



Therapeutic Potential of Bee and Scorpion Venom Phospholipase A2 (PLA2): A Narrative Review

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Abstract

Venomous arthropods such as scorpions and bees form one of the important groups with an essential role in medical entomology. Their venom possesses a mixture of diverse compounds, such as peptides, some of which have toxic effects, and enzymatic peptide Phospholipase A2 (PLA2) with a pharmacological potential in the treatment of a wide range of diseases. Bee and scorpion venom PLA2 group III has been used in immunotherapy, the treatment of neurodegenerative and inflammatory diseases. They were assessed for antinociceptive, wound healing, anti-cancer, anti-viral, anti-bacterial, anti-parasitic, and anti-angiogenesis effects. PLA2 has been identified in different species of scorpions and bees. The anti-leishmania, anti-bacterial, anti-viral, and anti-malarial activities of scorpion PLA2 still need further investigation. Many pieces of research have been stopped in the laboratory stage, and several studies need vast investigation in the clinical phase to show the pharmacological potential of PLA2. In this review, the medical significance of PLA2 from the venom of two arthropods, namely bees and scorpions, is discussed.

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What's Known

- The venom of arthropods such as scorpions and bees is a complex mixture of polypeptides, bioactive proteins, and enzymes.
- Phospholipase A2 (PLA2) is one of the important characterized enzymes in the venom, with different therapeutic potentials in medicine.

What's New

- Newly discovered mechanism of phospholipase A2 (PLA2) in disease treatment
- Considering the results of the latest research on bee and scorpion venom PLA2 in the treatment of different diseases
- New results related to the anti-viral activity and wound healing effects of bee venom PLA2

Introduction

Arthropods, as the largest phylum of animals, include the insect, arachnid, crustacean, and myriapod classes, which constitute approximately 80% of the known species on earth.¹⁻³ Bees and scorpions are two species in this phylum reported to be under investigation, with a focus on their venom based on its pharmacological, medical, and industrial significance.¹⁻⁴ Scorpions belong to the Arachnida class and order with a variety of about 2200 species.^{5, 6} They utilize an apparatus called the venom gland and telson in caching their prey, defending against predators, and some intraspecific communications.⁷ The venom contains a wide range of peptides, proteins, mucoproteins, enzymes such as L-amino acid oxidase, a serine protease, hyaluronidase, and metalloproteinase, nucleotides, salt, biogenic amines, and phospholipase A2 (PLA2).⁸⁻¹⁰ The peptides from scorpion venom were shown to have anti-cancer, anti-bacterial, anti-viral, anti-parasitic, and anti-epileptic properties, and can potentiate bradykinin activities as well.¹¹⁻¹⁸

Honey bees have an important role in pollinating and

honey production and have a venom gland in their abdominal cavity as a weapon to protect themselves against predators.¹⁹ The venom consisted of a mixture of a variety of compounds, including peptides (apamin, adolapin, melittin), bioactive amines, several non-peptide compounds (free amino acids and lipids), and enzymes (hyaluronidase and PLA2).²⁰⁻²³ Several studies demonstrated that bee venom has radio-protective, anti-nociceptive, anti-inflammatory, and anti-mutagenic activity.²⁴⁻³⁰ The PLA2 in the venom of arthropods such as bees and scorpions belongs to the PLA2 group III and has a wide range of pharmacological properties.³¹ PLA2 hydrolyzes glycerophospholipids at the sn-2 position and results in the release of fatty acids and lysophospholipids.³² In mammals, secretory phospholipase A2 (sPLA2) has an important role in proliferation, maturation, and inflammation,³³⁻³⁵ while bee venom sPLA2 of group III is also identical to the mammalian sPLA2s.³⁶ This review investigated the bee and scorpion venom PLA2 and its medical therapeutic potential.

