





Snake venom disintegrins update: insights about new findings

Gabriela de Oliveira Almeida¹ , Isadora Sousa de Oliveira^{2,3} , Eliane Candiani Arantes² ,
and Suely Vilela Sampaio^{1*} 

¹Department of Clinical Analysis, Toxicology and Food Science, School of Pharmaceutical Sciences of Ribeirão Preto, University of São Paulo, Ribeirão Preto, SP, Brazil.

²Department of BioMolecular Sciences, School of Pharmaceutical Sciences of Ribeirão Preto, University of São Paulo, Ribeirão Preto, SP, Brazil

³Department of Biotechnology and Biomedicine, Technical University of Denmark, Kongens Lyngby, Denmark.

Abstract

Snake venom disintegrins are low molecular weight, non-enzymatic proteins rich in cysteine, present in the venom of snakes from the families Viperidae, Crotalidae, Atractaspididae, Elapidae, and Colubridae. This family of proteins originated in venom through the proteolytic processing of metalloproteinases (SVMPs), which, in turn, evolved from a gene encoding an A Disintegrin And Metalloprotease (ADAM) molecule. Disintegrins have a recognition motif for integrins in their structure, allowing interaction with these transmembrane adhesion receptors and preventing their binding to proteins in the extracellular matrix and other cells. This interaction gives disintegrins their wide range of biological functions, including inhibition of platelet aggregation and antitumor activity. As a result, many studies have been conducted in an attempt to use these natural compounds as a basis for developing therapies for the treatment of various diseases. Furthermore, the FDA has approved Tirofiban and Eptifibatide as antiplatelet compounds, and they are synthesized from the structure of echistatin and barbourin, respectively. In this review, we discuss some of the main functional and structural characteristics of this class of proteins and their potential for therapeutic use.

Keywords:

disintegrins
SVMP
ADAM
snake venom
integrins
RGD domain

* Correspondence: suvilela@usp.br

<https://doi.org/10.1590/1678-9199-JVATITD-2023-0039>

Received: 17 June 2023; Accepted: 25 August 2023; Published online: 18 September 2023



Background

Snake venom is a secretion produced in the glands located on both sides of the animal's upper jaw. Its evolutionary function includes the defense and survival of the snake, as well as the immobilization and digestion of prey, aiding in its feeding. It is a complex cocktail, as its composition is formed by the mixture of various compounds, predominantly proteins, peptides, amino acids, nucleic acids, carbohydrates, lipids, and metals [1, 2]. After its production in pairs of homologous glands, venom is secreted into the base of the fangs, which can be located in the posterior region (opisthoglyphous) or anterior region of the animal's mouth, with the latter case having either short and fixed fangs (proteroglyphous) or long and movable fangs (solenoglyphous) [2, 3].

Snakebite envenomation is considered a Neglected Tropical Disease with high incidence and severity, mainly affecting poverty regions [4]. It is estimated that around 5.4 million snakebites occur worldwide each year, resulting in 1.8 to 2.7 million cases of envenomation and approximately 81,000 to 138,000 deaths [5]. Snake venom exhibits a highly complex composition, and due to the diverse toxins with a wide range of biological functions, various clinical manifestations resulting from envenomation are observed, including local and systemic effects [6]. However, beyond its toxic action, snake venom is also recognized for its high therapeutic potential, as its composition contains approximately 100 to 500 pharmacologically active compounds capable of acting on different target sites. For this reason, many studies have been conducted in the search for alternative therapies for various diseases [7].

In this context, snake venomomics has demonstrated great relevance for the more detailed analysis of venom components [8]. By using this strategy, which combines advances in proteomics and transcriptomics, it is possible to isolate venom compounds, estimate the content of toxins, as well as understand their biological and toxicological aspects [9]. Advances in these techniques have allowed the characterization of up to 20 families of proteins in the venom of a single snake, with some of these families containing up to 80 different toxins [10]. Despite the fascinating variability of compounds, most snake venoms are composed of four dominant protein families: phospholipase A₂ (PLA₂), three-finger toxins (3FTx), snake venom serine protease (SVSP), and snake venom metalloprotease (SVMP), along with secondary protein families, such as cysteine-rich secretory protein (CRISP), Kunitz peptides, L-amino acid oxidase (LAAO), natriuretic peptides, C-type lectins (CTL), disintegrins, among others [11].

In this review, we present the functional and structural aspects of disintegrins found in snake venom, as well as the evolutionary history of their emergence. We also discuss the potential applications of this class of peptides and the drugs already approved for therapeutic use.

What are snake venom disintegrins?

Snake venom disintegrins comprise a family of highly homologous, non-enzymatic polypeptides rich in cysteine (Cys). Their presence

is described in the venom of snakes from the families Viperidae, Crotalidae, Atractaspididae, Elapidae, and Colubridae [12]. This family of small proteins interacts specifically with integrins, a group of cell adhesion receptors on the surface of certain cells, including platelets, vascular endothelial cells, and some tumor cells [13, 14]. This way, disintegrins, by preventing such binding, interfere in intercellular and cell-matrix interactions, as well as signal transduction [12, 14].

Integrins: a family of heterodimeric receptors

Integrins are transmembrane receptors that regulate or trigger different cellular processes upon binding to specific extracellular ligands [15]. They are heterodimeric proteins formed by the non-covalent association of α and β chains. In vertebrates, at least 18 α subunits and 8 β subunits have been identified, which can form a total of 24 different heterodimers. The α and β subunits of integrins do not have detectable homology between them, but there are conserved regions among different α subunits (approximately 30% identity) and among β subunits (around 45%) [16].

Integrins can recognize ligands from the extracellular matrix, cell surfaces, and other soluble ligands, with the $\alpha\beta$ pairings of integrin subunits being determinants for binding specificity [16, 17]. Structurally, each integrin subunit consists of an extended multidomain extracellular region (up to 1104 residues in the α subunit and 778 residues in the β subunit), a transmembrane helix, and a short cytoplasmic tail (with 20 to 70 amino acids). The N-terminal portions of each subunit, located in the extracellular region, combine to form a globular ligand-binding "head" (Figure 1) [18, 19].

Integrins are present on the surface of many cell types and enable cell-cell interactions and interactions between cells and extracellular matrix proteins, including fibronectin, collagen, and laminin-1 [20]. These interactions are related to a wide range of biological effects, so the role of integrins is associated with physiological events such as cell adhesion [21], wound healing [22], regulation of neuronal connectivity [23], and synapses [24], as well as pathological effects as inflammation [17], tissue fibrosis [25], atherosclerotic plaque development [26]. They also interfere in various stages of cancer development and progression, including survival, proliferation, angiogenesis, migration, invasion, survival in circulation, extravasation, and metastatic growth [12, 15, 17, 27–31].

Snake venom disintegrins: evolution from metalloproteases

Snake venom disintegrins are peptides derived from the proteolytic processing of snake venom metalloproteinase (SVMP) precursors and carry in their structure the recognition motifs for integrins RGD, KGD, WGD, VGD, MGD, RTS, KTS [13, 32]. SVMPs are found in large quantities in snake venom and are the main components responsible for the hemorrhagic action after snakebite, interfering with the victim's hemostatic system [33, 34]. They are divided into different subclasses based on size and domain structure. Class P-I SVMPs contain only the typical

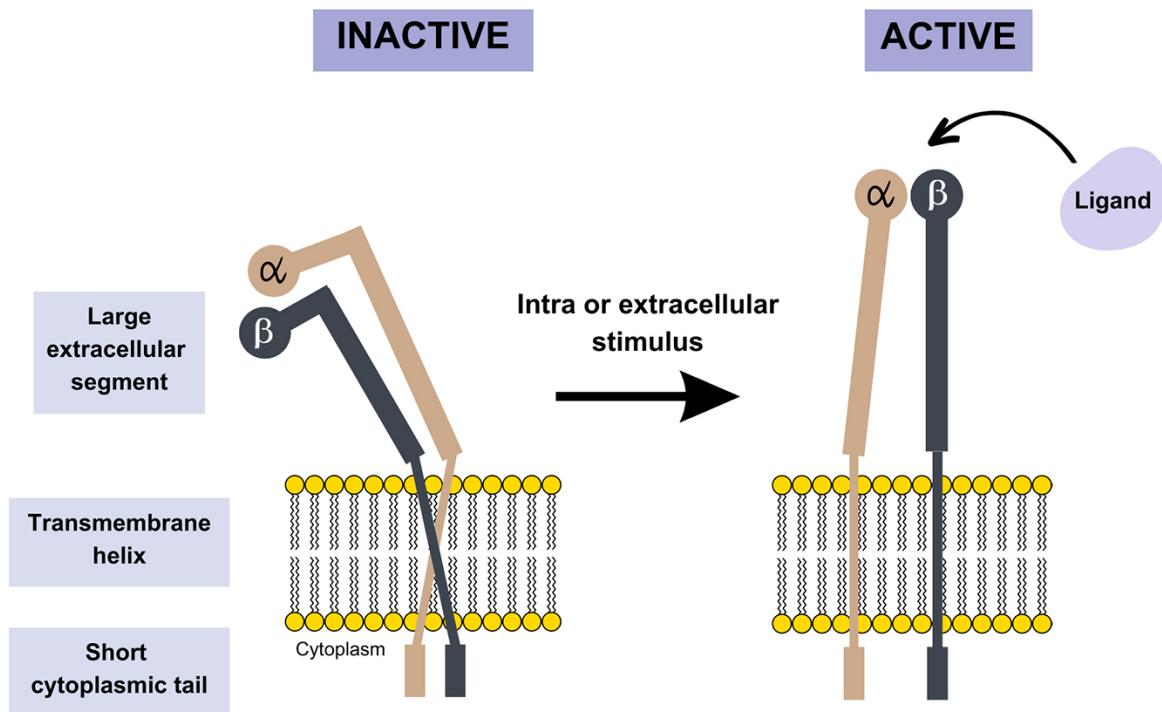


Figure 1. Integrin structure. Conversion of integrin from its inactive low-affinity conformation to the active high-affinity conformation for the ligand through intra- or extracellular stimuli.

metalloproteinase domain (M), composed of the pro-domain and proteolytic domain, and have a molecular mass of 20 to 30 kDa. Class P-II SVMs have a molecular mass of 30 to 60 kDa and are structurally composed of pro-domain, proteolytic domain, and disintegrin-like domain (DI). Class P-III SVMs (hemorrhagins) have a molecular mass between 60 to 100 kDa and are composed of a pro-domain, proteolytic domain, a disintegrin-like domain, and a cysteine-rich domain (C). In general, the hemorrhagic activity of these toxins depends on the M domain, but the DI and C domains are also important for their biological function. Thus, class P-III is recognized for its ability to induce higher and more diverse hemorrhagic activity when compared to class P-I and P-II SVMs [33, 35, 36].

Evidence from molecular phylogenetics suggests that SVMs evolved from a gene that encodes an A Disintegrin And Metalloprotease (ADAM) molecule, likely from an ancestral ADAM 7 or ADAM 28, belonging to the adamalysin family. Evolutionarily, SVMs were recruited to the snake venom gland at the base of the advanced snake radiation, after the divergence of Pareatidae from the remaining Caenophidians, during the Paleogene period of the Cenozoic Era. The evolutionary history of SVMs shows the loss of the cysteine-rich domain in class P-III, forming the SVMs-P-II, followed by the loss of the disintegrin-like domain and the formation of class P-I [35, 37].

Regarding domain organization and sequence, important similarities are observed between ADAMs and P-III SVMs, including the presence of the pro-domain, proteolytic domain, disintegrin-like domain, and cysteine-rich domain. Regarding

structural differences, ADAMs have an EGF domain, a transmembrane domain, and a cytoplasmic tail, which are not present in SVMs [38].

The evolutionary history of disintegrins occurred through positive Darwinian selection, and their presence in snake venom results from the proteolytic processing of P-II metalloproteinases or translation of short messenger RNAs without the metalloproteinase coding region [39–42]. Thus, the presence of both free metalloproteinases and disintegrins can be observed in the venom [43].

Discovery and distribution of snake venom disintegrins

Snake venom disintegrins emerged in the scientific community in 1987, when Stefan Niewiarowski and Tur-Fu Huang isolated a low molecular weight non-enzymatic protein from the venom of *Trimeresurus gramineus*. The researchers observed that the protein, called trigramin, could block the binding of fibrinogen to stimulated GPIIb/IIIa receptors on platelets, thus inhibiting platelet aggregation. Although introduced in Toxinology in 1987, the term “disintegrin” was first used in 1990 when it was described as a new class of peptides isolated from snake venom, rich in the amino acid cysteine and containing an RGD domain in their structure [44, 45]. Since then, numerous studies have been conducted searching for this class of compounds in snake venom (Table 1). Approximately ten years after its discovery, non-RGD disintegrins were identified, challenging the concept of the obligatory presence of the Arg-Gly-Asp amino acids, and

paving the way for the future discovery of different integrin recognition motifs [46, 47].

