Review Article

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 and 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 pray, 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 have 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 (PrPcs) of the cellular prion protein (PrPc). The overexpression of PrPc 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 (Aβ), 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, which 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-1β (IL-1β), TNFα, 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-κB), 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-1β 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 Ca2+, 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]		Neurodegenerative disease therapy	Prion	Blocking PrP(106-126)-mediated
Ye M et al.[70] Baek H et al.[74]			Alzheimer	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]		Anti-inflammatory effect	Multiple sclerosis Rheumatoid arthritis	Reducing the aggregation of immune cells
Shin D et al.[88]			Fibrosis radiation pneumonitis	Depletion of Tregs
Park et al.[97]			Allergic asthmatic	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) 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]			Alzheimer	Modulation of Tregs and production of IL-10
Kang G-H et al.[104]			Atherosclerosis	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 (*Trypanosoma brucei brucei)*	Killing or growth-inhibiting
		Gram-negative bacteria (*Enterobacter cloacae, Citrobacter freundii, Escherichia coli, Pseudomonas aeruginosa,* and *Klebsiella aerogenes*)	
		Gram-positive bacteria (*Staphylococcus aureus)*	
Deregnaucourt C et al.[121] Moreira LA et al.[120]		Malaria (*Plasmodium berghei and Plasmodium falciparum)*	1. Blocking oocyst formation of *Plasmodium berghei* in *Anopheles stephensi mosquito* 2. Growth arrest of the *intraerythrocytic* stage in *Plasmodium falciparum*

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	*Hemiscorpius lepturus*	Hemilipin	Anti-angiogenesis	Reducing the expression of VEGF-A, VEGF-C, VEGF-D, VEGFR-1, VEGFR-2, HGF, and CD105
Jridi et al.[125]		*Hemiscorpius lepturus*	Hemilipin2	Anti-angiogenesis	-
Krayem N et al.[134] and Krayem N et al.[132]		*Scorpio Maurus*	PLA2	Anti-angiogenesis and anti-tumor	Interference with α5β1 and αvβ3 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 α5β1 and αvβ3 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.

Conflict of Interest: None declared.

References

1 Jo M, Park MH, Kollipara PS, An BJ, Song HS, Han SB, et al. Anti-cancer effect of bee venom toxin and melittin in ovarian cancer cells through induction of death receptors and inhibition of JAK2/STAT3 pathway. Toxicol Appl Pharmacol. 2012;258:72-81. doi: 10.1016/j.taap.2011.10.009. PubMed PMID: 22027265.

2 Mamelak AN, Jacoby DB. Targeted delivery of antitumoral therapy to glioma and other malignancies with synthetic chlorotoxin (TM-601). Expert Opin Drug Deliv. 2007;4:175-86. doi: 10.1517/17425247.4.2.175. PubMed PMID: 17335414.

3 Remijsen Q, Verdonck F, Willems J. Parabutoporin, a cationic amphipathic peptide from scorpion venom: much more than an antibiotic. Toxicon. 2010;55:180-5. doi: 10.1016/j.toxicon.2009.10.027. PubMed PMID: 19874840.

4 Hider RC. Honeybee venom: a rich source of pharmacologically active peptides. Endeavour. 1988;12:60-5. doi: 10.1016/0160-9327(88)90082-8. PubMed PMID: 2458907.

5 Najafian M, Ghorbani A, Zargar M, Baradaran M, Baradaran N. Scorpion stings in pregnancy: an analysis of outcomes in 66 envenomed pregnant patients in Iran. J Venom Anim Toxins Incl Trop Dis. 2020;26:e20190039. doi: 10.1590/1678-9199-JVATITD-2019-0039. PubMed PMID: 32405289; PubMed Central PMCID: PMCPMC7204829.

6 Lourenco WR. Scorpions and life-history strategies: from evolutionary dynamics toward the scorpionism problem. J Venom Anim Toxins Incl Trop Dis. 2018;24:19. doi: 10.1186/s40409-018-0160-0. PubMed PMID: 30158956; PubMed Central PMCID: PMCPMC6106892.

7 Morgenstern D, Rohde BH, King GF, Tal T, Sher D, Zlotkin E. The tale of a resting gland: transcriptome of a replete venom gland from the scorpion Hottentotta judaicus. Toxicon. 2011;57:695-703. doi: 10.1016/j.toxicon.2011.02.001. PubMed PMID: 21329713.

8 Al-Asmari AK, Islam M, Al-Zahrani AM. In vitro analysis of the anticancer properties of scorpion venom in colorectal and breast cancer cell lines. Oncol Lett. 2016;11:1256-62. doi: 10.3892/ol.2015.4036. PubMed PMID: 26893728; PubMed Central PMCID: PMCPMC4734223.

9 Ding J, Chua PJ, Bay BH, Gopalakrishnakone P. Scorpion venoms as a potential source of novel cancer therapeutic compounds. Exp Biol Med (Maywood). 2014;239:387-93. doi: 10.1177/1535370213513991. PubMed PMID: 24599885.

10 Mander L, Liu HW. Comprehensive natural products II: chemistry and biology. 1st ed. Amsterdam: Elsevier; 2010.

11 Salem ML, Shoukry NM, Teleb WK, Abdel-Daim MM, Abdel-Rahman MA. In vitro and in vivo antitumor effects of the Egyptian scorpion Androctonus amoreuxi venom in an Ehrlich ascites tumor model. Springerplus. 2016;5:570. doi: 10.1186/s40064-016-2269-3. PubMed PMID: 27247867; PubMed Central PMCID: PMCPMC4864766.

12 Tong-ngam P, Roytrakul S, Sritanaudomchai H. BmKn-2 scorpion venom peptide for killing oral cancer cells by apoptosis. Asian Pac J Cancer Prev. 2015;16:2807-11. doi: 10.7314/apjcp.2015.16.7.2807. PubMed PMID: 25854366.

13 de la Salud Bea R, Petraglia AF, Ascuitto MR, Buck QM. Antibacterial Activity and Toxicity of Analogs of Scorpion Venom IsCT Peptides. Antibiotics (Basel). 2017;6. doi: 10.3390/antibiotics6030013. PubMed PMID: 28657596; PubMed Central PMCID: PMCPMC5617977.

14 Hong W, Li T, Song Y, Zhang R, Zeng Z, Han S, et al. Inhibitory activity and mechanism of two scorpion venom peptides against herpes simplex virus type 1. Antiviral Res. 2014;102:1-10. doi: 10.1016/j.antiviral.2013.11.013. PubMed PMID: 24315793; PubMed Central PMCID: PMCPMC7113736.

15 Gao B, Xu J, Rodriguez Mdel C, Lanz-Mendoza H, Hernandez-Rivas R, Du W, et al. Characterization of two linear cationic antimalarial peptides in the scorpion Mesobuthus eupeus. Biochimie. 2010;92:350-9. doi: 10.1016/j.biochi.2010.01.011. PubMed PMID: 20097251.

16 Flores-Solis D, Toledano Y, Rodriguez-Lima O, Cano-Sanchez P, Ramirez-Cordero BE, Landa A, et al. Solution structure and antiparasitic activity of scorpine-like peptides from Hoffmannihadrurus gertschi. FEBS Lett. 2016;590:2286-96. doi: 10.1002/1873-3468.12255. PubMed PMID: 27314815.

17 Dehong MFWSG. Antiepileptic effect of

scorpion venom on SD rats with Epilepsy induced by kainic acid [J]. Heilongjiang Medicine and Pharmacy. 2002;6.
18 Araujo RL, Gomez MV. Potentiation of bradykinin action on smooth muscle by a scorpion venom extract. Gen Pharmacol. 1976;7:123-6. doi: 10.1016/0306-3623(76)90047-1. PubMed PMID: 976731.
19 Hora ZA, Altaye SZ, Wubie AJ, Li J. Proteomics Improves the New Understanding of Honeybee Biology. J Agric Food Chem. 2018;66:3605-15. doi: 10.1021/acs.jafc.8b00772. PubMed PMID: 29558123.
20 Son DJ, Lee JW, Lee YH, Song HS, Lee CK, Hong JT. Therapeutic application of anti-arthritis, pain-releasing, and anti-cancer effects of bee venom and its constituent compounds. Pharmacol Ther. 2007;115:246-70. doi: 10.1016/j.pharmthera.2007.04.004. PubMed PMID: 17555825.
21 Rady I, Siddiqui IA, Rady M, Mukhtar H. Melittin, a major peptide component of bee venom, and its conjugates in cancer therapy. Cancer Lett. 2017;402:16-31. doi: 10.1016/j.canlet.2017.05.010. PubMed PMID: 28536009; PubMed Central PMCID: PMCPMC5682937.
22 Al-Ani I, Zimmermann S, Reichling J, Wink M. Pharmacological synergism of bee venom and melittin with antibiotics and plant secondary metabolites against multi-drug resistant microbial pathogens. Phytomedicine. 2015;22:245-55. doi: 10.1016/j.phymed.2014.11.019. PubMed PMID: 25765829.
23 Zhou J, Zhao J, Zhang S, Shen J, Qi Y, Xue X, et al. Quantification of melittin and apamin in bee venom lyophilized powder from Apis mellifera by liquid chromatography-diode array detector-tandem mass spectrometry. Anal Biochem. 2010;404:171-8. doi: 10.1016/j.ab.2010.05.014. PubMed PMID: 20580685.
24 Lee G, Bae H. Bee Venom Phospholipase A2: Yesterday's Enemy Becomes Today's Friend. Toxins (Basel). 2016;8:48. doi: 10.3390/toxins8020048. PubMed PMID: 26907347; PubMed Central PMCID: PMCPMC4773801.
25 Varanda EA, Monti R, Tavares DC. Inhibitory effect of propolis and bee venom on the mutagenicity of some direct- and indirect-acting mutagens. Teratog Carcinog Mutagen. 1999;19:403-13. PubMed PMID: 10587410.
26 Gajski G, Garaj-Vrhovac V. Radioprotective effects of honeybee venom (Apis mellifera) against 915-MHz microwave radiation-induced DNA damage in wistar rat lymphocytes: in vitro study. Int J Toxicol. 2009;28:88-98. doi: 10.1177/1091581809335051. PubMed PMID: 19482833.
27 Lee JY, Kang SS, Kim JH, Bae CS, Choi SH. Inhibitory effect of whole bee venom in adjuvant-induced arthritis. In Vivo. 2005;19:801-5. PubMed PMID: 15999553.
28 Baek YH, Huh JE, Lee JD, Choi DY, Park DS. Antinociceptive effect and the mechanism of bee venom acupuncture (Apipuncture) on inflammatory pain in the rat model of collagen-induced arthritis: Mediation by alpha2-Adrenoceptors. Brain Res. 2006;1073-1074:305-10. doi: 10.1016/j.brainres.2005.12.086. PubMed PMID: 16457792.
29 Orsolic N, Sver L, Verstovsek S, Terzic S, Basic I. Inhibition of mammary carcinoma cell proliferation in vitro and tumor growth in vivo by bee venom. Toxicon. 2003;41:861-70. doi: 10.1016/s0041-0101(03)00045-x. PubMed PMID: 12782086.
30 Orsolic N, Knezevic A, Sver L, Terzic S, Hackenberger BK, Basic I. Influence of honey bee products on transplantable murine tumours. Vet Comp Oncol. 2003;1:216-26. doi: 10.1111/j.1476-5810.2003.00029.x. PubMed PMID: 19379183.
31 Li JH, Zhang CX, Shen LR, Tang ZH, Cheng JA. Expression and regulation of phospholipase A2 in venom gland of the chinese honeybee, Apis cerana cerana. Arch Insect Biochem Physiol. 2005;60:1-12. doi: 10.1002/arch.20075. PubMed PMID: 16116618.
32 Kini RM. Excitement ahead: structure, function and mechanism of snake venom phospholipase A2 enzymes. Toxicon. 2003;42:827-40. doi: 10.1016/j.toxicon.2003.11.002. PubMed PMID: 15019485.
33 Sato H, Taketomi Y, Isogai Y, Miki Y, Yamamoto K, Masuda S, et al. Group III secreted phospholipase A2 regulates epididymal sperm maturation and fertility in mice. J Clin Invest. 2010;120:1400-14. doi: 10.1172/JCI40493. PubMed PMID: 20424323; PubMed Central PMCID: PMCPMC2860917.
34 Sato H, Kato R, Isogai Y, Saka G, Ohtsuki M, Taketomi Y, et al. Analyses of group III secreted phospholipase A2 transgenic mice reveal potential participation of this enzyme in plasma lipoprotein modification, macrophage foam cell formation, and atherosclerosis. J Biol Chem. 2008;283:33483-97. doi: 10.1074/jbc.M804628200. PubMed PMID: 18801741; PubMed Central PMCID: PMCPMC2662271.
35 Masuda S, Yamamoto K, Hirabayashi T, Ishikawa Y, Ishii T, Kudo I, et al. Human group

III secreted phospholipase A2 promotes neuronal outgrowth and survival. Biochem J. 2008;409:429-38. doi: 10.1042/BJ20070844. PubMed PMID: 17868035.
36 Valentin E, Ghomashchi F, Gelb MH, Lazdunski M, Lambeau G. Novel human secreted phospholipase A(2) with homology to the group III bee venom enzyme. J Biol Chem. 2000;275:7492-6. doi: 10.1074/jbc.275.11.7492. PubMed PMID: 10713052.
37 Guerin V, Dubarryr M, Robic D, Brachet F, Rautureau M, Andre C, et al. Microsphere entrapped bee-venom phospholipase A2 retains specific IgE binding capacity: a possible use for oral specific immunotherapy. J Microencapsul. 2002;19:761-5. doi: 10.1080/02652040210162612. PubMed PMID: 12569024.
38 Urbanek R, Kemeny DM, Richards D. Subclass of IgG anti-bee venom antibody produced during bee venom immunotherapy and its relationship to long-term protection from bee stings and following termination of venom immunotherapy. Clin Allergy. 1986;16:317-22. doi: 10.1111/j.1365-2222.1986.tb01963.x. PubMed PMID: 3742787.
39 Lichtenstein LM, Valentine MD, Sobotka AK. A case for venom treatment in anaphylactic sensitivity to hymenoptera sting. N Engl J Med. 1974;290:1223-7. doi: 10.1056/NEJM197405302902204. PubMed PMID: 4133096.
40 Ozdemir C, Kucuksezer UC, Akdis M, Akdis CA. Mechanisms of immunotherapy to wasp and bee venom. Clin Exp Allergy. 2011;41:1226-34. doi: 10.1111/j.1365-2222.2011.03812.x. PubMed PMID: 21729181.
41 Hunt KJ, Valentine MD, Sobotka AK, Benton AW, Amodio FJ, Lichtenstein LM. A controlled trial of immunotherapy in insect hypersensitivity. N Engl J Med. 1978;299:157-61. doi: 10.1056/NEJM197807272990401. PubMed PMID: 78446.
42 Muller U, Akdis CA, Fricker M, Akdis M, Blesken T, Bettens F, et al. Successful immunotherapy with T-cell epitope peptides of bee venom phospholipase A2 induces specific T-cell anergy in patients allergic to bee venom. J Allergy Clin Immunol. 1998;101:747-54. doi: 10.1016/S0091-6749(98)70402-6. PubMed PMID: 9648701.
43 Akdis CA, Akdis M, Blesken T, Wymann D, Alkan SS, Muller U, et al. Epitope-specific T cell tolerance to phospholipase A2 in bee venom immunotherapy and recovery by IL-2 and IL-15 in vitro. J Clin Invest. 1996;98:1676-83. doi: 10.1172/JCI118963. PubMed PMID: 8833918; PubMed Central PMCID: PMCPMC507602.
44 Irsch J, Konig C, Lohndorf A, Tesch H, Krieg T, Merk H, et al. The frequency of phospholipase A2 binding of basophilic granulocytes does not decrease during bee-venom-specific immunotherapy. Allergy. 1999;54:742-7. doi: 10.1034/j.1398-9995.1999.00952.x. PubMed PMID: 10442531.
45 Hori S, Nomura T, Sakaguchi S. Control of regulatory T cell development by the transcription factor Foxp3. Science. 2003;299:1057-61. doi: 10.1126/science.1079490. PubMed PMID: 12522256.
46 Akdis CA, Blesken T, Akdis M, Wuthrich B, Blaser K. Role of interleukin 10 in specific immunotherapy. J Clin Invest. 1998;102:98-106. doi: 10.1172/JCI2250. PubMed PMID: 9649562; PubMed Central PMCID: PMCPMC509070.
47 von Garnier C, Astori M, Kettner A, Dufour N, Heusser C, Corradin G, et al. Allergen-derived long peptide immunotherapy down-regulates specific IgE response and protects from anaphylaxis. Eur J Immunol. 2000;30:1638-45. doi: 10.1002/1521-4141(200006)30:6<1638::AID-IMMU1638>3.0.CO;2-R. PubMed PMID: 10898500.
48 Orsolic N. Bee venom in cancer therapy. Cancer Metastasis Rev. 2012;31:173-94. doi: 10.1007/s10555-011-9339-3. PubMed PMID: 22109081.
49 Jang MH, Shin MC, Lim S, Han SM, Park HJ, Shin I, et al. Bee venom induces apoptosis and inhibits expression of cyclooxygenase-2 mRNA in human lung cancer cell line NCI-H1299. J Pharmacol Sci. 2003;91:95-104. doi: 10.1254/jphs.91.95. PubMed PMID: 12686753.
50 Chaisakul J, Hodgson WC, Kuruppu S, Prasongsook N. Effects of Animal Venoms and Toxins on Hallmarks of Cancer. J Cancer. 2016;7:1571-8. doi: 10.7150/jca.15309. PubMed PMID: 27471574; PubMed Central PMCID: PMCPMC4964142.
51 Nabiuni M, Safaeinejad Z, Parivar K, Divsalar A, Nazari Z. Antineoplastic effects of honey bee venom. Zahedan J Res Med Sci. 2013;15:1-5.
52 Kong GM, Tao WH, Diao YL, Fang PH, Wang JJ, Bo P, et al. Melittin induces human gastric cancer cell apoptosis via activation of mitochondrial pathway. World J Gastroenterol. 2016;22:3186-95. doi: 10.3748/wjg.v22.i11.3186. PubMed PMID: 27003995; PubMed Central PMCID: PMCPMC4789993.

53 Gajski G, Garaj-Vrhovac V. Melittin: a lytic peptide with anticancer properties. Environ Toxicol Pharmacol. 2013;36:697-705. doi: 10.1016/j.etap.2013.06.009. PubMed PMID: 23892471.
54 Hong SJ, Rim GS, Yang HI, Yin CS, Koh HG, Jang MH, et al. Bee venom induces apoptosis through caspase-3 activation in synovial fibroblasts of patients with rheumatoid arthritis. Toxicon. 2005;46:39-45. doi: 10.1016/j.toxicon.2005.03.015. PubMed PMID: 15922390.
55 Moon DO, Park SY, Heo MS, Kim KC, Park C, Ko WS, et al. Key regulators in bee venom-induced apoptosis are Bcl-2 and caspase-3 in human leukemic U937 cells through downregulation of ERK and Akt. Int Immunopharmacol. 2006;6:1796-807. doi: 10.1016/j.intimp.2006.07.027. PubMed PMID: 17052670.
56 Cho HJ, Jeong YJ, Park KK, Park YY, Chung IK, Lee KG, et al. Bee venom suppresses PMA-mediated MMP-9 gene activation via JNK/p38 and NF-kappaB-dependent mechanisms. J Ethnopharmacol. 2010;127:662-8. doi: 10.1016/j.jep.2009.12.007. PubMed PMID: 19969058.
57 Rahman KM, Sarkar FH, Banerjee S, Wang Z, Liao DJ, Hong X, et al. Therapeutic intervention of experimental breast cancer bone metastasis by indole-3-carbinol in SCID-human mouse model. Mol Cancer Ther. 2006;5:2747-56. doi: 10.1158/1535-7163.MCT-06-0221. PubMed PMID: 17121921.
58 Li B, Gu W, Zhang C, Huang XQ, Han KQ, Ling CQ. Growth arrest and apoptosis of the human hepatocellular carcinoma cell line BEL-7402 induced by melittin. Onkologie. 2006;29:367-71. doi: 10.1159/000094711. PubMed PMID: 16974113.
59 Fletcher JE, Jiang MS. Possible mechanisms of action of cobra snake venom cardiotoxins and bee venom melittin. Toxicon. 1993;31:669-95. doi: 10.1016/0041-0101(93)90375-s. PubMed PMID: 8342168.
60 Shier WT. Activation of high levels of endogenous phospholipase A2 in cultured cells. Proc Natl Acad Sci U S A. 1979;76:195-9. doi: 10.1073/pnas.76.1.195. PubMed PMID: 106389; PubMed Central PMCID: PMCPMC382904.
61 Altinbas B, Topuz BB, Yilmaz MS, Aydin C, Savci V, Jochem J, et al. The mediation of the central histaminergic system in the pressor effect of intracerebroventricularly injected melittin, a phospholipase A2 activator, in normotensive rats. Prostaglandins Leukot Essent Fatty Acids. 2012;87:153-8. doi: 10.1016/j.plefa.2012.08.006. PubMed PMID: 22995146.
62 Grandison L. Stimulation of anterior pituitary prolactin release by melittin, an activator of phospholipase A2. Endocrinology. 1984;114:1-7. doi: 10.1210/endo-114-1-1. PubMed PMID: 6418521.
63 Lad PJ, Shier WT. Activation of microsomal guanylate cyclase by a cytotoxic polypeptide: melittin. Biochem Biophys Res Commun. 1979;89:315-21. doi: 10.1016/0006-291x(79)90980-x. PubMed PMID: 38790.
64 Putz T, Ramoner R, Gander H, Rahm A, Bartsch G, Thurnher M. Antitumor action and immune activation through cooperation of bee venom secretory phospholipase A2 and phosphatidylinositol-(3,4)-bisphosphate. Cancer Immunol Immunother. 2006;55:1374-83. doi: 10.1007/s00262-006-0143-9. PubMed PMID: 16485125.
65 Putz T, Ramoner R, Gander H, Rahm A, Bartsch G, Bernardo K, et al. Bee venom secretory phospholipase A2 and phosphatidylinositol-homologues cooperatively disrupt membrane integrity, abrogate signal transduction and inhibit proliferation of renal cancer cells. Cancer Immunol Immunother. 2007;56:627-40. doi: 10.1007/s00262-006-0220-0. PubMed PMID: 16947021.
66 Brandner S, Klein MA, Frigg R, Pekarik V, Parizek P, Raeber A, et al. Neuroinvasion of prions: insights from mouse models. Exp Physiol. 2000;85:705-12. doi: 10.1111/j.1469-445x.2000.02091.x. PubMed PMID: 11187965.
67 Sim VL. Prion disease: chemotherapeutic strategies. Infect Disord Drug Targets. 2012;12:144-60. doi: 10.2174/187152612800100161. PubMed PMID: 22420513.
68 Kolko M, DeCoster MA, de Turco EB, Bazan NG. Synergy by secretory phospholipase A2 and glutamate on inducing cell death and sustained arachidonic acid metabolic changes in primary cortical neuronal cultures. J Biol Chem. 1996;271:32722-8. doi: 10.1074/jbc.271.51.32722. PubMed PMID: 8955105.
69 Jeong JK, Moon MH, Bae BC, Lee YJ, Seol JW, Park SY. Bee venom phospholipase A2 prevents prion peptide induced-cell death in neuronal cells. Int J Mol Med. 2011;28:867-73. doi: 10.3892/ijmm.2011.730. PubMed PMID: 21701769.
70 Ye M, Chung HS, Lee C, Yoon MS, Yu AR, Kim JS, et al. Neuroprotective effects of bee venom phospholipase A2 in the

3xTg AD mouse model of Alzheimer's disease. J Neuroinflammation. 2016;13:10. doi: 10.1186/s12974-016-0476-z. PubMed PMID: 26772975; PubMed Central PMCID: PMCPMC4715334.
71 Block ML, Hong JS. Microglia and inflammation-mediated neurodegeneration: multiple triggers with a common mechanism. Prog Neurobiol. 2005;76:77-98. doi: 10.1016/j.pneurobio.2005.06.004. PubMed PMID: 16081203.
72 Jana M, Palencia CA, Pahan K. Fibrillar amyloid-beta peptides activate microglia via TLR2: implications for Alzheimer's disease. J Immunol. 2008;181:7254-62. doi: 10.4049/jimmunol.181.10.7254. PubMed PMID: 18981147; PubMed Central PMCID: PMCPMC2701549.
73 Muehlhauser F, Liebl U, Kuehl S, Walter S, Bertsch T, Fassbender K. Aggregation-Dependent interaction of the Alzheimer's beta-amyloid and microglia. Clin Chem Lab Med. 2001;39:313-6. doi: 10.1515/CCLM.2001.048. PubMed PMID: 11388654.
74 Baek H, Park SY, Ku SJ, Ryu K, Kim Y, Bae H, et al. Bee Venom Phospholipase A2 Induces Regulatory T Cell Populations by Suppressing Apoptotic Signaling Pathway. Toxins (Basel). 2020;12. doi: 10.3390/toxins12030198. PubMed PMID: 32235689; PubMed Central PMCID: PMCPMC7150970.
75 Hirsch EC, Hunot S. Neuroinflammation in Parkinson's disease: a target for neuroprotection? Lancet Neurol. 2009;8:382-97. doi: 10.1016/S1474-4422(09)70062-6. PubMed PMID: 19296921.
76 Awad K, Abushouk AI, AbdelKarim AH, Mohammed M, Negida A, Shalash AS. Bee venom for the treatment of Parkinson's disease: How far is it possible? Biomed Pharmacother. 2017;91:295-302. doi: 10.1016/j.biopha.2017.04.065. PubMed PMID: 28477460.
77 Kim HW, Kwon YB, Han HJ, Yang IS, Beitz AJ, Lee JH. Antinociceptive mechanisms associated with diluted bee venom acupuncture (apipuncture) in the rat formalin test: involvement of descending adrenergic and serotonergic pathways. Pharmacol Res. 2005;51:183-8. doi: 10.1016/j.phrs.2004.07.011. PubMed PMID: 15629266.
78 Olson KE, Gendelman HE. Immunomodulation as a neuroprotective and therapeutic strategy for Parkinson's disease. Curr Opin Pharmacol. 2016;26:87-95. doi: 10.1016/j.coph.2015.10.006. PubMed PMID: 26571205; PubMed Central PMCID: PMCPMC4716884.
79 Doo AR, