nigricollis*	Phospholipase A2 (PLA_2)	Rat clonal β-cell lines (BRIN-BD11)	Identified isoforms of phospholipase A_2 and effectively stimulate insulin release from BRIN-	[152]

Family	Scientific name	Venom peptides/proteins	Experimental model	Observation	Reference
				BD11 cells	
Arthritis					
Elapidae	*Naja kaouthia*	Crude venom (CV)	Albino Wistar rats	Protection against arthritis induced oxidative damages	[155]
Elapidae	*Naja naja*	NN-32	Albino Wistar rats	Targets complex pathophysiological processes such as cancer, arthritis, and inflammation	[156]
Viperidae	*Crotalus durissus*	Phospholipase A2 (PLA_2)	Human plasma	Increase in the levels of PLA_2 in patients with rheumatoid arthritis than in those with osteoarthritis	[157]
Elapidae	*Naja naja*	Phospholipase A2 (PLA_2)	Rats	Correlation of acute inflamed joints bathed in synovial fluids containing high levels of PLA_2 in patients with rheumatoid arthritis	[158]
Elapidae	*Naja kaouthia*	Cytotoxin I	Albino Wistar rats	Protective activity of nanogold conjugated with snake venom protein toxin, NKCT1, against osteoarthritis	[159]
Viperidae	*Bothrops asper*	Metalloproteinase BaP1	Wistar rats (WTs)	Metalloproteinase BaP1 has pro-nociceptive activity in joints	[160]
Inflammation					
Elapidae	*Hydrophis cyanocinctus*	Hydrostatin-SN1 (H-SN1)	Human embryonic kidney cell lines (HEK293), human colon cancer cell lines (HT29), normal fibroblast cell lines (L929), and BALB/c mice	Significant anti-inflammatory activity under *in vitro* and *in vivo* conditions	[163]
Viperidae	*Bothrops jararaca, Bothrops jararacussu*	Crude venom (CV)	Swiss mice	Reduction in the inflammatory response to the venom injection	[164]
Viperidae	*Bothrops jararacussu*	Crude venom (CV)	Mice	Increased productionof IL-1β, COX-2 expression, and neutrophil chemotaxis induced by venom	[165]
Viperidae	*Crotalus durissus terrificus*	Crotoxin B secreted phospholipase A_2 ($CB\text{-}sPLA_2$)	Swiss mice	Lipid droplets recognition acute phase of inflammation, which involved in both development, and resolution of the inflammatory process	[166]
Viperidae	*Bothrops moojeni*	Metalloprotease (BmooMP-alpha-I)	C57BL/6 mice	A novel perspective to treat intestinal inflammatory diseases	[167]
Elapidae	*Hydrophis cyanocinctus*	Hydrostatin-TL1 (H-TL1)	Normal fibroblast cell lines (L929), BALB/c mice	For the development of new agents to treat IBD, sepsis acute shock, and other inflammatory diseases associated with TNF-α	[168]
Analgesic					
Viperidae	*Gloydius ussuriensis*	Gln49 phospholipase A_2 ($Gln49\text{-}PLA_2$)	Kunming white mice	Function of voltage-dependent ion channels, blocking neuronal signal transduction, and the blockade of potassium channels in nerve terminal	[171]
Viperidae	*Bothrops asper*	Crude venom (CV)	CD-1 mice	An alternative to reduces the pain, and distress of animals	[172]
Viperidae	*Bothrops atrox*	Crude venom (CV)	Swiss Webster mice	Signal reduction in edema and nociception	[173]