Pharmacological Function of Bee Venom PLA2

Specific Immunotherapy (SIT)

Specific immunotherapy is defined as an increase in the allergen doses via the subcutaneous route.³⁷ Nowadays, bee venom injection is used to treat bee venom allergy in 95% of sensitive patients with local and systemic anaphylactic reactions.³⁸⁻⁴¹ Bee venom immunotherapy has an important role in specific immunotherapy, providing natural immunity against venom allergens, but it sometimes leads to allergic side effects among 20-40% of the patients.^{40, 42} In these patients, PLA2 is responsible for allergens and immunogenic particles up to 80%.⁴²⁻⁴⁴ The PLA2 in bee venom consisted of 12% whole venom proteins.⁴⁴ In PLA2, three T-cell epitopes have been identified, including PLA45-62 (PI), PLA82-92 (PII), and PLA113-124 (PIII).⁴²

In venom therapy, T helper type 1 (Th1) (Interleukin-2 [IL-2] and Interferon-gamma [IFN- γ]) and T helper type 2 (Th2) (IL-4, IL-5, and IL-13) cells shift to IL-10 secreting Type 1 regulatory T-cells (Tr1 cell), and this process leads to a decrease in T-cell responsiveness. So, Th1- and Th2-type cytokine secretions and T-cell proliferation are suppressed.⁴⁰ Regulatory T-cells (Tregs) have an important role in allergic reactions by retaining immune homeostasis and regulatory functions.⁴⁵ Additionally, Tregs suppress immunoglobulin E (IgE) antibody production and increase immunoglobulin G4 (IgG4) production

as non-inflammatory isotypes.^{40, 46} Some studies have shown that venom immunotherapy reduces the PLA-IgE antibody but increases immunoglobulin G2a (IgG2a), which can inhibit anaphylactic reactions.⁴⁷

Cancer Therapy

Bee venom can induce apoptosis in cancer cells and inhibit their growth by increasing intracellular Ca²⁺ and reactive oxygen species (ROS).⁴⁸⁻⁵⁰ The two important compounds in bee venom are melittin (an amphiphilic peptide) and PLA2, which induce necrosis, cytolysis, and apoptosis through the enhancement of Ca²⁺ entry and calpain activity, as well as death receptor signaling activation.^{1, 51-53} Actually, in the apoptosis process, caspase-3 is activated by bee venom in the synovial fibroblasts.⁵⁴ Several studies have revealed that cancer cells are destroyed by the activation of matrix metalloproteinase (MMP) and caspase, a mechanism that is related to bee venom anti-tumor activity.^{48, 55-57}

Several cancer cells, such as leukemic cells and breast, prostate, lung, liver, renal, mammary, and bladder cancer cells, can be treated by melittin and PLA2 of bee venom.^{29, 48, 49, 58} The melittin in bee venom is a PLA2 activator.⁵⁹⁻⁶² The activation of PLA2 via melittin, as an antiapoptotic factor, indicates the anti-tumor activity of bee venom,⁴⁸ which can disrupt the cell membrane by moving the anions and increasing their cytotoxic effect.⁶³ Moreover, PLA2 can also influence the proliferation of tumor cells.⁴⁸ In renal cancer, it was shown that bee venom PLA2 with the combined effect of phosphatidylinositol-(3, 4)-bisphosphate (PtdIns (3, 4) P2) has a synergistic effect in inducing cell death.^{64, 65}

Neurodegenerative Disease Therapy

The potential mechanism in group III sPLA2, such as bee venom PLA2, is a therapeutic strategy for prion diseases, as a family of neurodegenerative diseases, which is characterized by gliosis and neuronal vacuolation.⁶⁶ Prion diseases are disorders that occur with the misfolding of the isoform or protease-resistant prion protein (PrP^{sc}) of the cellular prion protein (PrP^c). The overexpression of PrP^c by prion protein (PrP) peptide 106-126 induces neurotoxicity.⁶⁷ PLA2, which is expressed in the peripheral and central nervous system (CNS),^{35, 68} activates the protein kinase B (AKT) in mammals and regulates neuronal survival and outgrowth.³⁶ In neuritogenesis, sPLA2 modulates phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) signaling, so that PrP (106-126)-mediated neurotoxicity is blocked.^{35, 69}