Initially, disintegrins were studied for their inhibition of platelet aggregation due to the ability to interact with the transmembrane GPIIb/IIIa receptors (or α IIB β 3 integrin) present on the surface of platelets [39, 48–50]. Fibrinogen is a bivalent molecule capable of simultaneously binding to the activated GPIIb/IIIa receptor on two different platelets, forming bridges between the activated platelets [51–54]. Thus, disintegrins inhibit platelet aggregation by preventing the interaction of the α IIB β 3 integrin with fibrinogen.

Subsequently, in addition to their action on platelet receptors, many disintegrins have been isolated and characterized for their effects on other cells, demonstrating various biological functions, including interference with human neutrophil chemotaxis to sites of inflammation and tissue injury [55], antiparasitic activity [56], antiviral activity [57] and antitumor action through induction of apoptosis [50] and cytotoxicity [58], as well as inhibition of important steps in tumor development and progression, like adhesion [46, 59–63], angiogenesis [59, 64–67], migration [59, 62, 63, 68, 69] and metastasis [69–72].

Structural characterization of snake venom disintegrins

Snake venom disintegrins can be structurally classified into two major groups: monomeric and dimeric (Figure 2). Monomeric

disintegrins are composed of three classes [73]. The first class consists of short disintegrins with 41 to 51 amino acid residues and four disulfide bonds. The second class comprises medium disintegrins with approximately 70 amino acids and six disulfide bonds. The third class of monomeric disintegrins contains long disintegrins with about 84 residues and seven disulfide bridges [74]. The second group of disintegrins is the dimeric disintegrins, which are further classified as homo- or heterodimers when the subunits are identical or different, respectively [73]. The subunits of dimeric disintegrins are composed of around 67 residues with ten cysteines, which are involved in forming four intrachain and two interchain disulfide bonds [74].

These proteins are highly homologous, and this structural similarity is primarily associated with the alignment of cysteine residues [75]. Figure 3 shows the analysis of multiple sequence alignments of disintegrin domains from five different structural classes, including Echistatin [76], Obtustatin [77], Barbourin [78], Tzabcanin [79], Cotiarin [80], Batroxostatin [81], Jarastatin [82, 83], Jararacin [82–84], Bitistatin [85], Salmosin-3 [86], Schistatin [87], Contortrostatin [48], CC5 [88], CC8 [88], EC3 [46] and EMF10 [47], highlighting conserved cysteine residues (Figure 3).

Regarding binding specificity, the correct pairing of cysteine residues is essential for exposing the motif that mediates the interaction with integrins and determining their inhibition [74]. In this context, the family of snake venom disintegrins can be divided into seven groups, each with a specific pattern

Table 1. Snake venom disintegrins isolation.

| Disintegrin | Snake venom species | Motif | Publication data | Ref. |
|---------------|--|-------|------------------|-------|
| Trigramin | <i>Trimeresurus gramineus</i> | RGD | November-87 | [44] |
| Echistatin | <i>Echis carinatus</i> | RGD | December-88 | [76] |
| Applagin | <i>Agkistrodon piscivorus piscivorus</i> | RGD | October-89 | [110] |
| Albolabrin | <i>Trimeresurus albolabris</i> | RGD | May-90 | [111] |
| Elegantin | <i>Trimeresurus elegans</i> | RGD | May-90 | [111] |
| Flavordin | <i>Trimeresurus flavoviridis</i> | RGD | July-90 | [112] |
| Batroxostatin | <i>Bothrops atrox</i> | RGD | September-90 | [81] |
| Eristostatin | <i>Eristicophis macmahoni</i> | RGD | November-90 | [45] |
| Rhodostomin | <i>Calloselasma rhodostoma</i> | RGD | November-90 | [45] |
| Triflavin | <i>Protobothrops flavoviridis</i> | RGD | February-91 | [113] |
| Barbourin | <i>Sistrurus miliarius barbouri</i> | KGD | May-91 | [78] |
| Basilicin | <i>Crotalus basilicus</i> | RGD | January-93 | [84] |
| Cerastin | <i>Cerastes cereastes</i> | RGD | January-93 | [84] |
| Cereberin | <i>Crotalus viridis cereberus</i> | RGD | January-93 | [84] |
| Crotatoxin | <i>Crotalus atrox</i> | RGD | January-93 | [84] |
| Cotiarin | <i>Bothrops cotiara</i> | RGD | January-93 | [84] |
| Durissin | <i>Crotalus durissus durissus</i> | RGD | January-93 | [84] |
| Jararacin | <i>Bothrops jararaca</i> | RGD | January-93 | [84] |
| Lachesin | <i>Lachesis mutus</i> | RGD | January-93 | [84] |
| Lutosin | <i>Crotalus viridis lutosus</i> | RGD | January-93 | [84] |
| Molossin | <i>Crotalus molossus molossus</i> | RGD | January-93 | [84] |

Table 1. Cont.

| Disintegrin | Snake venom species | Motif | Publication data | Ref. |
|---------------------|--|---------|------------------|-------|
| Viridin | <i>Crotalus viridis viridis</i> | RGD | January-93 | [84] |
| Contortrostatin | <i>Agkistrodon contortrix contortrix</i> | RGD | January-94 | [114] |
| Multisquamatin | <i>Echis multisquamatus</i> | RGD | January-94 | [114] |
| Flavostatin | <i>Trimeresurus flavoviridis</i> | RGD | May-96 | [49] |
| Bitistatin | <i>Bitis arietans</i> | RGD | October-97 | [115] |
| Salmosin | <i>Agkistrodon Halys Brevicaudus</i> | RGD | July-98 | [116] |
| Accutin | <i>Agkistrodon acutus</i> | RGD | November-98 | [64] |
| EC3 | <i>Echis carinatus</i> | VGD/MLD | April-99 | [46] |
| Rhodocetin | <i>Calloselasma rhodostoma</i> | ? | May-99 | [117] |
| Jarastatin | <i>Bothrops jararaca</i> | RGD | September-99 | [82] |
| EMF-10 | <i>Eristicophis macmahoni</i> | RGD/MGD | September-99 | [47] |
| EC6 | <i>Echis carinatus</i> | MLD/RGD | October-00 | [118] |
| Alternagin-C | <i>Bothrops alternatus</i> | ECD | December-00 | [119] |
| Lebein | <i>Macrovipera lebetina</i> | RGD | May-01 | [120] |
| Trimestatin | <i>Trimeresurus flavoviridis</i> | RGD | September-01 | [121] |
| Piscivostatin | <i>Agkistrodon piscivorus piscivorus</i> | RGD/KGD | September-01 | [121] |
| Saxatillin | <i>Gloydus saxatilis</i> | RGD | January-02 | [66] |
| CC5 | <i>Cerastes cereastes</i> | RGD | January-02 | [88] |
| CC8 | <i>Cerastes cereastes</i> | RGD/WRG | January-02 | [88] |
| Ocellatusin | <i>Echis ocellatus</i> | RGD | February-02 | [122] |
| Bothrasperin | <i>Bothrops asper</i> | RGD | March-03 | [123] |
| Obtustatin | <i>Macrovipera lebetina</i> | KTS | May-03 | [77] |
| EO4 | <i>Echis ocellatus</i> | | June-03 | [124] |
| EO5 | <i>Echis ocellatus</i> | MLD/VGD | June-03 | [124] |
| VA6 | <i>Vipera ammodytes</i> | RGD | June-03 | [124] |
| VB7 | <i>Vipera berus</i> | RGD/KGD | June-03 | [124] |
| VLO4 | <i>Vipera lebetina obtusa</i> | | June-03 | [124] |
| VLO5 | <i>Vipera lebetina obtusa</i> | VGD/MLD | June-03 | [124] |
| Adinbitor | <i>Agkistrodon halys brevicaudus stejneger</i> | RGD | June-04 | [125] |
| Viperistatin | <i>Vipera palestinae</i> | KTS | November-04 | [126] |
| Bothrostatin | <i>Bothrops jararaca</i> | RGD | April-05 | [127] |
| Jerdostatin | <i>Trimeresurus jerdonii</i> | RTS | December-05 | [128] |
| Lebestatin | <i>Macrovipera lebetina</i> | KTS | December-05 | [59] |
| Mojastin-1 and -2 | <i>Crotalus scutulatus scutulatus</i> | RGD | April-06 | [129] |
| DisBa-01 | <i>Bothrops alternatus</i> | RGD | October-07 | [128] |
| Viplebedin-2 | <i>Vipera lebetina</i> | VGD/MLD | July-09 | [113] |
| Disintegrin protein | <i>Naja naja</i> | ? | August-12 | [130] |
| Disintegrin | <i>Atropoides mexicanus</i> | RGD | December-14 | [61] |
| Sasaimin | <i>Cerrophidion sasai</i> | RGD | December-14 | [61] |
| Simusmin | <i>Crotalus simus</i> | RGD | December-14 | [61] |
| Tzabcanin | <i>Crotalus simus tzabcan</i> | RGD | September-15 | [79] |
| Disintegrin_CC | <i>Cerastes cereastes</i> | RGD | December-17 | [131] |
| Disintegrin | <i>Crotalus durissus collilineatus</i> | Non-RGD | October-18 | [132] |
| Cerastategrin | <i>Cerastes cereastes</i> | RGD | September-20 | [133] |

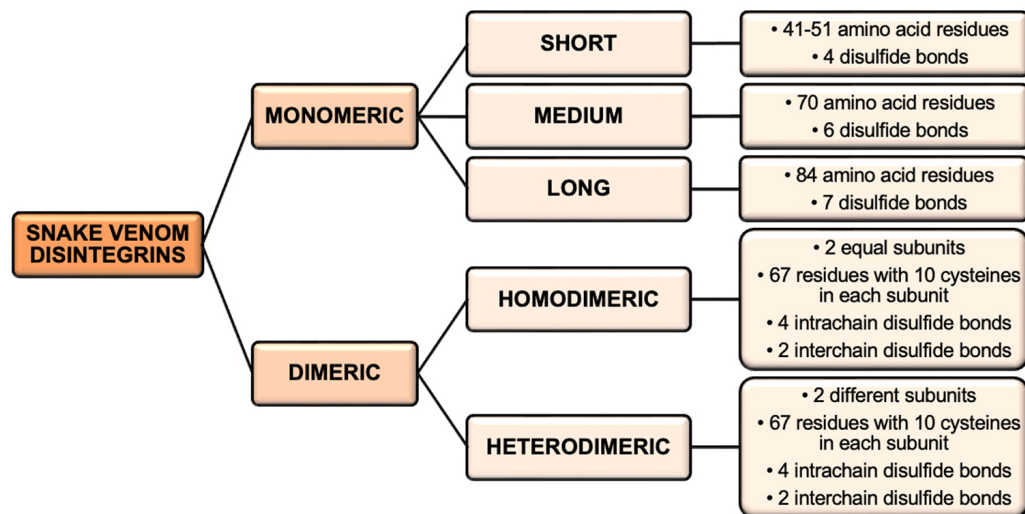


Figure 2. Structural classification of disintegrins.



Figure 3. Multiple alignments among selected disintegrins from different structural classes. Cysteine residues are highlighted in gray. The integrin-binding RGD motif is represented in red, and non-RGD motifs are in blue.

of sequence and disulfide bond formation between cysteine residues (Figure 4). Group 1 includes the disintegrin-like domain of proteins from the ADAM/SVMP subfamily. Its disulfide pattern is defined as Cys1-Cys5, Cys2-Cys3, Cys4-Cys10, Cys7-Cys9, Cys8-Cys13, Cys11-Cys14, while Cys6 and Cys12 form connections with other domains of the protein. Group 2 consists of disintegrins similar to Bitistatin A, and Cys1-Cys4, Cys2-Cys7, Cys3-Cys6, Cys5-Cys11, Cys8-Cys10, Cys9-Cys13, Cys12-Cys14 characterize their disulfide pattern. Group 3 is formed by disintegrins similar to Bitistatin B, and their disulfide bond pattern consists of Cys1-Cys7, Cys2-Cys6, Cys3-Cys4, Cys5-Cys11, Cys8-Cys10, Cys9-Cys13, Cys12-Cys14. Group 4

consists of monomeric disintegrins similar to Kistrin, and the disulfide pattern of these molecules is Cys1-Cys5, Cys2-Cys4, Cys3-Cys9, Cys6-Cys8, Cys7-Cys11, Cys10-Cys12. Group 5 is the Salmosin group, also composed of monomeric disintegrins, and their disulfide pattern is Cys1-Cys3, Cys2-Cys4, Cys5-Cys8, Cys7-Cys9, Cys6-Cys11, Cys10-Cys12. Group 6 includes dimeric disintegrins, with an intrachain disulfide pattern characterized by Cys1-Cys7, Cys4-Cys6, Cys5-Cys9, Cys8-Cys10, while Cys2 and Cys3 form a disulfide bridge with the other subunit of the dimer. Lastly, group 7 comprises short disintegrins, and the disulfide pattern of these molecules can be described as Cys1-Cys4, Cys2-Cys7, Cys3-Cys6, and Cys5-Cys8 [89].

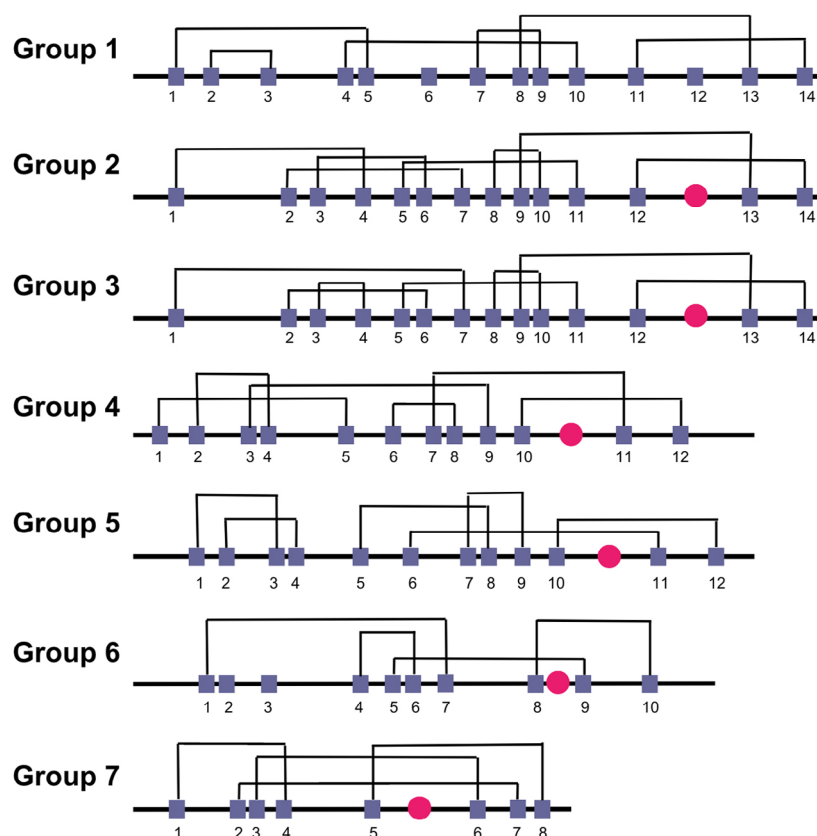


Figure 4. Disulfide bonding pattern for each group within the disintegrin family. (**Group 1:**) DAM/SVMP subfamily-like disintegrin domain proteins; (**Group 2:**) Bitistatin A-like disintegrins; (**Group 3:**) Bitistatin B-like disintegrins; (**Group 4:**) Kistrin-like disintegrins; (**Group 5:**) Salmosin-like disintegrins; (**Group 6:**) Dimeric disintegrins; (**Group 7:**) Short disintegrins. Purple squares indicate cysteine residues, while pink circle indicates the integrin-binding motif.

Function and potential applications of snake venom disintegrins

Snake venom disintegrins can selectively bind to integrins, which are strongly tied to the specific motifs found in their structure [90] (Figure 5). This way, during envenomation, they exhibit a wide array of functions, serving various crucial roles, like binds to platelet receptors, impeding their aggregation, and resulting in the onset of bleeding disorders [91]. Consequently, disintegrins contribute to disrupting hemostatic processes (Table 2).

Some snake venom disintegrins can inhibit bone resorption *in vitro* [92] and can also be used as a diagnostic tool. An example, we cite bitistatin, which can potentially be used in molecular imaging of thromboembolic diseases [93].

It has also been demonstrated that disintegrins can interfere with the chemotaxis of human neutrophils to sites of inflammation and tissue injury [55] and exhibit antiparasitic activity against *Leishmania infantum* promastigotes [56].

Intriguingly, certain disintegrins have demonstrated notable anti-tumor and anti-angiogenic properties (Table 3). This remarkable feature opens up new possibilities for their utilization as potential therapeutic agents in cancer treatment, and by targeting tumor growth and impeding blood vessel formation, these disintegrins exhibit promising potential in medical research and innovation.

Snake venom disintegrins: from lab bench to market

Animal venoms are rich mixtures of components that may have important pharmacological actions. Many of these components have already been extensively studied to become drugs, and after approval by the Food and Drug Administration (FDA), turned into widely used molecules [94].

A very important example of a drug derived from animal toxins is captopril (Capoten®, Bristol-Myers Squibb, New York, NY, EUA), which is widely used against hypertension [95]. This was the first animal-derived drug approved by the FDA in 1981, which mechanism is responsible for inhibiting the angiotensin-converting enzyme (ACE). Thus, the production of angiotensin II is also inhibited, reducing hypertension effects, and increasing the hypotensive action of bradykinin, known as a bradykinin potentiating factor (BPF) [96–99]. Although it is a very effective natural molecule, the captopril used in medicaments is a synthetic molecule based on the miniaturization of the original molecule and chemically modified to be administered orally [94, 100]. In sequence, in 1985, the FDA approved Enalapril (Vasotec®, Merck, Darmstadt, Germany), which was also used to treat hypertension and congestive heart failure [94, 101].

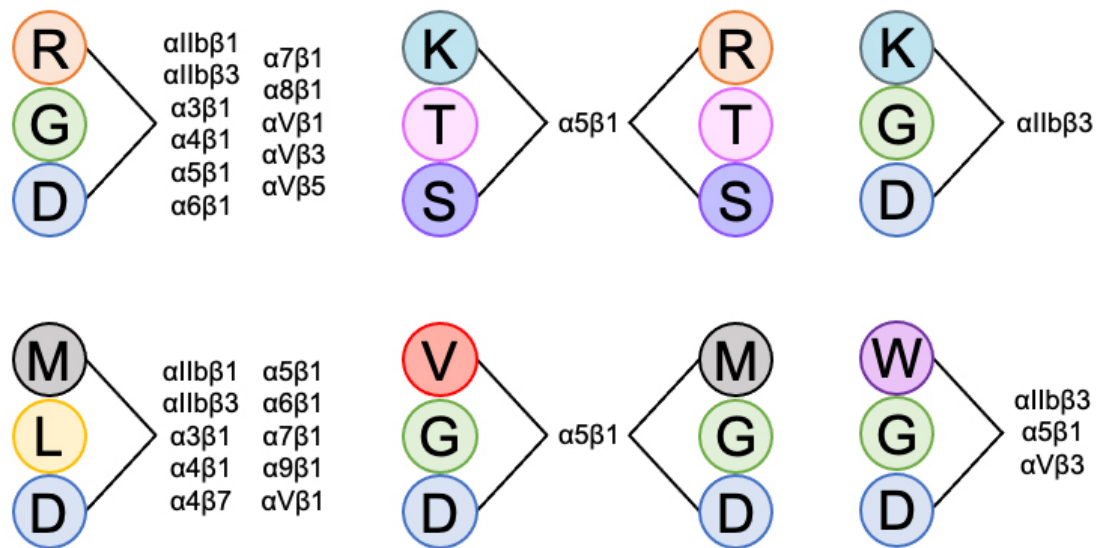
Some disintegrins have been extensively studied and are nowadays FDA-approved drugs as well. Tirofiban (Aggrastat®,

Table 2. Snake venom disintegrins that can act on the hemostatic system.

| Disintegrin (snake venom) | Motif | Integrins | Action | Ref. |
|--|-------------|------------------------|---|-----------|
| Accutin (<i>Agkistrodon acutus</i>) | RGD | αIIbβ3 | Inhibit human platelet aggregation induced by ADP, collagen, fibrinogen, thrombin and the thromboxane analogue U46619 Inhibit platelet aggregation of platelet-rich plasma | [134] |
| Albolabrin (<i>Trimeresurus albolabris</i>) | RGD | αIIbβ3 | Block platelet-fibrinogen interaction Inhibit ADP-induced platelet aggregation of platelet-rich plasma | [111,135] |
| Applagin (<i>Agkistrodon piscivorus piscivorus</i>) | RGD | αIIbβ3 | Block platelet aggregation induced by ADP, collagen, thrombin, and arachidonic acid | [110] |
| Barbourin (<i>Sistrurus miliarius barbouri</i>) | KGD | αIIbβ3 | Inhibit fibrinogen to bind αIIbβ3 integrin | [78] |
| Basilicin (<i>Crotalus basiliscus</i>) | RGD | αvβ3 α5β1 αIIbβ3 | Inhibit platelet aggregation, adhesion to vitronectin, and fibrinogen to binding integrins | [136] |
| Bitistatin (<i>Bitis arietans</i>) | RGD | αIIbβ3 | Block platelet-fibrinogen interaction Inhibit ADP-induced platelet aggregation of platelet-rich plasma | [135] |
| CC5 (<i>Cerastes cereastes</i>) | RGD | αIIbβ3 | Inhibit ADP-induced platelet aggregation of platelet-rich plasma | [88] |
| CC8 (<i>Cerastes cereastes</i>) | RGD/ WRG | αIIbβ3 | Inhibit ADP-induced platelet aggregation of platelet-rich plasma | [88] |
| Cerastin (<i>Cerastes cereastes</i>) | RGD | αvβ3 α5β1 αIIbβ3 | Inhibit platelet aggregation, adhesion to vitronectin, and fibrinogen to binding integrins | [136] |
| Cereberin (<i>Crotalus viridis cereberus</i>) | RGD | αvβ3 α5β1 αIIbβ3 | Inhibit platelet aggregation, adhesion to vitronectin, and fibrinogen to binding integrins | [136] |
| Contortrostatin (<i>Agkistrodon contortrix contortrix</i>) | RGD | αIIbβ3 | Inhibit ADP-induced platelet aggregation of platelet-rich plasma from humans, dogs and rabbits | [114] |
| Crotatoxin (<i>Crotalus atrox</i>) | RGD | αvβ3 α5β1 αIIbβ3 | Inhibit platelet aggregation, adhesion to vitronectin, and fibrinogen to binding integrins | [136] |
| Cotiarin (<i>Bothrops cotiara</i>) | RGD | αvβ3 α5β1 αIIbβ3 | Inhibit platelet aggregation, adhesion to vitronectin, and fibrinogen to binding integrins | [136] |
| Durissin (<i>Crotalus durissus durissus</i>) | RGD | αvβ3 α5β1 αIIbβ3 | Inhibit platelet aggregation, adhesion to vitronectin, and fibrinogen to binding integrins | [136] |
| EC3 (<i>Echis carinatus</i>) | VGD/ MLD | αIIbβ3 | Inhibit fibrinogen to bind αIIbβ3 integrin | [137] |
| Echistatin (<i>Echis carinatus</i>) | RGD | αIIbβ3 | Block platelet-fibrinogen interaction Inhibit ADP-induced platelet aggregation of platelet-rich plasma | [135] |
| Elegantin (<i>Trimeresurus elegans</i>) | RGD | αIIbβ3 | Inhibit ADP-induced platelet aggregation of platelet-rich plasma | [111] |
| EMF-10 (<i>Eristicophis macmahoni</i>) | RGD/ MGD | αIIbβ3 | Inhibit ADP-induced platelet aggregation | [47] |
| Eristostatin (<i>Eristicophis macmahoni</i>) | RGD | αIIbβ3 | Able to bind in ADP-, thrombin-induced, and resting platelet | [138] |
| Flavordin (<i>Trimeresurus flavoviridis</i>) | RGD | αIIbβ3 | Block platelet-fibrinogen interaction Inhibit ADP-induced platelet aggregation of platelet-rich plasma | [135] |
| Jararacin (<i>Bothrops jararaca</i>) | RGD | αvβ3 α5β1 αIIbβ3 | Inhibit ADP- and thrombin-induced platelet aggregation Inhibit adhesion to vitronectin, and fibrinogen to binding integrins | [136,139] |
| Jarastatin (<i>Bothrops jararaca</i>) | RGD | αIIbβ3 | Inhibit ADP- and thrombin-induced platelet aggregation | [139] |
| Jerdostatin (<i>Trimeresurus jerdonii</i>) | RTS | αIIbβ3 | Inhibit fibrinogen to bind αIIbβ3 integrin | [140] |
| Lachesin (<i>Lachesis mutus</i>) | RGD | αvβ3 α5β1 αIIbβ3 | Inhibit platelet aggregation, adhesion to vitronectin, and fibrinogen to binding integrins | [136] |

Table 2. Cont.

| Disintegrin (snake venom) | Motif | Integrins | Action | Ref. |
|---|-------------|---|---|-------|
| Lebein (<i>Macrovipera lebetina</i>) | RGD | ? | Inhibit ADP-induced platelet aggregation of platelet-rich plasma | [120] |
| Lutosin (<i>Crotalus viridis lutosus</i>) | RGD | $\alpha v\beta 3$ $\alpha 5\beta 1$ $\alpha IIb\beta 3$ | Inhibit platelet aggregation, adhesion to vitronectin, and fibrinogen to binding integrins | [136] |
| Mojastin-1 and -2 (<i>Crotalus scutulatus scutulatus</i>) | RGD | $\alpha 5\beta 1$ | Inhibit ADP-induced platelet aggregation of whole blood | [129] |
| Molossin (<i>Crotalus molossus molossus</i>) | RGD | $\alpha v\beta 3$ $\alpha 5\beta 1$ $\alpha IIb\beta 3$ | Inhibit platelet aggregation, adhesion to vitronectin, and fibrinogen to binding integrins | [136] |
| Multisquamatin (<i>Echis multisquamatus</i>) | RGD | $\alpha IIb\beta 3$ | Inhibit ADP-induced platelet aggregation of platelet-rich plasma from humans, dogs and rabbits | [114] |
| Rhodocetin (<i>Calloselasma rhodostoma</i>) | ? | ? | Inhibit collagen-induced platelet aggregation | [117] |
| Saxatillin (<i>Gloydius saxatilis</i>) | RGD | $\alpha IIb\beta 3$ | Inhibit the interaction of integrins and fibrinogen Inhibit ADP-induced platelet aggregation | [66] |
| Triflavin (<i>Protobothrops flavoviridis</i>) | RGD | $\alpha IIb\beta 3$ | Inhibit ADP-induced and resting platelet | [113] |
| Trigramin (<i>Trimeresurus gramineus</i>) | RGD | $\alpha IIb\beta 3$ | Inhibit the interaction of ADP-induced platelet and fibrinogen Inhibit chymotrypsin-treated platelet aggregation Bind to resting platelet | [44] |
| Viplebedin-2 (<i>Vipera lebetina</i>) | VGD/ MLD | ? | Inhibit ADP- and collagen-induced platelet aggregation Inhibit platelet adhesion | [137] |
| Viridin (<i>Crotalus viridis viridis</i>) | RGD | $\alpha v\beta 3$ $\alpha 5\beta 1$ $\alpha IIb\beta 3$ | Inhibit platelet aggregation, adhesion to vitronectin, and fibrinogen to binding integrins | [136] |

**Figure 5.** Interaction of snake venom disintegrin motifs with different integrins.

Medicure International, Inc., Winnipeg, Manitoba, Canada) is also a synthetic drug based on the RGD domain of echistatin from *Echis carinatus* [102]. Furthermore, it has a chemical modification that increases its interaction with platelet glycoproteins, specifically with their GPIIb/IIIa receptors [76]. Thus, this

drug can inhibit platelet aggregation and other thrombotic actions due to its competition with fibrinogen for the recognition site of the RGD domain in the GPIIb/IIIa receptor [102, 103]. Tirofiban was approved by the FDA in 1998 as a treatment for acute coronary syndrome [104].

Table 3. Discovery of snake venom disintegrins that can act as anticancer agents.

| Disintegrin (snake venom) | Motif | Cell line (cancer type) | Integrins | Action | Ref. |
|--|-------------|--|--|--|-----------|
| Accutin (<i>Agkistrodon acutus</i>) | RGD | HUVEC (human non-cancer cell) | $\alpha v\beta 3$ | Induce apoptosis Inhibit angiogenesis <i>in vitro</i> and <i>in vivo</i> | [141] |
| Albolabrin (<i>Trimeresurus albolabris</i>) | RGD | B16-F10 (murine melanoma) | $\alpha 5\beta 1$ $\alpha v\beta 3$ $\alpha 6\beta 1$ | Inhibit cell-matrix attachment <i>in vitro</i> Inhibit metastasis of tumor cells | [142] |
| Alternagin-C (<i>Bothrops alternatus</i>) | ECD | HUVEC (human non-cancer cell) MDA-MB-231 (human breast cancer) HMEC-1 (human cells from tumor microenvironment) Human fibroblasts | $\alpha 2\beta 1$ | Modulates cell adhesion, migration and proliferation Inhibit adhesion, viability and migration of VEGF-induced cell Inhibit angiogenesis <i>in vitro</i> Infer in tumor progression | [143–145] |
| Barbourin (<i>Sistrurus mliarius barbouri</i>) | KGD | B16-F10 (murine melanoma) | $\alpha v\beta 3$ $\alpha v\beta 1$ | Inhibit cell adhesion | [146] |
| Bitistatin (<i>Bitis arietans</i>) | RGD | HUVEC (human non-cancer cell) | $\alpha v\beta 3$ | Inhibit cell adhesion | [147] |
| CC5 (<i>Cerastes cereastes</i>) | RGD | A5 (murine non-cancer cell) JY (human lymphoblastoid cell) K562 (human myelogenous leukemia) CHO K1 (murine non-cancer cell) | $\alpha 5\beta 1$ $\alpha v\beta 3$ | Inhibit cell adhesion | [88] |
| CC8 (<i>Cerastes cereastes</i>) | RGD/ WRG | A5 (murine non-cancer cell) JY (human lymphoblastoid cell) K562 (human myelogenous leukemia) CHO K1 (murine non-cancer cell) | $\alpha 5\beta 1$ $\alpha v\beta 3$ | Inhibit cell adhesion | [88] |
| Contortrostatin (<i>Agkistrodon contortrix contortrix</i>) | RGD | M24 met (human metastatic melanoma) | $\alpha 5\beta 1$ $\alpha v\beta 1$ | Inhibit cell adhesion <i>in vitro</i> Inhibit lung colonization <i>in vivo</i> | [148] |
| DisBa-01 (<i>Bothrops alternatus</i>) | RGD | HMEC-1 (human non-cancer cell) MDA-MB-231 (human breast cancer) B16-F10 (murine melanoma) | $\alpha v\beta 3$ | Inhibit angiogenesis Inhibit cell adhesion and proliferation | [149] |
| Disintegrin (<i>Crotalus durissus collilineatus</i>) | Non-RGD | MDA-MB-231 (human breast cancer) | ? | Inhibit cell migration | [132] |
| EC3 (<i>Echis carinatus</i>) | VGD/ MLD | A5 (murine non-cancer cell) VNRC3 (murine non-cancer cell) CHO (murine non-cancer cell) JY (human lymphoblastoid cell) K562 (human myelogenous leukemia) Jurkat (human acute T cell leukemia) CHO K1 (murine non-cancer cell) RPMI886 (human chronic myelogenous leukaemia) | $\alpha 11\beta 3$ $\alpha 5\beta 1$ $\alpha v\beta 3$ $\alpha 4\beta 1$ $\alpha 4\beta 7$ | Inhibit cell adhesion | [46] |
| EC6 (<i>Echis carinatus</i>) | MLD/ RGD | A5 (murine non-cancer cell) K562 (human myelogenous leukemia) Jurkat (human acute T cell leukemia) | $\alpha 5\beta 1$ $\alpha 4\beta 1$ | Inhibit cell adhesion | [118] |
| Echistatin (<i>Echis carinatus</i>) | RGD | A5 (murine non-cancer cell) JY (human lymphoblastoid cell) K562 (human myelogenous leukemia) SW480 (human colon adenocarcinoma) Jurkat (human acute T cell leukemia) | $\alpha 5\beta 1$ $\alpha v\beta 3$ | Inhibit cell adhesion Inhibit angiogenesis | [150] |
| EMF-10 (<i>Eristicophis macmahoni</i>) | RGD/ MGD | K562 (human myelogenous leukemia) | $\alpha 5\beta 1$ | Inhibit cell adhesion | [47] |

Table 3. Cont.

| Disintegrin (snake venom) | Motif | Cell line (cancer type) | Integrins | Action | Ref. |
|---|---------|--|--|---|--------------|
| EO5 (<i>Echis ocellatus</i>) | MLD/VGD | A5 (murine non-cancer cell) K562 (human myelogenous leukemia) Jurkat (human acute T cell leukemia) | $\alpha 4\beta 1$ | Blocked cell adhesion | [124] |
| Eristostatin (<i>Eristicophis macmahoni</i>) | RGD | A375 (human malignant melanoma) HT1080 (human fibrosarcoma) | $\alpha 1\text{Ib}\beta 3$ $\alpha 5\beta 1$ $\alpha \text{v}\beta 3$ | Inhibit cell adhesion | [151] |
| Jerdostatin (<i>Trimeresurus jerdonii</i>) | RTS | JY (human lymphoblastoid cell) K562 (human myelogenous leukemia) SW480 (human colon adenocarcinoma) Jurkat (human acute T cell leukemia) | $\alpha 1\text{Ib}\beta 3$ $\alpha 5\beta 1$ $\alpha 1\beta 1$ $\alpha 2\beta 1$ $\alpha 6\beta 1$ $\alpha \text{v}\beta 3$ $\alpha 4\beta 1$ $\alpha 9\beta 1$ | Inhibit cell adhesion | [140] |
| Lebein (<i>Macrovipera lebetina</i>) | RGD | LS174, HCT116, and HT29 (human colon adenocarcinoma) SK-MEL-28 and LU-1205 (human melanoma) | $\alpha 5\beta 1$ $\alpha \text{v}\beta 3$ | Induce apoptosis Inhibit cell migration and adhesion Inhibit angiogenesis by down-regulating VEGF and NRP1 Expression | [152,153] |
| Lebestatin (<i>Macrovipera lebetina</i>) | KTS | CHO (murine non-cancer cell) HT29-D4 (human colonic adenocarcinoma) HT1080 (human fibrosarcoma) K562 (human myelogenous leukemia) IGROV1 (human ovarian adenocarcinoma) HMEC-1 (human non-cancer cell) PC12 (rat pheochromocytoma) | $\alpha 1\beta 1$ | Inhibit cell migration and adhesion Inhibit angiogenesis | [59] |
| Mojastin-1 and -2 (<i>Crotalus scutulatus scutulatus</i>) | RGD | BXPC-3 (human pancreatic adenocarcinoma) | $\alpha 3\beta 1$ | Inhibit cell proliferation, migration and adhesion Induce apoptosis | [154] |
| Obtustatin (<i>Macrovipera lebetina</i>) | KTS | A5 (murine non-cancer cell) K562 (human myelogenous leukemia) Jurkat (human acute T cell leukemia) | $\alpha 1\beta 1$ | Inhibit angiogenesis <i>in vivo</i> | [77,150] |
| Purpureomaculin (<i>Trimeresurus purpureomaculatus</i>) | RGD | MCF-7 (human breast adenocarcinoma) | $\alpha \text{v}\beta 5$ | Inhibit cell growth | [155] |
| Rhodocetin (<i>Calloselasma rhodostoma</i>) | ? | HT1080 (human fibrosarcoma) | $\alpha 2\beta 1$ | Inhibit cell adhesion and migration | [156] |
| Rhodostomin (<i>Calloselasma rhodostoma</i>) | RGD | B16-F10 (murine melanoma) HUVEC (human non-cancer cell) | $\alpha \text{v}\beta 3$ | Inhibit angiogenesis Suppress tumor growth <i>in vivo</i> Inhibit cell proliferation | [157] |
| Saxatillin (<i>Gloydus saxatilis</i>) | RGD | HUVEC and SMC (human non-cancer cells) MDAH2774 (human ovarian cancer cells) | $\alpha \text{v}\beta 3$ | Inhibit cell proliferation, migration and adhesion Inhibit angiogenesis Inhibit tumor metastasis | [66,158,159] |
| Triflavin (<i>Protobothrops flavoviridis</i>) | RGD | B16-F10 (murine melanoma) | $\alpha 1\text{Ib}\beta 3$ | Inhibit cell adhesion | [160] |
| Tzabcanin (<i>Crotalus simus tzabcan</i>) | RGD | A-357 (human malignant melanoma) Colo-205 (human colorectal adenocarcinoma) MCF-7 (human breast adenocarcinoma) A-549 (human lung adenocarcinoma) | $\alpha \text{v}\beta 3$ | Inhibit cell migration and adhesion | [79,161] |

Table 3. Cont.

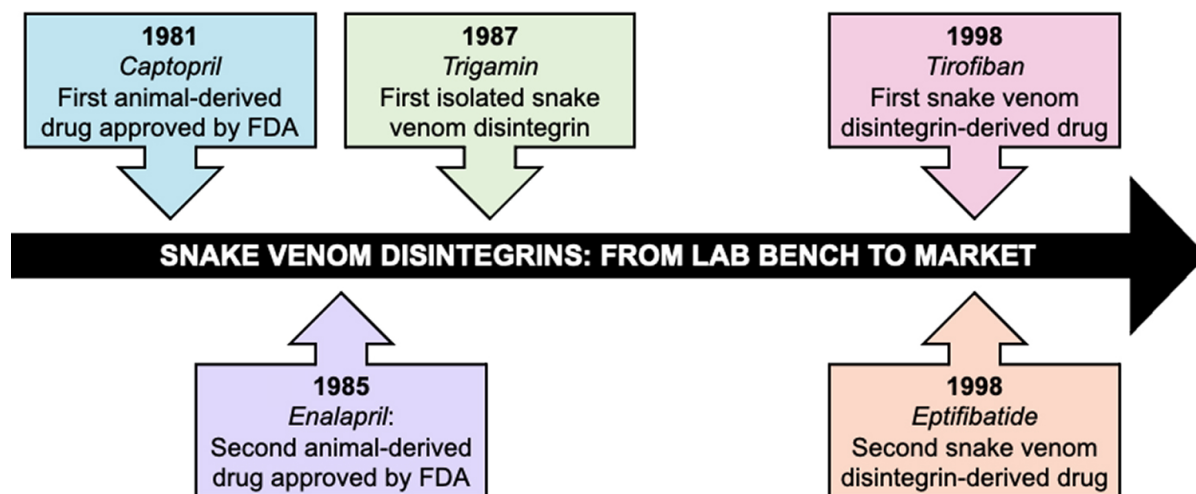
| Disintegrin (snake venom) | Motif | Cell line (cancer type) | Integrins | Action | Ref. |
|---|-------------|--|-------------------|-----------------------|-------|
| VA6 (<i>Vipera ammodytes</i>) | RGD | A5 (murine non-cancer cell) K562 (human myelogenous leukemia) Jurkat (human acute T cell leukemia) | $\alpha 5\beta 1$ | Inhibit cell adhesion | [124] |
| VB7 (<i>Vipera berus</i>) | RGD/ KGD | A5 (murine non-cancer cell) K562 (human myelogenous leukemia) Jurkat (human acute T cell leukemia) | $\alpha 5\beta 1$ | Inhibit cell adhesion | [124] |
| Viperistatin (<i>Vipera palestinae</i>) | KTS | A5 (murine non-cancer cell) JY (human lymphoblastoid cell) K562 (human myelogenous leukemia) SW480 (human colon adenocarcinoma) | $\alpha 1\beta 1$ | Inhibit cell adhesion | [126] |
| VLO5 (<i>Vipera lebetina obtusa</i>) | VGD/ MLD | A5 (murine non-cancer cell) K562 (human myelogenous leukemia) Jurkat (human acute T cell leukemia) | $\alpha 4\beta 1$ | Block cell adhesion | [124] |

Another antiplatelet compound, Eptifibatide (Integrilin®, Millennium Pharmaceuticals, Inc.), was also approved by the FDA in 1998, and licensed in 2005, to Schering-Plough [94]. Its development coincided with the research for the synthetic peptide analogs of barbourin, a disintegrin from *Sistrurus miliarius barbouri* [78]. The conservative substitution of arginine (R) amino acids with lysine (K) in barbourin enhances its specificity towards the platelet glycoprotein complex GPIIb/IIIa compared to other disintegrins containing the RGD motif [78]. However, this specificity may also be influenced by the size of the peptide ring formed by disulfide bridges and the amino acids near the KGD domain. As a result, new peptides have been synthesized for potential clinical use, such as Eptifibatide, a synthetic heptapeptide that is more resistant to proteolysis [105–107].

Since the approval of the first venom-derived drug and the beginning of disintegrins' saga in Toxinology [44], it took over 10 years of research and effort for the first medication derived from snake venom disintegrins also to be approved

(Figure 6). However, it was already known that venoms and their components could cause modifications in the human body, and their applicability in clinical settings had been recognized.

Currently, a product based on snake venom toxins has been attracting attention: Heterologous Fibrin Sealant. This sealant is composed of a thrombin-like enzyme from *Crotalus durissus terrificus* venom and fibrinogen-rich cryoprecipitate extracted from the blood of *Bubalus bubalis buffaloes*. It can be used for the treatment of chronic venous ulcers, as demonstrated in phase I/II clinical trials, highlighting its effectiveness and safety [108]. While there are currently no clinical studies using snake venom disintegrins, human disintegrins, especially ADAMs, have been targeted for the therapy of other pathological conditions in clinical trials, such as cirrhosis and portal hypertension (NCT04267406), epithelial dysfunction (NCT00898859), idiopathic pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension (NCT05478226), among others [109].

**Figure 6.** Timeline of snake venom disintegrins, from the beginning of disintegrins' saga in Toxinology until their FDA approval.

Conclusion

Snake venom disintegrins' saga was started in 1987 and classified these molecules as small peptides that can inhibit the function of integrins, which are cell surface receptors involved in various cellular processes like cell adhesion, migration, and signaling. Integrins are important for cell adhesion to extracellular matrix proteins, mediating cell-cell interactions, and interfering in integrin-mediated processes, as snake venom disintegrins can have various effects on cells and tissues.

Among their unique properties, snake venom disintegrins can inhibit platelet aggregation, *i.e.*, bind to integrins on platelets, preventing their aggregation and potentially disrupting the clotting process. Consequently, two important antiplatelet drugs were based on disintegrins from snake venoms, and they are on the market nowadays.

Moreover, snake venom disintegrins have shown anti-cancer properties by targeting integrins that are overexpressed in specific cancer cells and blocking integrin-mediated signaling pathways. These disintegrins can also inhibit tumor growth and metastasis. Notably, although snake venom disintegrins possess therapeutic potential, they exhibit high potency and can manifest toxicity. Thus, rigorous investigation is required before contemplating snake venom disintegrin use in medical applications.

Abbreviations

ACE: angiotensin-converting enzyme; ADAM: a disintegrin and metalloprotease; BPF: bradykinin potentiating factor; C: cysteine-rich domain; CRISP: cysteine-rich secretory protein; CTL: C-type lectins; DI: disintegrin-like domain; FDA: Food and Drug Administration; 3FTx: three-finger toxins; LAO: L-amino acid oxidase; M: typical metalloproteinase domain; PLA₂: phospholipase A₂; SVMP: snake venom metalloproteases; SVSP: snake venom serine protease.

Availability of data and materials

Not applicable.

Funding

This study was supported by *Fundação de Amparo à Pesquisa do Estado de São Paulo* (FAPESP, São Paulo Research Foundation, scholarships to GOA n. 2020/15670-5 and n. 2022/05554-3 and to ISO n. 2020/13176-3 and n. 2022/08964-8, grants to ECA n. 2019/10173-6 and n. 2021/11936-3 and to SVS n. 2022/04804-6), *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior* (CAPES, Coordination of Superior Level Staff Improvement, scholarship to GOA n. 88887.661488/2022-00) and *Conselho Nacional de Desenvolvimento Científico e Tecnológico* (CNPq, The National Council for Scientific and Technological Development, scholarships to ECA n. 309399/2021-1 and SVS n. 303781/2022-0).

Competing interests

The authors declare that they have no competing interests.

Author contributions

GOA and ISO conceived the main idea of this work and drafted the manuscript. ECA provided essential contributions to the manuscript. SVS was a major contributor to writing the manuscript. SVS and ECA review the final manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

References

- Munawar A, Ali S, Akrem A, Betzel C. Snake Venom Peptides: Tools of Biodiscovery. *Toxins*. 2018 Nov;10(11):474.
- Casewell NR, Jackson TNW, Laustsen AH, Sunagar K. Causes and Consequences of Snake Venom Variation. *Trends Pharmacol Sci*. 2020 Aug;41(8):570–81.
- Westeen EP, Durso AM, Grundler MC, Rabosky DL, Davis Rabosky AR. What makes a fang? Phylogenetic and ecological controls on tooth evolution in rear-fanged snakes. *BMC Evol Biol*. 2020;20:80.
- Chippaux JP. Snakebite envenomation turns again into a neglected tropical disease! *J Venom Anim Toxins incl Trop Dis*. 2017;23:38. <https://doi.org/10.1186/s40409-017-0127-6>.
- World Health Organization. Snakebite envenoming [Internet]. 2021 [cited 2023 May 11]. Available from: <https://www.who.int/news-room/fact-sheets/detail/snakebite-envenoming>.
- Gutiérrez JM, Calvete JJ, Habib AG, Harrison RA, Williams DJ, Warrell DA. Snakebite envenoming. *Nat Rev Dis Primers*. 2017 Sep 14;3:17063.
- Mohamed Abd El-Aziz, Garcia Soares, Stockand. Snake Venoms in Drug Discovery: Valuable Therapeutic Tools for Life Saving. *Toxins (Basel)*. 2019 Oct;11(10):564.
- Calvete JJ, Juárez P, Sanz L. Snake venomomics. Strategy and applications. *J Mass Spectrom*. 2007 Nov;42(11):1405–14.
- Lomonte B, Fernández J, Sanz L, Angulo Y, Sasa M, Gutiérrez JM, Calvete JJ. Venomous snakes of Costa Rica: Biological and medical implications of their venom proteomic profiles analyzed through the strategy of snake venomomics. *J Proteomics*. 2014 Jun 13;105:323–39.
- Tasoulis T, Pukala TL, Isbister GK. Investigating Toxin Diversity and Abundance in Snake Venom Proteomes. *Front Pharmacol*. 2022 Jan 14;12:768015.
- Tasoulis T, Isbister G. A Review and Database of Snake Venom Proteomes. *Toxins (Basel)*. 2017 Sep 18;9(9):290.
- Arruda Macedo J, Fox J, Souza Castro M. Disintegrins from Snake Venoms and their Applications in Cancer Research and Therapy. *Curr Protein Pept Sci*. 2015;16(6):532–48.
- Lucena S, Castro R, Lundin C, Hofstetter A, Alaniz A, Suntravat M, Sánchez EE. Inhibition of pancreatic tumoral cells by snake venom disintegrins. *Toxicol*. 2015 Jan;93:136–43.
- Cesar PHS, Braga MA, Trento MVC, Menaldo DL, Marcussi S. Snake Venom Disintegrins: An Overview of their Interaction with Integrins. *Curr Drug Targets*. 2019;20(4):465–77.
- Bianconi D, Unseld M, Prager G. Integrins in the Spotlight of Cancer. *Int J Mol Sci*. 2016 Dec 6;17(12):2037.
- Takada Y, Ye X, Simon S. The integrins. *Genome Biol*. 2007;8:215.
- Mezu-Ndubuisi OJ, Maheshwari A. The role of integrins in inflammation and angiogenesis. *Pediatr Res*. 2021 May;89(7):1619–26.
- Arnaout MA, Mahalingam B, Xiong JP. Integrin structure allostery, and bidirectional signaling. *Annu Rev Cell Dev Biol*. 2014;30:381–410.
- Morse EM, Brahme NN, Calderwood DA. Integrin Cytoplasmic Tail Interactions. *Biochemistry*. 2014 Feb 11;53(5):810–20.

20. Tsuji T. Physiological and Pathological Roles of $\alpha 3 \beta 1$ Integrin. *J Membr Biol.* 2004 Aug 1;200(3):115–32.
21. Bachmann M, Kukkurainen S, Hytönen VP, Wehrle-Haller B. Cell Adhesion by Integrins. *Physiol Rev.* 2019 Oct 1;99(4):1655–99.
22. Koivisto L, Heino J, Häkkinen L, Larjava H. Integrins in Wound Healing. *Adv Wound Care.* 2014 Dec 1;3(12):762–83.
23. Lilja J, Ivaska J. Integrin activity in neuronal connectivity. *J Cell Sci.* 2018 Jun 15;131(12):jcs212803.
24. Park YK, Goda Y. Integrins in synapse regulation. *Nat Rev Neurosci.* 2016 Dec;17(12):745–56.
25. Conroy KP, Kitto LJ, Henderson NC. αv integrins: key regulators of tissue fibrosis. *Cell Tissue Res.* 2016 Sep;365(3):511–9.
26. Finney AC, Stokes KY, Pattillo CB, Orr AW. Integrin signaling in atherosclerosis. *Cell Mol Life Sci.* 2017 Jun;74(12):2263–82.
27. Seguin L, Desgrosellier JS, Weis SM, Cheresh DA. Integrins and cancer: regulators of cancer stemness, metastasis, and drug resistance. *Trends Cell Biol.* 2015;25:234–40.
28. Desgrosellier JS, Cheresh DA. Integrins in cancer: biological implications and therapeutic opportunities. *Nat Rev Cancer.* 2010 Jan;10(1):9–22.
29. Niu J, Li Z. The roles of integrin $\alpha v \beta 6$ in cancer. *Cancer Lett.* 2017 Sep 10;403:128–37.
30. Hamidi H, Ivaska J. Every step of the way: integrins in cancer progression and metastasis. *Nat Rev Cancer.* 2018 Sep;18(9):533–48.
31. Adorno-Cruz V, Liu H. Regulation and functions of integrin $\alpha 2$ in cell adhesion and disease. *Genes Dis.* 2019 Mar;6(1):16–24.
32. Lazarovici P, Marcinkiewicz C, Lelkes PI. From Snake Venom's Disintegrins and C-Type Lectins to Anti-Platelet Drugs. *Toxins (Basel).* 2019 May 27;11(5):303.
33. Markland FS, Swenson S. Snake venom metalloproteinases. *Toxicon.* 2013;62:3–18.
34. Takeda S. ADAM and ADAMTS Family Proteins and Snake Venom Metalloproteinases: A Structural Overview. *Toxins (Basel).* 2016 May 17;8(5):155.
35. Sanz L, Harrison RA, Calvete JJ. First draft of the genomic organization of a PIII-SVMP gene. *Toxicon.* 2012 Sep 15;60(4):455–69.
36. Zychar BC, Clissa PB, Carvalho E, Alves AS, Baldo C, Faquim-Mauro EL, Gonçalves LRC. Modulation of Adhesion Molecules Expression by Different Metalloproteases Isolated from *Bothrops* Snakes. *Toxins (Basel).* 2021 Nov;13(11):803.
37. Casewell NR. On the ancestral recruitment of metalloproteinases into the venom of snakes. *Toxicon.* 2012 Sep 15;60(4):449–54.
38. Stone AL, Kroeger M, Sang QXA. Structure–Function Analysis of the ADAM Family of Disintegrin-Like and Metalloproteinase-Containing Proteins (Review). *J Protein Chem.* 1999 May;18(4):447–65.
39. Okuda D, Koike H, Morita T. A New Gene Structure of the Disintegrin Family: A Subunit of Dimeric Disintegrin Has a Short Coding Region. *Biochemistry.* 2002;41:14248–54.
40. Juarez P, Comas I, Gonzalez-Candelas F, Calvete JJ. Evolution of Snake Venom Disintegrins by Positive Darwinian Selection. *Mol Biol Evol.* 2008 Nov;25(11):2391–407.
41. Calvete JJ. Brief History and Molecular Determinants of Snake Venom Disintegrin Evolution. In: Kini RM, Clemetson KJ, Markland FS, McLane MA, Morita T, editors. *Toxins and Hemostasis* [Internet]. Dordrecht: Springer Netherlands; 2010 [cited 2023 May 18]. p. 285–300. Available from: http://link.springer.com/10.1007/978-90-481-9295-3_18.
42. Moura-da-Silva A, Almeida M, Portes-Junior J, Nicolau C, Gomes-Neto F, Valente R. Processing of Snake Venom Metalloproteinases: Generation of Toxin Diversity and Enzyme Inactivation. *Toxins (Basel).* 2016 Jun;8(6):183.
43. Kini RM, Evans HJ. Structural domains in venom proteins: Evidence that metalloproteinases and nonenzymatic platelet aggregation inhibitors (disintegrins) from snake venoms are derived by proteolysis from a common precursor. *Toxicon.* 1992 Mar;30(3):265–93.
44. Huang TF, Holt JC, Lukasiewicz H, Niewiarowski S. Trigramin. A low molecular weight peptide inhibiting fibrinogen interaction with platelet receptors expressed on glycoprotein IIb-IIIa complex. *J Biol Chem.* 1987 Nov 25;262(33):16157–63.
45. Gould RJ, Polokoff MA, Friedman PA, Huang T-F, Holt JC, Cook JJ, Niewiarowski S. Disintegrins: A Family of Integrin Inhibitory Proteins from Viper Venoms. *Proc Soc Exp Biol Med.* 1990 Nov;195(2):168–71.
46. Marcinkiewicz C, Calvete JJ, Marcinkiewicz MM, Raida M, Vijay-Kumar S, Huang Z, Lobb RR, Niewiarowski S. EC3, a Novel Heterodimeric Disintegrin from *Echis carinatus* Venom, Inhibits $\alpha 4$ and $\alpha 5$ Integrins in an RGD-independent Manner. *J Biol Chem.* 1999 Apr 30;274(18):12468–73.
47. Marcinkiewicz C, Calvete JJ, Vijay-Kumar S, Marcinkiewicz MM, Raida M, Schick P, Lobb RR, Niewiarowski S. Structural and Functional Characterization of EMF10, a Heterodimeric Disintegrin from *Eristocophis macmahoni* Venom That Selectively Inhibits $\alpha 5 \beta 1$ Integrin. *Biochemistry.* 1999 Oct 5;38(40):13302–9.
48. Mohit Trikha, Yves A. De Clerck, Francis S. Markland. Contortrostatin, a Snake Venom Disintegrin, Inhibits $\beta 1$ Integrin-mediated Human Metastatic Melanoma Cell Adhesion and Blocks Experimental Metastasis. *Cancer Res.* 1994 Sep 15;54(18):4993–8.
49. Kawasaki T, Sakai Y, Taniuchi Y, Sato K, Maruyama K, Shimizu M, Kaku S, Yano S, Inagaki O, Tomioka K, Yanagisawa I, Takenaka T. Biochemical characterization of a new disintegrin, flavostatin, isolated from *Trimeresurus flavoviridis* venom. *Biochimie.* 1996;78(4):245–52.
50. Yeh CH, Peng HC, Yih JB, Huang TF. A new short chain RGD-containing disintegrin, accutin, inhibits the common pathway of human platelet aggregation. *Biochim Biophys Acta.* 1998 Nov 27;1425(3):493–504.
51. Nieswandt B, Varga-Szabo D, Elvers M. Integrins in platelet activation. *J Thromb Haemost.* 2009 Jul;7(Suppl 1):206–9.
52. Austin SK. Haemostasis. *Medicine.* 2017;45:204–8.
53. McFadyen JD, Schaff M, Peter K. Current and future antiplatelet therapies: emphasis on preserving haemostasis. *Nat Rev Cardiol.* 2018 Mar;15(3):181–91.
54. Bledzka K, Qin J, Plow EF. Integrin $\alpha IIb \beta 3$. Platelets [Internet]. Elsevier; 2019 [cited 2023 May 16]. p. 227–41. Available from: <https://linkinghub.elsevier.com/retrieve/pii/B9780128134566000126>.
55. Mariano-Oliveira A, Coelho ALJ, Terruggi CHB, Selistre-de-Araújo HS, Barja-Fidalgo C, De Freitas MS. Alternagin-C, a nonRGD-disintegrin, induces neutrophil migration via integrin signaling: Effects of alternagin-C on neutrophil functions. *Eur J Biochem.* 2003 Dec;270(24):4799–808.
56. Allane D, Oussedik-Oumehdi H, Harrat Z, Seve M, Laraba-Djebari F. Isolation and characterization of an anti-leishmanial disintegrin from *Cerastes cerastes* venom. *J Biochem Mol Toxicol.* 2018 Feb;32(2).
57. Hubbard S, Choudhary S, Maus E, Shukla D, Swenson S, Markland FS Jr, Tiwari V. Contortrostatin, a Homodimeric Disintegrin Isolated from Snake Venom Inhibits Herpes Simplex Virus Entry and Cell Fusion. *Antivir Ther.* 2012;17(7):1319–26.
58. Hailey S, Adams E, Penn R, Wong A, McLane MA. Effect of the disintegrin eristostatin on melanoma–natural killer cell interactions. *Toxicon.* 2013 Jan;61:83–93.
59. Olfa K-Z, José L, Salma D, Amine B, Najet SA, Nicolas A, Maxime L, Raoudha Z, Kamel M, Jacques M, Jean-Marc S, Mohamed EA, Naziha Marrakchi. Lebestatin, a disintegrin from *Macrovipera* venom, inhibits integrin-mediated cell adhesion, migration and angiogenesis. *Lab Invest.* 2005 Dec;85(12):1507–16.
60. Sánchez EE, Rodríguez-Acosta A, Palomar R, Lucena SE, Bashir S, Soto JG, Pérez JC. Colombistatin: a disintegrin isolated from the venom of the South American snake (*Bothrops colombiensis*) that effectively inhibits platelet aggregation and SK-Mel-28 cell adhesion. *Arch Toxicol.* 2009 Mar;83(3):271–9.
61. Ângulo Y, Castro A, Lomonte B, Rucavado A, Fernández J, Calvete JJ, Gutiérrez JM. Isolation and characterization of four medium-size disintegrins from the venoms of Central American viperid snakes of the genera *Atropoides*, *Bothrops*, *Cerrophidion* and *Crotalus*. *Biochimie.* 2014 Dec;107(Pt B):376–84.
62. Saviola AJ, Burns PD, Mukherjee AK, Mackessy SP. The disintegrin tzabcanin inhibits adhesion and migration in melanoma and lung cancer cells. *Int J Biol Macromol.* 2016 Jul;88:457–64.
63. Montealegre-Sánchez L, Gimenes SNC, Lopes DS, Teixeira SC, Solano-Redondo L, De Melo Rodrigues V, Jiménez-Charris E. Antitumoral Potential of Lansbermin-I, a Novel Disintegrin from *Porthidium lansbergii* lansbergii

- Venom on Breast Cancer Cells. *Curr Top Med Chem*. 2019;19(22):2069–78.
64. Yeh CH, Peng H-C, Huang T-F. Accutin, a New Disintegrin, Inhibits Angiogenesis *In Vitro* and *In Vivo* by Acting as Integrin $\alpha v\beta 3$ Antagonist and Inducing Apoptosis. *Blood*. 1998 Nov 1;92(9):3268–76.
 65. Kang IC, Lee YD, Kim DS. A Novel Disintegrin Salmosin Inhibits Tumor Angiogenesis. *Cancer Res*. 1999 Aug 1;59(15):3754–60.
 66. Hong SY, Koh YS, Chung KH, Kim DS. Snake venom disintegrin, saxatilin, inhibits platelet aggregation, human umbilical vein endothelial cell proliferation, and smooth muscle cell migration. *Thromb Res*. 2002 Jan 1;105(1):79–86.
 67. Zhou Q, Nakada MT, Arnold C, Shieh KY, Markland Jr. FS. Contortrostatin, a dimeric disintegrin from *Agkistrodon contortrix contortrix*, inhibits angiogenesis. *Angiogenesis*. 1999;3(3):259–69.
 68. Tian J, Paquette-Straub C, Sage EH, Funk SE, Patel V, Galileo D, McLane MA. Inhibition of melanoma cell motility by the snake venom disintegrin eristostatin. *Toxicon*. 2007 Jun 1;49(7):899–908.
 69. Galán JA, Sánchez EE, Rodríguez-Acosta A, Soto JG, Bashir S, McLane MA, Paquette-Straub C, Pérez JC. Inhibition of lung tumor colonization and cell migration with the disintegrin crotatroxin 2 isolated from the venom of *Crotalus atrox*. *Toxicon*. 2008 Jun 1;51(7):1186–96.
 70. Danen EHJ, Marcinkiewicz C, Cornelissen IM, Van Kraats AA, Pachter JA, Ruiter DJ, Niewiarowski S, van Muijen GN. The Disintegrin Eristostatin Interferes with Integrin $\alpha 4\beta 1$ Function and with Experimental Metastasis of Human Melanoma Cells. *Exp Cell Res*. 1998 Jan 10;238(1):188–96.
 71. Kang IC, Kim DS, Jang Y, Chung KH. Suppressive Mechanism of Salmosin, a Novel Disintegrin in B16 Melanoma Cell Metastasis. *Biochem Biophys Res Commun*. 2000 Aug 18;275(1):169–73.
 72. McLane MA, Kuchar MA, Brando C, Santoli D, Paquette-Straub CA, Miele ME. New Insights on Disintegrin-Receptor Interactions: Eristostatin and Melanoma Cells. *Haemostasis*. 2001 May-Dec;31(3-6):177–82.
 73. Walsh EM, Marcinkiewicz C. Non-RGD-containing snake venom disintegrins, functional and structural relations. *Toxicon*. 2011 Sep 15;58(4):355–62.
 74. Assumpcao TCF, Ribeiro JMC, Francischetti IMB. Disintegrins from Hematophagous Sources. *Toxins (Basel)*. 2012 May;4(5):296–322.
 75. Calvete JJ. The continuing saga of snake venom disintegrins. *Toxicon*. 2013 Feb;62:40–9.
 76. Gan ZR, Gould RJ, Jacobs JW, Friedman PA, Polokoff MA. Echistatin. A potent platelet aggregation inhibitor from the venom of the viper, *Echis carinatus*. *J Biol Chem*. 1988 Dec 25;263(36):19827–32.
 77. Marcinkiewicz C, Weinreb PH, Calvete JJ, Kiesel DG, Mousa SA, Tuszynski GP, Lobb RR. Obustatin: a potent selective inhibitor of $\alpha 1\beta 1$ integrin *in vitro* and angiogenesis *in vivo*. *Cancer Res*. 2003 May 1;63(9):2020–3.
 78. Scarborough RM, Rose JW, Hsu MA, Phillips DR, Fried VA, Campbell AM, Nannizzi I, Charo IF. Barbourin. A GPIIb-IIIa-specific integrin antagonist from the venom of *Sistrurus m. barbouri*. *J Biol Chem*. 1991 May 25;266(15):9359–62.
 79. Saviola AJ, Modahl CM, Mackessy SP. Disintegrins of *Crotalus simus tzabcan* venom: Isolation, characterization and evaluation of the cytotoxic and anti-adhesion activities of tzabcanin, a new RGD disintegrin. *Biochimie*. 2015 Sep;116:92–102.
 80. Tashima AK, Sanz L, Camargo ACM, Serrano SMT, Calvete JJ. Snake venomomics of the Brazilian pitvipers *Bothrops cotiara* and *Bothrops fonsecai*. Identification of taxonomy markers. *J Proteomics*. 2008 Oct 7;71(4):473–85.
 81. Rucinski B, Niewiarowski S, Holt JC, Soszka T, Knudsen KA. Batroxostatin, an Arg-Gly-Asp-containing peptide from *Bothrops atrox*, is a potent inhibitor of platelet aggregation and cell interaction with fibronectin. *Biochim Biophys Acta*. 1990 Sep 24;1054(3):257–62.
 82. Coelho ALJ, de Freitas MS, Oliveira-Carvalho AL, Moura-Neto V, Zingali RB, Barja-Fidalgo C. Effects of Jarastatin, a Novel Snake Venom Disintegrin, on Neutrophil Migration and Actin Cytoskeleton Dynamics. *Expl Cell Res*. 1999 Sep 15;251(2):379–87.
 83. Wermelinger LS, Geraldo RB, Frattani FS, Rodrigues CR, Juliano MA, Castro HC, Zingali RB. Integrin inhibitors from snake venom: Exploring the relationship between the structure and activity of RGD-peptides. *Arch Biochem Biophys*. 2009 Feb;482(1-2):25–32.
 84. Scarborough RM, Rose JW, Naughton MA, Phillips DR, Nannizzi L, Arfsten A, Campbell AM, Charo IF. Characterization of the integrin specificities of disintegrins isolated from *American pit viper* venoms. *J Biol Chem*. 1993 Jan 15;268(2):1058–65.
 85. Shebuski RJ, Ramjit DR, Bencen GH, Polokoff MA. Characterization and Platelet Inhibitory Activity of Bitistatin, a Potent Arginine-Glycine-Aspartic Acid-Containing Peptide from the Venom of the *Viper Bitis arietans*. *J Biol Chem*. 1989 Dec 25;264(36):21550–6.
 86. Dongsu Park, Incheol Kang, Hakdai Kim, Kwanghoe Chung, Doo-sik Kim, Yungdae Yun. Cloning and Characterization of Novel Disintegrins from *Agkistrodon halys* Venom. *Mol Cells*. 1998 Oct 31;8(5):578–84.
 87. Bilgrami S, Tomar S, Yadav S, Kaur P, Kumar J, Jabeen T, Sharma S, Singh TP. Crystal Structure of Schistatin, a Disintegrin Homodimer from Saw-scaled Viper (*Echis carinatus*) at 2.5 Å Resolution. *J Mol Biol*. 2004 Aug 13;341(3):829–37.
 88. Calvete JJ, Fox JW, Agelan A, Niewiarowski S, Marcinkiewicz C. The Presence of the WGD Motif in CC8 Heterodimeric Disintegrin Increases Its Inhibitory Effect on $\alpha 1\beta 3$, $\alpha v\beta 3$, and $\alpha 5\beta 1$ Integrins. *Biochemistry*. 2002 Feb 12;41(6):2014–21.
 89. Vasconcelos AA, Estrada JC, David V, Wermelinger LS, Almeida FCL, Zingali RB. Structure-Function Relationship of the Disintegrin Family: Sequence Signature and Integrin Interaction. *Front Mol Biosci*. 2021 Dec 3;8:783301.
 90. Kolvekar N, Bhattacharya N, Sarkar A, Chakrabarty D. How snake venom disintegrins affect platelet aggregation and cancer proliferation. *Toxicon*. 2023 Jan 1;221:106982.
 91. Calvete JJ, Marcinkiewicz C, Monleón D, Esteve V, Celda B, Juárez P, Sanz L. Snake venom disintegrins: evolution of structure and function. *Toxicon*. 2005 Jun 15;45(8):1063–74.
 92. Sato M, Sardana MK, Grasser WA, Garsky VM, Murray JM, Gould RJ. Echistatin is a potent inhibitor of bone resorption in culture. *J Cell Biol*. 1990 Oct;111(4):1713–23.
 93. Knight LC, Romano JE. Functional expression of bitistatin, a disintegrin with potential use in molecular imaging of thromboembolic disease. *Protein Expr Purif*. 2005 Feb;39(2):307–19.
 94. Bordon K de CF, Cologna CT, Fornari-Baldo EC, Pinheiro-Júnior EL, Cerni FA, Amorim FG, Anjolette FAP, Cordeiro FA, Wiezel GA, Cardoso IA, Ferreira IG, Oliveira IS, Boldrini-França J, Pucca MB, Baldo MA, Arantes EC. From Animal Poisons and Venoms to Medicines: Achievements, Challenges and Perspectives in Drug Discovery. *Front Pharmacol*. 2020 Jul 24;11:1132.
 95. Weber MA, Schiffrin EL, White WB, Mann S, Lindholm LH, Kenerson JG, Flack JM, Carter BL, Materson BJ, Ram CVS, Cohen DL, Cadet JC, Jean-Charles RR, Taler S, Kountz D, Townsend RR, Chalmers J, Ramirez AJ, Bakris GL, Wang J, Schutte AE, Bisognano, JD, Touyz RM, Sica D, Harrap SB. Clinical Practice Guidelines for the Management of Hypertension in the Community: A Statement by the American Society of Hypertension and the International Society of Hypertension. *J Clin Hypertens (Greenwich)*. 2014 Jan;16(1):14–26.
 96. Ferreira SH. A bradykinin-potentiating factor (BPF) present in the venom of *Bothrops jararaca*. *Br J Pharmacol Chemother*. 1965 Feb;24(1):163–9.
 97. Ferreira SH, Rocha e Silva M. Potentiation of bradykinin and eledoisin by BPF (bradykinin potentiating factor) from *Bothrops jararaca* venom. *Experientia*. 1965 Jun 15;21(6):347–9.
 98. Ferreira SH, Bartelt DC, Greene LJ. Isolation of bradykinin-potentiating peptides from *Bothrops jararaca* venom. *Biochemistry*. 1970 Jun 23;9(13):2583–93.
 99. Ferreira SH, Greene LJ, Alabaster VA, Bakhle YS, Vane JR. Activity of Various Fractions of Bradykinin Potentiating Factor against Angiotensin I Converting Enzyme. *Nature*. 1970 Jan 24;225(5230):379–80.
 100. Cushman DW, Cheung HS, Sabo EF, Ondetti MA. Design of potent competitive inhibitors of angiotensin-converting enzyme. Carboxyalkanoyl and mercaptoalkanoyl amino acids. *Biochemistry*. 1977;16:5484–91.
 101. Patchett A. The chemistry of enalapril. *Br J Clin Pharmacol*. 1984;18(Suppl 2):201S-7S.

102. Topol EJ, Byzova TV, Plow EF. Platelet GPIIb-IIIa blockers. *Lancet*. 1999 Jan 16;353(9148):227–31.
103. Hartman GD, Egbertson MS, Halczenko W, Laswell WL, Duggan ME, Smith RL, Naylor AM et al. Non-peptide fibrinogen receptor antagonists. 1. Discovery and design of exosite inhibitors. *J Med Chem*. 1992 Nov 27;35(24):4640–2.
104. Lang SH, Manning N, Armstrong N, Misso K, Allen A, Di Nisio M, Kleijnen J. Treatment with tirofiban for acute coronary syndrome (ACS): a systematic review and network analysis. *Curr Med Res Opin*. 2012 Mar;28(3):351–70.
105. Scarborough RM, Naughton MA, Teng W, Rose JW, Phillips DR, Nannizzi L, Arfsten A, Campbell AM, Charo IF. Design of potent and specific integrin antagonists. Peptide antagonists with high specificity for glycoprotein IIb-IIIa. *J Biol Chem*. 1993 Jan 15;268(2):1066–73.
106. Scarborough RM. Development of eptifibatide. *Am Heart J*. 1999 Dec;138(6 Pt 1):1093–104.
107. Tcheng JE, O'Shea JC. Eptifibatide: a potent inhibitor of the platelet receptor integrin glycoprotein IIb/IIIa. *Expert Opin Pharmacother*. 2002 Aug;3(8):1199–210.
108. Abbade LPF, Barraviera SRCS, Silveiras MRC, Lima ABBDCO, Haddad GR, Gatti MAN, Medolago NB, Carneiro MTR, Santos LD, Ferreira Jr RS, Barraviera B. Treatment of Chronic Venous Ulcers With Heterologous Fibrin Sealant: A Phase I/II Clinical Trial. *Front Immunol*. 2021 Feb 23;12:627541.
109. Search Results. Beta ClinicalTrials.gov [Internet]. [cited 2023 Jul 14]. Available from: <https://clinicaltrials.gov/search?term=disintegrin&page=1>.
110. Chao BH, Jakubowski JA, Savage B, Chow EP, Marzec UM, Harker LA, Maraganore JM. *Agkistrodon piscivorus piscivorus* platelet aggregation inhibitor: a potent inhibitor of platelet activation. *Proc Natl Acad Sci*. 1989 Oct;86(20):8050–4.
111. Williams J, Rucinski B, Holt J, Niewiarowski S. Elegantin and albolabrin purified peptides from viper venoms; homologies with the RGDS domain of fibrinogen and von Willebrand factor. *Biochim Biophys Acta*. 1990 May 31;1039:81–9.
112. Musial J, Niewiarowski S, Rucinski B, Stewart GJ, Cook JJ, Williams JA, Edmunds Jr LH. Inhibition of platelet adhesion to surfaces of extracorporeal circuits by disintegrins. RGD-containing peptides from viper venoms. *Circulation*. 1990 Jul;82(1):261–73.
113. Huang TF, Sheu JR, Teng CM, Chen SW, Liu CS. Triflavin, an antiplatelet Arg-Gly-Asp-containing peptide, is a specific antagonist of platelet membrane glycoprotein IIb-IIIa complex. *J Biochem*. 1991 Feb;109(2):328–34.
114. Trikha M, Rote WE, Manley PJ, Lucchesi BR, Markland FS. Purification and characterization of platelet aggregation inhibitors from snake venoms. *Thromb Res*. 1994 Jan 1;73(1):39–52.
115. Calvete JJ, Schrader M, Raida M, McLane MA, Romero A, Niewiarowski S. The disulphide bond pattern of bitistatin, a disintegrin isolated from the venom of the viper *Bitis arietans*. *FEBS Lett*. 1997 Oct 20;416(2):197–202.
116. Kang IC, Chung KH, Lee SJ, Yun Y, Moon HM, Kim DS. Purification and Molecular Cloning of a Platelet Aggregation Inhibitor from the Snake (*Agkistrodon Halys Brevicaudus*) Venom. *Thromb Res*. 1998 Jul 15;91(2):65–73.
117. Wang R, Kini RM, Chung MCM. Rhodocetin, a Novel Platelet Aggregation Inhibitor from the Venom of *Calloselasma rhodostoma* (Malayan Pit Viper): Synergistic and Noncovalent Interaction between Its Subunits. *Biochemistry*. 1999 Jun 8;38(23):7584–93.
118. Marcinkiewicz C, Taooka Y, Yokosaki Y, Calvete JJ, Marcinkiewicz MM, Lobb RR, Niewiarowski S, Sheppard D. Inhibitory Effects of MLDG-containing Heterodimeric Disintegrins Reveal Distinct Structural Requirements for Interaction of the Integrin $\alpha\beta 1$ with VCAM-1, Tenascin-C, and Osteopontin. *J Biol Chem*. 2000 Oct 13;275(41):31930–7.
119. Souza DHF, Iemma MRC, Ferreira LL, Faria JP, Oliva MLV, Zingali RB, Niewiarowski S, Selistre-de-Araújo HS. The Disintegrin-like Domain of the Snake Venom Metalloprotease Alternagin Inhibits $\alpha\beta 1$ Integrin-Mediated Cell Adhesion. *Arch Biochem Biophys*. 2000 Dec 15;384(2):341–50.
120. Gasmi A, Srairi N, Guermazi S, Dkhil H, Karoui H, El Aye M. Amino acid structure and characterization of a heterodimeric disintegrin from *Vipera lebetina* venom. *Biochim Biophys Acta*. 2001 May 5;1547(1):51–6.
121. Okuda D, Morita T. Purification and Characterization of a New RGD/KGD-Containing Dimeric Disintegrin, Piscivostatin, from the Venom of *Agkistrodon piscivorus piscivorus*: The Unique Effect of Piscivostatin on Platelet Aggregation. *J Biochem*. 2001;130:407–15.
122. Smith JB, Theakston RDG, Coelho ALJ, Barja-Fidalgo C, Calvete JJ, Marcinkiewicz C. Characterization of a monomeric disintegrin, ocellatusin, present in the venom of the Nigerian carpet viper, *Echis ocellatus*. *FEBS Lett*. 2002 Feb 13;512(1-3):111–5.
123. Pinto A, Angulo Y, Jiménez R, Lomonte B. Isolation of bothrasperin, a disintegrin with potent platelet aggregation inhibitory activity, from the venom of the snake *Bothrops asper*. *Rev Biol Trop*. 2003 Mar;51(1):253–60.
124. Calvete JJ, Moreno-Murciano MP, Theakston RDG, Kisiel DG, Marcinkiewicz C. Snake venom disintegrins: novel dimeric disintegrins and structural diversification by disulphide bond engineering. *Biochem J*. 2003 Jun 15;372(Pt 3):725–34.
125. Wang JH, Wu Y, Ren F, Lü L, Zhao BC. Cloning and Characterization of Adinbitor, a Novel Disintegrin from the Snake Venom of *Agkistrodon halys brevicaudus stejneger*. *Acta Biochim Biophys Sin (Shanghai)*. 2004 Jun;36(6):425–9.
126. Kisiel DG, Calvete JJ, Katzhendler J, Fertala A, Lazarovici P, Marcinkiewicz C. Structural determinants of the selectivity of KTS-disintegrins for the $\alpha 1\beta 1$ integrin. *FEBS Lett*. 2004 Nov 19;577(3):478–82.
127. Fernandez JH, Silva CA, Assakura MT, Camargo ACM, Serrano SMT. Molecular cloning, functional expression, and molecular modeling of bothrostatin, a new highly active disintegrin from *Bothrops jararaca* venom. *Biochem Biophys Res Commun*. 2005 Apr 8;329(2):457–64.
128. Sanz L, Chen RQ, Pérez A, Hilario R, Juárez P, Marcinkiewicz C, Monleón D, Celda B, Xiong YL, Pérez-Payá E, Calvete JJ. cDNA Cloning and Functional Expression of Jerdostatin, a Novel RTS-disintegrin from *Trimeresurus jerdonii* and a Specific Antagonist of the $\alpha 1\beta 1$ Integrin. *J Biol Chem*. 2005 Dec 9;280(49):40714–22.
129. Sánchez EE, Galán JA, Russell WK, Soto JG, Russell DH, Pérez JC. Isolation and characterization of two disintegrins inhibiting ADP-induced human platelet aggregation from the venom of *Crotalus scutulatus scutulatus* (Mohave Rattlesnake). *Toxicol Appl Pharmacol*. 2006 Apr 1;212(1):59–68.
130. Thangam R, Gunasekaran P, Kaveri K, Sridevi G, Sundarraj S, Paulpandi M, Kannan S. A novel disintegrin protein from *Naja naja* venom induces cytotoxicity and apoptosis in human cancer cell lines in vitro. *Proc Biochem*. 2012 Aug;47(8):1243–9.
131. Allane D, Oussedik-Oumehdi H, Harrat Z, Seve M, Laraba-Djebari F. Isolation and characterization of an anti-leishmanial disintegrin from *Cerastes cerastes* venom. *J Biochem Mol Toxicol*. 2018 Feb;32(2):e202018.
132. Oliveira IS de, Manzini RV, Ferreira IG, Cardoso IA, Bordon K de CF, Machado ART, Antunes LMG, Rosa JC, Arantes EC. Cell migration inhibition activity of a non-RGD disintegrin from *Crotalus durissus collilineatus* venom. *J Venom Anim Toxins incl Trop Dis*. 2018 Oct;24:28. doi: 10.1186/s40409-018-0167-6. eCollection 2018.
133. Ameziani M, Chérifi F, Kiheli H, Saoud S, Hariti G, Kellou-Taïri S, Laraba-Djebari F. Isolation and Functional Identification of an Antiplatelet RGD-Containing Disintegrin from *Cerastes cerastes* Venom. *Protein J*. 2020 Oct;39(5):574–90.
134. Yeh CH, Peng HC, Yih JB, Huang TF. A new short chain RGD-containing disintegrin, accutin, inhibits the common pathway of human platelet aggregation. *Biochim Biophys Acta*. 1998 Nov 27;1425(3):493–504.
135. Musial J, Niewiarowski S, Rucinski B, Stewart GJ, Cook JJ, Williams JA, Edmunds Jr LH. Inhibition of platelet adhesion to surfaces of extracorporeal circuits by disintegrins. RGD-containing peptides from viper venoms. *Circulation*. 1990 Jul;82(1):261–73.
136. Scarborough RM, Rose JW, Naughton MA, Phillips DR, Nannizzi L, Arfsten A, Campbell AM, Charo IF. Characterization of the integrin specificities of disintegrins isolated from American pit viper venoms. *J Biol Chem*. 1993 Jan 15;268(2):1058–65.
137. Vija H, Samel M, Siigur E, Aaspõllu A, Tõnismägi K, Trummal K, Subbi J, Siigur J. VGD and MLD-motifs containing heterodimeric disintegrin vipledin-2 from *Vipera lebetina* snake venom. Purification and cDNA cloning. *Comp Biochem Physiol B Biochem Mol Biol*. 2009 Jul;153(3):253–60.

138. McLane MA, Kowalska MA, Silver L, Shattil SJ, Niewiarowski S. Interaction of disintegrins with the $\alpha\text{IIb}\beta_3$ receptor on resting and activated human platelets. *Biochem J*. 1994 Jul 15;301(Pt-2):429–36.
139. Wermelinger LS, Geraldo RB, Frattani FS, Rodrigues CR, Juliano MA, Castro HC, Zingali RB. Integrin inhibitors from snake venom: Exploring the relationship between the structure and activity of RGD-peptides. *Arch Biochem Biophys*. 2009 Feb;482(1-2):25–32.
140. Sanz L, Chen RQ, Pérez A, Hilario R, Juárez P, Marcinkiewicz C, Monleón D, Celda B, Xiong YL, Pérez-Payá E, Calvete JJ. cDNA Cloning and Functional Expression of Jerdostatin, a Novel RTS-disintegrin from *Trimeresurus jerdonii* and a Specific Antagonist of the $\alpha_1\beta_1$ Integrin. *J Biol Chem*. 2005 Dec 9;280(49):40714–22.
141. Yeh CH, Peng HC, Huang TF. Accutin, a New Disintegrin, Inhibits Angiogenesis *In Vitro* and *In Vivo* by Acting as Integrin $\alpha_v\beta_3$ Antagonist and Inducing Apoptosis. *Blood*. 1998 Nov 1;92(9):3268–76.
142. Soszka T, Knudsen KA, Beviglia L, Rossi C, Poggi A, Niewiarowski S. Inhibition of murine melanoma cell-matrix adhesion and experimental metastasis by albolabrin, an RGD-containing peptide isolated from the venom of *Trimeresurus albolabris*. *Exp Cell Res*. 1991 Sep;196(1):6–12.
143. Dos Santos PK, Altei WF, Danilucci TM, Lino RLB, Pachane BC, Nunes ACC, Selistre-de-Araujo HS. Alternagin-C (ALT-C), a disintegrin-like protein, attenuates $\alpha_2\beta_1$ integrin and VEGF receptor 2 signaling resulting in angiogenesis inhibition. *Biochimie*. 2020 Jul;174:144–58.
144. Selistre-de-Araujo HS, Cominetti MR, Terruggi CHB, Mariano-Oliveira A, De Freitas MS, Crépin M, Figueiredo CC, Morandi V. Alternagin-C, a disintegrin-like protein from the venom of *Bothrops alternatus*, modulates $\alpha_2\beta_1$ integrin-mediated cell adhesion, migration and proliferation. *Braz J Med Biol Res*. 2005 Oct;38(10):1505–11.
145. Moritz MENDO, Eustáquio LMS, Micocci KC, Nunes ACC, Dos Santos PK, De Castro Vieira T, Selistre-de-Araujo HS. Alternagin-C binding to $\alpha_2\beta_1$ integrin controls matrix metalloproteinase-9 and matrix metalloproteinase-2 in breast tumor cells and endothelial cells. *J Venom Anim Toxins incl Trop Dis*. 2018 Apr 25;24:13. doi: 10.1186/s40409-018-0150-2.
146. Beviglia L, Stewart GJ, Niewiarowski S. Effect of four disintegrins on the adhesive and metastatic properties of B16F10 melanoma cells in a murine model. *Oncol Res*. 1995;7(1):7–20.
147. Juliano D, Wang Y, Marcinkiewicz C, Rosenthal LA, Stewart GJ, Niewiarowski S. Disintegrin Interaction with $\alpha_v\beta_3$ Integrin on Human Umbilical Vein Endothelial Cells: Expression of Ligand-Induced Binding Site on β_3 Subunit. *Exp Cell Res*. 1996 May 25;225(1):132–42.
148. Trikha M, De Clerck YA, Markland FS. Contortrostatin, a Snake Venom Disintegrin, Inhibits β_1 Integrin-mediated Human Metastatic Melanoma Cell Adhesion and Blocks Experimental Metastasis. *Cancer Res*. 1994 Sep 15;54(18):4993–8.
149. Ramos OHP, Kauskot A, Cominetti MR, Bechyne I, Salla Pontes CL, Chareyre F, Manent J, Vassy R, Giovannini M, Légrand C, Selistre-de-Araujo HS, Crépin M, Bonnefoy A. A novel $\alpha(v)\beta_3$ -blocking disintegrin containing the RGD motive, DisBa-01, inhibits bFGF-induced angiogenesis and melanoma metastasis. *Clin Exp Metastasis*. 2008;25(1):53–64.
150. McLane MA, Joerger T, Mahmoud A. Disintegrins in health and disease. *Front Biosci*. 2008 May 1;13:6617–37.
151. Pfaff M, McLane MA, Beviglia L, Niewiarowski S, Timpl R. Comparison of Disintegrins with Limited Variation in the RGD Loop in Their Binding to Purified Integrins $\alpha\text{IIb}\beta_3$, $\alpha_v\beta_3$ and $\alpha_5\beta_1$ and in Cell Adhesion Inhibition. *Cell Adhes Commun*. 1994 Dec;2(6):491–501.
152. Hammouda MB, Montenegro MF, Sánchez-del-Campo L, Zakraoui O, Aloui Z, Riahi-Chebbi I, Karoui H, Rodríguez-López JN, Essafi-Benkhadir K. Lebein, a Snake Venom Disintegrin, Induces Apoptosis in Human Melanoma Cells. *Toxins (Basel)*. 2016 Jul;8(7):206.
153. Zakraoui O, Marcinkiewicz C, Aloui Z, Othman H, Grépin R, Haoues M, Essafi M, Srhiri-Abid N, Gasmi A, Karoui H, Pages G, Essafi-Benkhadir K. Lebein, a snake venom disintegrin, suppresses human colon cancer cells proliferation and tumor-induced angiogenesis through cell cycle arrest, apoptosis induction and inhibition of VEGF expression. *Mol Carcinog*. 2017 Jan;56(1):18–35.
154. Lucena S, Castro R, Lundin C, Hofstetter A, Alaniz A, Suntravat M, Sánchez EE. Inhibition of pancreatic tumoral cells by snake venom disintegrins. *Toxicon*. 2015 Jan;93:136–43.
155. Tan CH, Liew JL, Navanesan S, Sim KS, Tan NH, Tan KY. Cytotoxic and anticancer properties of the Malaysian mangrove pit viper (*Trimeresurus purpureomaculatus*) venom and its disintegrin (*purpureomaculin*). *J Venom Anim Toxins incl Trop Dis*. 2020 Jul 17;26:e20200013. doi: 10.1590/1678-9199-JVATITD-2020-0013. eCollection 2020.
156. Eble JA, Niland S, Dennes A, Schmidt-Hederich A, Bruckner P, Brunner G. Rhodocetin antagonizes stromal tumor invasion in vitro and other $\alpha_2\beta_1$ integrin-mediated cell functions. *Matrix Biol*. 2002 Nov;21(7):547–58.
157. Yeh CH, Peng HC, Yang RS, Huang TF. Rhodostomin, A Snake Venom Disintegrin, Inhibits Angiogenesis Elicited by Basic Fibroblast Growth Factor and Suppresses Tumor Growth by A Selective $\alpha_v\beta_3$ Blockade of Endothelial Cells. *Mol Pharmacol*. 2001 May;59(5):1333–42.
158. Kim DS, Jang YJ, Jeon OH, Kim DS. Saxatillin, a Snake Venom Disintegrin, Suppresses TNF- α -induced Ovarian Cancer Cell Invasion. *J Biochem Mol Biol*. 2007 Mar 31;40(2):290–4.
159. Kim KS, Kim DS, Chung KH, Park YS. Inhibition of angiogenesis and tumor progression by hydrodynamic cotransfection of angiostatin K1-3, endostatin, and saxatillin genes. *Cancer Gene Ther*. 2006 Jun;13(6):563–71.
160. Sheu JR, Huang TF. Triflavin, an Arg-Gly-Asp-containing peptide, inhibits B16-F10 mouse melanoma cell adhesion to matrix proteins via direct binding to tumor cells. *J Biomed Sci*. 1996 Sep-Oct;3(5):359–64.
161. Saviola AJ, Burns PD, Mukherjee AK, Mackessy SP. The disintegrin tzabcanin inhibits adhesion and migration in melanoma and lung cancer cells. *Int J Biol Macromol*. 2016 Jul;88:457–64.