Cancer

Cancer, the second leading cause of mortality across the world, according to global statistics in 2018 ranges about 18.1 million new cases, and 9.6 million deaths [96]. Animal venom toxins exhibit effective anticancer properties, and are possible therapeutic drugs for cancer [97]. Toxins that are purified from various snake venoms are very effective in cancer cell multiplication, migration, invasion, apoptosis, and neo-vascularization [98]. Several studies suggested that low dose of jararhagin induced antiproliferation and induction of apoptosis in SKMel-28 cells, which also increased the expression of cell cycle checkpoint and apoptosis [98, 99]. Another study revealed that CTX III could inhibit the EGF-mediated endothelial-mesenchymal transition (EMT) in MDAMB-231 cells, which could suppress the EGF-induced cell invasion, migration over EGFR-mediated PI3K/Akt, and ERK1/2 signaling pathways [100]. *C. vipera* (Sahara sand viper)-LAAO has been triggered anti-proliferative activity through H2O2 generation, which could increase H2O2 and TBARS levels accompanied by the depletion of catalase activity in MCF-7 treated cells [101]. Further data provides evidences that the anticancer activity of LAAO from *C. rhodostoma* (Malayan pit viper) venom in human colon cancer by significant increase in the activity of caspase-3 and reduction in Bcl-2 levels in human colon cancer tissues [13]. In another study same authors demonstrated same results with the venom of *C. purpureomaculatus* (Shore pit viper) [102]. Moreover, rusvinoxidase induces apoptosis by intrinsic and extrinsic pathways in MCF-7 cells by DNA fragmentation due to activation of caspase-7 rather than caspase-3 [103]. Another study evidenced that the expression of p-JNK and p17 increased apoptosis induced by crotoxin in SK-MES-1 cells [104]. Demonstration of SVT inhibition in lung cancer cells through induction of apoptosis by up-regulation of caspase-3, 8, 9, Bax, p21, and p53, but decreased cIAP and Bcl2 expression has also been documented [105]. Furthermore, CTX-I and CTX-II isolated form *N. oxiana* (Ladle snake) venom exert their cytotoxic effect in cytosol, which accumulates in lysosomes, and leading to the activation of apoptotic pathways in cancer cells [106]. Induction of apoptosis and autophage by PLA2 and BnSP-6 apoptosis and autography in MDA-MB-231 cells has also been noticed [107].

Cardiovascular disease

Cardiovascular diseases have been considered as a disease of men, which has translated into a lack of awareness and risk in women at the health policy and clinical level. Globally, cardiovascular disease is the most leading cause of death in both women and men [108].

Snakes use their venom to immobilize preys, and to defend against predators. Snake venoms target physiological systems, especially circulation, respiratory and locomotion that evolved to target cardiovascular, neuromuscular systems and locomotion [109]. PLA2 purified from *B. marajoensis* (Marajo lancehead) venom induced hypotension, bradycardia and at the same time simultaneously blocks the electrical conduction in the heart in Wistar rats [110]. Another study suggested that the venom of the *Bitis* species can be considered as an arsenal of molecules, which leads the victim of hypotensive shock, and requires special attention in cases of an envenoming [111]. Further, *Bj*-PRO-10c is known to induce NO production, and the gene expression of arginiosuccinate synthetase (ASS), and endothelial NOS in the brains of spontaneously hypertensive rats, by improving baroreflex sensitivity, which may reveal novel approaches for treating diseases with impaired baroreflex function [112]. Snake venom factors do not alter cardiac performance, collateral blood flow to the clotting system but decrease the myocardium in mongrel dogs [113]. Snake venom factors could reduce polymorphonuclear (PMN) recruitment and activate myocardial ischemia, and coronary reperfusion to reduce tissue injury in feral baboons [114]. Evidences accumulate that the anti-hypertensive and vasorelaxation effects of BPP-5α in spontaneous hypertensive rats could be due to endothelial and nitric oxide (NO) dependent mechanism, which are unrelated to the inhibition of the hydrolytic activities of ACE [115]. Cardiovascular disturbance observed after envenoming by Malayan krait might be involved in autonomic reflex and vascular nitric oxide mechanisms in rats [116]. Better understanding about the sequence, structure, and functional relationships of *B. rhinoceros* (Gabino viper) could lead to clinical studies and to investigate the potential application of this components or venom furthermore to being used to treat human haemostatic disorders, including heart attack, strokes, and hypotension [117].

Renal disease

Polycystic kidney disease is one of the life-threatening genetic diseases characterized by multiple fluid-filled cysts present in the kidney [118]. Cyst formation and enlargement progressively compromise normal renal parenchyma functions and, with time, further severely distort the entire kidney, which lead to end-stage renal failure [118]. Snake venoms, which have greater phospholipase activity, might induce myotoxicity with myoglobinuria could be results in renal lesions [119, 120]. Although investigations have been performed on the direct nephrotoxic effect of coral snake venoms the studies are still insufficient in the literature [121]. Renoprotective effect of mambaquaretin-1 showed the lowering of cAMP levels of V2R expressing cells, which inhibited the dDAVP (1-deamino-8D-arginine vasopressin) and could induce cAMP production in a dose-dependent manner in polycystic kidney disease (*pcy*) mice [122]. HSV-induced glomerulonephritis is correlated with both ECM production and degradation systems in Sprague Dawley rats, which is particularly important for the repair process [123]. More findings indicated that the bone marrow-derived from the endothelial cells can contribute glomerular endothelial cell turnover and also to the regeneration of the glomerular microvasculature by the same venom in pathologic conditions in TIE2/lZ mice model [124]. Another study stated that venom of *D. acutus* with Chinese herbal medicine (P-19) could possess inhibitory effect on glomerular disease in ddY mice [125]. Moreover, *B. alternatus* (crossed pit viper) venom was known to morphological and functional changes in Wistar-Hannover rats renal tissue, with enhanced Na+/K+-ATPase expression and activity subsequently could attenuate renal dysfunction during venom-induced damage [126]. *B. moojeni* (Brazilian lancehead) venom induced in Wistar rats was known to cause extreme changes in renal physiology, including a drop in RVR associated with diuresis, natriuresis, and kaliuresis [127]. Furthermore, LAAO from *B. marajoensis* venom might be responsible for the nephrotoxicity and renal cytotoxicity in MDCK renal cell lines [128], and thus could be used for the treatment of renal cancer. Recent study suggested that *M. latticolaris* and *M. browni* (Brown's coral snake) venoms could alters the renal physiological parameters and cause nephrotoxic effects with the involvement of oxidative stress in Wistar rats [129].

Pulmonary disease

Chronic obstructive pulmonary disease (COPD) is the third chief cause of death in worldwide [130]. COPD is one of the most commonly disease results in chronic cigarette smoking and it is increasingly recognized, which the early life lung development, health, exposure to airway pollutants, and social deprivation are the major risk factors to develop COPD [130]. Several studies has been described that the harmful effects of venoms are due to the enzymatic activities of the venoms, which could cause endothelial damage or activation, rather than a direct pro-coagulant effect [131-133]. The therapeutic effect of FIIa could be by reducing thrombi, which could restore blood flow in the lung and improve cardiovascular function in rabbits by *D. acutus* venom [134]. Another investigation revealed that jararhagin from *B. jararaca* (Yarara snake) can induce pulmonary bleeding after intravenous injection in CD-1 mice. Under certain conditions coagulation tests may not be affected. Jararhagin affects lung microvessels by proteolytic activity and also inhibits the action of plasma proteinase inhibitors [135]. Further, rFII isolated from *D. acutus* venom has a protective effect on taurocholate-induced SAP in rats is mainly depending on the direct degradation of TNF-α [136]. Moreover, P-III SVMPs from the venom of *B. caribbaeus* (Saint Lucia viper) was known to induce pulmonary hemorrhage and thrombocytopenia in CD-1 mice, with increased FDP, and without causing blood incoagulability [137].

Neurodegenerative disease

Neurodegenerative diseases are induced by the abnormality in one or more genes that mainly code for proteins of the neuroectoderm and its derivatives [138]. Behavioral changes are well-established features of degenerative diseases such as Parkinson disease, frontotemporal dementia, and Alzheimer disease [139]. Neurodegenerative diseases are characterized by the loss of brain function, which result in motor deficits, tremors, and postural instability [140]. Earlier study revealed that p-BTX-I from *B. atrox* (common lancehead) could induce neuritogenesis in PC12 cells are mediated by the trkA receptor, PI3K-AKT, and MAPK-ERK pathways which are triggered by NGF, which suggest that synthetic peptides p-BTX-I protects PC12 cells from MPP^+toxicity [141]. Another study suggested that the LMWF of *B. jararaca* showed neuroprotective activity in cultured hippocampal cells with oxidative stress induced by H_2O_2 [142]. The advantage of direct post-column analysis of four venom proteomes described by microfluidic on-line screening methodology. The coupling of the miniaturized separation techniques to the microfluidic on-line assay and sensitive fluorescence detections, which showed the multiple, sensitive, and robust analyses are possible in a short time frame with the minimal amount of venom [143]. The snake venom toxin Fasciculin 2 has been reported to act as a potent reversible inhibitor of acetylcholinesterase, which could be further used in the treatment of cognitive impairments is associated with Alzheimer's disease [144]. The role of NGF is regulating the metalloproteinase-mediated events, parameters like physiological, pathological, and therapeutic concentrations of NGF, relative localization of binding partners and the possible regulation of platelet reactivity through inhibition of GPVI/sheddase activities has been reported [145]. The dual potency of venom protein-derived peptides for inhibition of amyloidosis from the cell viability against the toxicity and destabilization of amyloid to monomeric entities suggests a possibility of good opportunity to explore these molecules as a therapeutic agent for both prevention and maintenance of Alzhemier's disease [146].

Diabetes mellitus

It is well known that Diabetes mellitus is a serious metabolic disease across worldwide. It is mainly classified into type 1 diabetes and type 2 diabetes and 90-95% diabetic patients are type 2 diabetes mellitus is characterized by insulin resistance, which result in decreasing insulin actions on targeted tissues [147]. Recently, diverse venom peptides have emerged as pharmacological implements and remedial for type 1 diabetes and type 2 diabetes [148]. N. *atra* venom is known to reduce hyperglycemia, decrease urinary protein, enhance renal function and structure, prevent oxidative stress and lipid metabolism products, and restrict

inflammatory factor infiltration in Wistar rats [149]. Further, PCA has the ability of anti-fibrotic activities in diabetic rats, such as modulates the balance between inflammatory cytokine levels and collagen content, modulates MMP expressions, and sustains the MMP-TIMP balance [150]. Enhanced VEGF signaling is in islets could also contribute with β cell injury, microvascular failure, and diabetes in spontaneously diabetic Torii (SDT) rats [151]. Furthermore, phospholipase A2 from *N. nigricollis* (black-necked spitting cobra) are effectively stimulated insulin, which release from BRIN-BD11 cells at the concentration of 1 μM, which is not cytotoxic to the cells and suggesting that the possible therapy for Type 2 diabetes [152].

Arthritis

Arthritis is a type of inflammation which affects the joints. The foremost symptoms of arthritis are joint pain and stiffness which is basically related with increasing age. Osteoarthritis and rheumatoid arthritis are two most common types of arthritis [153]. Cobra venom has a great potential for treating several pathological conditions, including joint pains and other disorders [154]. Earlier study reveals that *N. kaouthia* (monocled cobra) venom has been showed significant protection against arthritis-induced oxidative damages in male albino rats [155]. The study has proven that NN-32 from *N. naja* (Indian cobra) venom could targets complex pathophysiological processes such as cancer, arthritis, and inflammation in male albino rats [156]. It is known that there are significantly increasing levels of PLA2 in patients with rheumatoid arthritis than osteoarthritis and the plasma PLA2 is highest in those patients with active rheumatoid arthritis [157]. Further correlation of acute inflamed joints is agreeable in the synovial fluids containing high level of PLA2 in patients with rheumatoid arthritis [158]. The protective activity of nanogold conjugated with snake venom protein toxin, NKCT1 *N. kaouthia*, against osteoarthritis in albino Wistar rats by limiting the inflammatory markers at the molecular level has been reported [159]. The experiment provides evidence of metalloproteinase BaP1 from *B. asper* has pro-nociceptive activity in joints. MMPs are involved in the inflammatory joint hyper-nociception and induce COX-2 expression in Wistar rats [160].

Inflammation

Although inflammation is not a disease per se, it is the retort to infection or wound and is perilous for both innate and adaptive immunity in the human body. It is documented as a fragment of the multifaceted biological response of vascular tissues, which are detrimental to stimuli for instance, pathogens, injured cells and irritations [161]. Inflammatory reactions are commonly observed in every victim bitten by venomous snakes, honeybees, and scorpions [162]. Researches reveal that the tumor necrosis factor receptor-1 (TNFR1) and specific binding peptides and Hydrostatin-SN1 (H-SN1), which has been purified from *H. cyanocinctus* (annulated sea snake) venom glands T7 phage were proven to display the significant changes in anti-inflammatory activities under *in vitro* and *in vivo* conditions [163]. Inflammation is part of the responsibility for the tissue damage induced by *B. rhinoceros* snake venom, which the steroidal anti-inflammatory drug dexamethasone could reduce the myotoxic effects of these venoms and reduce the inflammatory response in Swiss mice [164]. Increased production of IL-1β, COX-2 expression, and neutrophil chemotaxis are induced by *B. jararacussu* venom in mice could induce an early onset edema dependent on the prostanoid production and neutrophil migration [165]. Phospholipase A2 from snake venom could induce lipid droplets formation in immunocompetent cells and also the inflammatory process [166]. Other findings suggested that the novel perspective to treat intestinal inflammatory diseases, highlighting the potential anti-inflammatory role of metalloproteases in C57BL/6 mice, and its effectiveness as a therapeutic alternative in the immunopathological conditions [167]. Another study documented that H-TL1 from the *H. cyanocinctus* venom gland T7 phage display library, effectively antagonized the TNF-α/TNFR1 interaction, alleviated the cytotoxicity, and inflammation associated with TNF-α *in vitro* and *in vivo*, suggesting promising hopes for the development of new agents to treat inflammatory bowel disease, sepsis acute shock, and other inflammatory diseases, which are associated with elevation of TNF-α [168].

Analgesic

An essential component of the prevention of pain signaling system is binding of some venom-toxins with sensitive receptors, ion channels and thus potentially blocks the signals [169]. Thus, animal toxins act as analgesic properties and manifest healing in experimental arthritis and save from potentially destructive influences of inflammation. Ultimately, these toxins can be used as a new category of anti-inflammatory drugs for basic pain signaling, channelopathies and receptor expression [170]. The investigation has also demonstrated that peptides in venom-derived toxins exhibit improved analgesic potencies and lesser side effects than current therapeutic drugs that are used clinically [170]. The main mechanism of analgesic actions of Gln49-PLA2 from *G. ussurensis* (Ussuri pit viper) venom is via affecting the function of voltage-dependent ion channels, blocking neuronal signal transduction by the potentiation of sodium channels, and the blockade of potassium channels in the nerve terminal of Kunming white mice [171]. Furthermore, the prophylactic use of the analgesic tramadol does not affect the outcome of the anti-venom potency assay while using *B. asper* (velvet snake) venom and poly-specific anti-venom. Therefore, represents an alternative way to reduce the pain and distress of animals in this test. Finally, there is a significant correlation between the neutralization of lethality and of coagulant activity of *B. asper* venom *in vitro* [172]. More study reveals that CSE is significantly reduced the venom-induced edema and nociception, which could be exhibits a central mechanism for pain inhibition and may also inhibit prostaglandin synthesis in Swiss Webster mice [173].

CONCLUSION

Peptides are recognized for being high selectivity, safe and well tolerated compounds. Due to their high selectivity, the venom peptides can act as effective tools in *in vitro* as well as in *in vivo* studies as possible therapeutic agents. Further studies will be need for therapeutic applications of venom peptides linked with protection, pharmacokinetics and distribution. Optimization of the delivery of peptide to exterior and core targets will assist to govern the possibility of using these peptides as potential candidates for effective drug development. This makes a reason for the augmented attention in using peptides for further pharmaceutical research and development and their usage in clinical practices. Peptide therapeutics is at present being appraised in clinical trials. Most of the venoms possess bioactive peptides, which have been already proven potential as effective agents against a number of diseases. An advance in transcriptomics and proteomics research has vividly changed the manner and rate of venom peptide discovery. An emerging trend looks forward the discovery of venom peptides with new structure and unforeseen mechanism of action will be the focus for future research. Simultaneously, this advanced knowledge will be applied for the development of higher throughput strategies targets identification. The present research clearly threw light that venom peptides are the effective tools in the treatment of various disease conditions.

ABBREVIATION

3FTx: Three-finger toxins, AChE: Acetylcholinesterases, ADAM: A disintegrin and metalloproteinase, ANP: Atrial natriuretic peptide, BNP: B-type natriuretic peptide, BuChE: Butyrylcholinesterase, CNP: C-type natriuretic peptide, CRiSP: Cysteine rich secretory protein, CTL: C-type lectin, CTX I: Cross linked C-telopeptide of Type I Collagen, CTX III: Cross linked C-telopeptide of Type III Collagen, DIS: Disintegrins, EGF: Epidermal Growth Factor, FAD: Flavin Adenine Dinucleotide, IL-1b: Interleukin 1 beta, IL-6:Interleukin 6, KUN: Kunitz peptides, LAAO: L-amino acid oxidases, MAPK-ERK: Microtubule associated protein Kinase–Extra cellular Signal, Related Kinases, MCF-7:Michigan Cancer Foundation-7, MPP+:Mitochondrial processing peptidase, NGF: Nerve growth factor, NKCT–1: *Naja kaouthia* cytotoxin 1, NN-32:*Naja naja* toxin fraction 32, NP: Natriuretic peptide, P13K-AKT: Phosphatidylinositol 3-Kinase–Protein Kinase B, p-BTX-1:Ptychodiscus brevis toxin 1, PC 12:Pheochromocytoma 12, p-JNK: Phosphorylated c-Jun N-terminal Kinase, PGF: Placental growth factor, PLA2:Phospholipase A2, TBARS: Thiobarbituric Acid Reactive substances, TNF-α: Tumour

Necrosis Factor alpha, SVMP: Metalloproteases, SVSP: Serine proteases, VEGF: Vascular endothelial growth factor

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

The authors declare there is no conflict of interests.

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