The potential mechanism in group III sPLA2, such as bee venom PLA2, is a therapeutic strategy for prion disease characterized by gliosis and neuronal vacuolation.⁶⁶ In fact, bee venom PLA2 is a protective agent against PrP(106-126)-mediated neurotoxicity in prion diseases.⁶⁹ Alzheimer's disease is another degenerative disease of the CNS that is relevant to neurotoxic microglial activation.^{70, 71} Microglia activation has an important role in the accumulation of amyloid-beta (A β), which is associated with the progression of this disease via the secretion of tumor necrosis factor-alpha (TNF- α), IL-6, IL-1, and free radicals as inflammatory molecules.^{72, 73} A study has indicated that bee venom PLA2 decreases the activation of neurotoxic microglial in triple-transgenic (3xTg) mouse models.⁷⁰ On the other hand, bee venom PLA2 alters the apoptotic signal pathway and induces Treg expansion. In fact, bvPLA2 increases CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) and PD-1 (programmed cell death protein 1) as anti-apoptotic molecules.⁷⁴

Parkinson's disease (PD) is another age-related neurodegenerative disease that is extremely common after Alzheimer's disease and is characterized by the degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc).⁷⁵⁻⁷⁷ PD is associated with the accumulation of post-translationally modified alpha-synuclein (α -syn), which results in the activation of microglial, interleukin-1 β (IL-1 β), TNF α , nicotinamide adenine dinucleotide phosphate (NADPH) oxidase enzyme, and ROS, affecting the CNS and speeding up PD pathogenesis.⁷⁸ Several studies have illustrated that bee venom PLA2 can inhibit the apoptosis of dopaminergic neurons and protect glutamate-induced neurotoxicity.^{76, 79-83} Technically, bee venom phospholipase A2 (bvPLA2) promotes the survival of dopaminergic neurons through Treg overexpansion.⁸⁴ On the other hand, in transgenic mice, it was shown that bee venom PLA2 can decrease the activation of microglia in A53T transgenic mice, so that α -syn, which is accumulated in the spinal cord, is reduced. This can be considered as a novel strategy for the treatment of PD.⁸³

Anti-inflammatory Effect

Bee venom is used as anti-inflammatory medication in the treatment of chronic inflammatory diseases such as multiple sclerosis and rheumatoid arthritis.⁸⁵⁻⁹⁰ Recent investigations have shown that bee venom PLA2 is responsible for the anti-inflammation effects by reducing the aggregation of immune cells.^{88, 91-93}

Shine and others found that bee venom PLA2 has therapeutic effects via the depletion of Tregs and is a good candidate for the treatment of fibrosis and radiation pneumonitis.⁸⁸ These Tregs are influenced by bee venom PLA2 in the airways, which leads to the prevention of the chronic obstructive disease of allergic asthmatic symptoms, influencing the release of IL-4, IL-5, and IL-13, the production of allergen-specific IgE, and the aggregation of eosinophils and basophils in the airways.⁹⁴⁻⁹⁷

Bee venom PLA2 is capable of neuroprotection and suppressing the microglial activation, which is activated in degenerative neurons such as PD.⁸⁴ Bee venom PLA2 can induce Treg differentiation and suppress the secretion of prostaglandin E2 (PGE2) by a cluster of differentiation 26 (CD206)+dendritic cells (DCs). PLA2-stimulated DCs release PGE2 which binds to a cluster of differentiation 4 (CD4)+T cells on the prostaglandin E2 (PGE2) receptor 2 subtype (EP2) and regulates the expression of forkhead box P3 (Foxp3).⁸⁴ So, bee venom PLA2 can be a pharmacological candidate for treating neuro-inflammatory diseases such as PD.

It has been demonstrated that in the treatment of PD, bee venom PLA2 (bvPLA2) has anti-inflammatory effects and neuro-protective activity by the inhibition of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP).⁹⁸ It has also been noted that bee venom PLA2 has an important role in anti-inflammatory effects and Alzheimer's disease amelioration through the modulation of Tregs and production of IL-10.^{99, 100} Bee venom PLA2 can ameliorate memory impairment by the inhibition of nuclear factor kappa B (NF- κ B), a key transcription factor,¹⁰¹ and inhibit the phosphorylation of signal transducer and activator of transcription 3 (STAT3), leading to the anti-inflammatory effects.¹⁰¹

It was shown that bee venom PLA2 can modulate the Treg cell population and prevent Cis-diamminedichloroplatinum (cisplatin)-induced renal inflammation and nephrotoxicity.^{91, 102} In 2014, Kim and others found that bee venom PLA2 has hepatoprotective effects by modulating the Treg and inducing IL-10 in acetaminophen-induced acute toxicity in liver and kidneys.¹⁰³ The investigation showed that bee venom PLA2 decreases lipid accumulation in the aorta and foam cells formation by increasing Treg cells. Technically, increasing the Treg cells leads to an increase in high-density lipoprotein cholesterol (HDL-C) and a decrease in low-density lipoprotein cholesterol (LDL-C). Therefore, bee venom PLA2 can be a potential therapeutic agent for atherosclerosis disease.¹⁰⁴

Antinociceptive Effect

Bee venom is used to treat diseases such as tendonitis, wounds, bursitis, shingles, and even burns.¹⁰⁵ In addition, it is also used as an antinociceptive in patients.^{20, 77, 86, 105, 106} Studies have indicated that pre-treatment by bee venom PLA2 has three crucial roles in patients using oxaliplatin, which is widely prescribed for lung, ovarian, and breast cancers. It can prevent oxaliplatin-induced neuropathic pains by inhibiting the development of cold and mechanical allodynia, inhibiting macrophage infiltration, and decreasing IL-1 β in the lumbar dorsal root ganglia.¹⁰⁷⁻¹¹⁰

Wound-healing Effects

Bee venom can promote wound healing by enhancing the responses of toll-like receptor 3 in keratinocytes. In other words, it increases the uptake of polyinosinic: polycytidylic acid, and affects the production of IL-8 in keratinocytes, leading to the therapeutic potential of bee venom PLA2 for healing skin wounds.¹¹¹

Atopic dermatitis, also known as atopic eczema, is a biphasic inflammatory skin disorder.¹¹² It was shown that bee venom PLA2 reduces atopic skin lesion inflammation in n Balb/c mouse models, induced by 2,4-dinitrochlorobenzene (DNCB), and house dust mite, *Dermatophagoides farinae* extract (DFE).¹¹³ Bee venom PLA2 inhibited the cytokine levels, serum IgE, the infiltration of mast cells (MCs), and epidermal thickness in an atopic dermatitis model, induced by the interaction of DNCB and DFE with CD206 mannose receptor.¹¹⁴

Anti-virus Activity

Hewawaduge and others indicated that bee venom PLA2 blocks the receptors on the cell surface involved in virus attachment and inhibits virus replication, revealing the *in vitro* antiviral activity of bee venom PLA2 against coxsackievirus (H3), adenovirus (AdV), enterovirus-71 (EV-71), vesicular stomatitis virus (VSV), and herpes simplex virus (HSV).¹¹⁵ It was demonstrated that the p3bv peptide (amino acids 21 to 35 of bee venom PLA2) inhibits human immunodeficiency virus 1 (HIV-1) replication by binding to CXC-chemokine receptor 4 (CXCR4).¹¹⁶ Therefore, the pharmacological potential of bee venom PLA2 against viruses was suggested.

Anti-parasitic and Anti-bacterial Activities

Bee venom PLA2 was shown to have a specific role in killing or inhibiting gram-negative bacteria (*Enterobacter cloacae*, *Citrobacter*

freundii, *Escherichia coli*) and *Trypanosoma brucei brucei*, which causes sleep sickness in tropical counties.^{117, 118} The antibacterial activity of bee venom PLA2 was demonstrated against gram-positive bacteria, such as *Staphylococcus aureus*, and gram-negative bacteria, including *Escherichia coli*, *Pseudomonas aeruginosa*, and *Klebsiella aerogenes*.¹¹⁹ It was noted that the expression of bee venom PLA2 is decreased in transgenic mosquitos (*Anopheles stephensi*) by blocking the oocyst formation of *Plasmodium berghei* and interfering with the transmission of the parasite.¹²⁰ Additionally, bee venom PLA2 can induce stage-specific growth arrest in intraerythrocytic *Plasmodium falciparum* by modifying serum lipoproteins.¹²¹

All information related to the pharmacological function of bee venom PLA2 is gathered in table 1.

Pharmacological Function of Scorpion Venom PLA2

Anti-angiogenesis and Anti-tumoral Activity

So far, several PLA2s have been identified in the venoms of different scorpion species, including enterotoxin from *Heterometrus laoticus*,¹²³ hemilipin and hemilipin2 from the Iranian scorpion *Hemiscorpius lepturus*,^{124, 125} phospholipin and imperatoxin from *Pandinus imperator*,^{126, 127} phaiodactylipin from *Anuroctonus phaiodactylus*,¹²⁸ and PLA2 from *Scorpio maurus*,¹²⁹ and *Heterometrus fulvipes*.¹³⁰ Angiogenesis is defined as the growth of new vessels from existing vessels.¹³¹ Hemilipin is a heterodimeric protein, sPLA2 enzyme, which has been isolated from the venom of the Iranian scorpion *Hemiscorpius lepturus*. This enzyme reduces the expression levels of three important proangiogenic factors, including the vascular endothelial growth factor-A, -C, and -D (VEGF-A, VEGF-C, VEGF-D), the vascular endothelial growth factor receptor-1 and -2 (VEGFR-1 and VEGFR-2), hepatocyte growth factor (HGF), and endoglin expression (CD105). It also induces an anti-angiogenesis effect *in vivo* and *in vitro*, both on human umbilical vein endothelial cells (HUVECs) and human pulmonary artery endothelial cells (HPAECs), as well as the chick embryo chorioallantoic membrane (CAM).¹²⁴

Hemilipin2, a new heterodimeric PLA2 that has been identified in the Iranian scorpion *Hemiscorpius lepturus*, was shown to have anti-angiogenesis activity. A small subunit of Hemilipin2 was demonstrated *in vitro* and *in vivo* to have anti-angiogenesis activity in HUVECs, HPAECs, and CAM models, without any apoptotic or cytotoxic effect.¹²⁵ The recombinant protein of heterodimeric PLA2 found in *Scorpio*

Table 1: Pharmacological function of bee venom Phospholipase A2

References	Source	Pharmacological function	Disease	Mechanism
Akdis CA et al. ⁴⁶ von Garnier C et al. ⁴⁷ Hori S et al. ⁴⁵ von Ozdemir C et al. ⁴⁰	Bee venom	Specific immunotherapy (SIT)	Allergy	1. Conversion Th1 and Th2 cells to IL-10, suppressing the T cell proliferation and cytokine secretions 2. Suppressing IgE antibody production by Tregs and increasing IgG4 production 3. Reducing PLA-IgE antibody but increasing IgG2a for anaphylactic reaction inhibition
Lad PJ et al. ⁶³ Jang M-H et al. ⁴⁹ Oršolić N et al. ²⁹ Moon D-O et al. ⁵⁵ Rahman KW et al. ⁵⁷ Putz T et al. ⁶⁴ Li B et al. ⁵⁸ Putz T et al. ⁶⁵ Cho H-J et al. ⁵⁶ Ozdemir C et al. ⁴⁰ Oršolić N et al. ⁴⁸ Nabiuni M et al. ⁵¹ Gajski G et al. ⁵³ Chaisakul J et al. ⁵⁰ Kong G-M et al. ⁵²		Cancer therapy	Leukemic cells Breast cancer Prostate cancer Lung cancer Liver cancer Renal cancer Mammary cancer Bladder cancer	1. Increasing intracellular Ca ²⁺ , reactive oxygen species (ROS), enhancing calpain activity, and death receptor signaling activation 2. Activation of matrix metalloproteinase (MMP), and caspase 3. disrupting the cell membrane 4. Inducing cell death with the cooperation of phosphatidylinositol-(3, 4)-bisphosphate (PtdIns (3, 4) P2)
Brandner S et al. ⁶⁶ Jeong J-K et al. ⁶⁹ Ye M et al. ⁷⁰ Baek H et al. ⁷⁴		Neurodegenerative disease therapy	Prion Alzheimer	Blocking PrP(106-126)-mediated 1. Decreasing the activation of neurotoxic microglia 2. Increases CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) and PD-1 (Programmed cell death protein 1)
Doo A-R et al. ⁸⁰ Doo A-R et al. ⁷⁹ Lee SM et al. ⁸¹ Chung ES et al. ⁸⁴ Ye M et al. ⁸³ Awad K et al. ⁷⁶			Parkinson	1. Inhibiting the apoptosis of dopaminergic neurons and protecting glutamate-induced neurotoxicity 2. Promote the survival of dopaminergic neurons through Treg overexpression 3. Reducing the accumulation of α-syn in the spinal cord
Lee J-D et al. ²⁷ Castro HJ et al. ⁸⁷ Liu X et al. ⁸⁵ Lee G et al. ⁹³ Shin D et al. ⁸⁸		Anti-inflammatory effect	Multiple sclerosis Rheumatoid arthritis	Reducing the aggregation of immune cells
Park et al. ⁹⁷			Fibrosis radiation pneumonitis Allergic asthmatic	Depletion of Tregs Production of allergen-specific IgE and aggregation of eosinophils and basophils
Hirsch E et al. ¹²² Block ML et al. ⁷¹ Chung ES et al. ⁸⁴			Parkinson	1. Suppressing the secretion of prostaglandin E2 (PGE2) by CD206 (cluster of differentiation 26) CD206 + dendritic cells (DCs) 2. Neuroprotective activity by inhibition of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)
Chen C-H et al. ¹⁰⁰ Baek H et al. ⁷⁴ Kang G-H et al. ¹⁰⁴			Alzheimer Atherosclerosis	Modulation of Tregs and production of IL-10 Increasing the Treg cells, increasing high-density lipoprotein cholesterol (HDL-C), and decreasing low-density lipoprotein cholesterol (LDL-C)
Arany I et al. ¹⁰² Kim H et al. ¹⁰³			Liver injury	Modulation of the Treg cell Treg and inducing IL-10 in acetaminophen-induced acute toxicity
Arany I et al. ¹⁰² Kim H et al. ⁹¹			Kidney injury	Modulate Treg cells population and prevent Cis-diamminedichloroplatinum (cisplatin)-induced renal inflammation and nephrotoxicity
Muggia FM et al. ¹⁰⁸ Petit T et al. ¹⁰⁹ Alcindor T et al. ¹⁰⁷ Li D et al. ¹¹⁰		Antinociceptive effect	-	Inhibition of the development of cold and mechanical allodynia and the inhibition of macrophage infiltration and decreasing the IL-1β

Nakashima A et al. ¹¹¹	Wound healing effects	Skin wounds	Increasing the polyinosinic: polycytidylic acid (poly(I: C)) uptake and production of IL-8 in keratinocyte
Jung KH et al. ¹¹³ Shin D et al. ¹¹⁴		Atopic dermatitis	Interaction with CD206 mannose receptor
Fenard D et al. ¹¹⁶ Hewawaduge C et al. ¹¹⁵	Anti-virus activity	Coxsackievirus (H3), Adenovirus (AdV), Enterovirus-71 (EV-71), Vesicular stomatitis virus (VSV), Herpes simplex virus (HSV), and Human immunodeficiency virus 1 (HIV-1)	Blocking cell surface receptors
Boulanger N et al. ¹¹⁷ Perumal Samy et al. ¹¹⁹ Boutrin MCF at al. ¹¹⁸	Antiparasite and anti-bacterial activities	Sleep sickness (<i>Trypanosoma brucei brucei</i>) Gram-negative bacteria (<i>Enterobacter cloacae</i> , <i>Citrobacter freundii</i> , <i>Escherichia coli</i> , <i>Pseudomonas aeruginosa</i> , and <i>Klebsiella aerogenes</i>) Gram-positive bacteria (<i>Staphylococcus aureus</i>)	Killing or growth-inhibiting
Deregnacourt C et al. ¹²¹ Moreira LA et al. ¹²⁰		Malaria (<i>Plasmodium berghei</i> and <i>Plasmodium falciparum</i>)	1. Blocking oocyst formation of <i>Plasmodium berghei</i> in <i>Anopheles stephensi</i> mosquito 2. Growth arrest of the <i>intraerythrocytic</i> stage in <i>Plasmodium falciparum</i>

Table 2: Pharmacological function of scorpion venom Phospholipase A2

References	Source	Species of scorpion	Enzymes name	Pharmacological function	Mechanism
Jridi et al. ¹²⁴	Scorpion venom	<i>Hemiscorpius lepturus</i>	Hemilipin	Anti-angiogenesis	Reducing the expression of VEGF-A, VEGF-C, VEGF-D, VEGFR-1, VEGFR-2, HGF, and CD105
Jridi et al. ¹²⁵		<i>Hemiscorpius lepturus</i>	Hemilipin2	Anti-angiogenesis	-
Krayem N et al. ¹³⁴ and Krayem N et al. ¹³²		<i>Scorpio Maurus</i>	PLA2	Anti-angiogenesis and anti-tumor	Interference with $\alpha 5\beta 1$ and $\alpha v\beta 3$ integrin receptors function

Maurus has shown anti-angiogenesis effects on HUVECs through the inhibition of migration, invasion, and adhesion activities,¹³² while angiogenesis is a key process in metastasis and tumor growth,¹³³ which lends to its important role in cancer therapy. Native and recombinant proteins of PLA2 derived from *Scorpio Maurus* venom have demonstrated anti-tumor activities through interference with the function of $\alpha 5\beta 1$ and $\alpha v\beta 3$ integrin receptors in human vascular endothelial cells (HMEC-1).¹³⁴

All information related to the pharmacological function of scorpion venom PLA2 is presented in table 2.

Discussion

Venomous arthropods such as scorpions and bees are among the important groups with an essential significance in medical entomology.¹³⁵

Their venom possesses a mixture of diverse compounds, such as peptides, some of which have toxic effects, and enzymatic peptide PLA2, with pharmacological potential in the treatment of a wide range of diseases.⁹ Therefore, studying the effectiveness of venom peptides is an extremely important task, which can lead to the introduction of new drug candidates in the treatment of various diseases. Bee and scorpion venom PLA2 group III has been used in immunotherapy and the treatment of neurodegenerative and inflammatory diseases. They were assessed for antinociceptive, wound-healing, anti-cancer, anti-viral, antibacterial, anti-parasitic, and anti-angiogenesis effects.

Conclusion

PLA2 group III has been identified in different species of scorpions and bees. The

anti-leishmania, anti-bacterial, anti-viral, and anti-malarial activities of scorpion PLA2 still require further investigation. Many researches in this area have been stopped in the laboratory stage, and several studies need vast investigation in the clinical phase to show the pharmacological potential of PLA2.

Authors' Contribution

P.S.A and K.A contributed to Study Design and Study Implementation, P.S.A, K.A, H.A, and D.M contributed to Analysis and Interpretation of Data, Major Contribution to Writing. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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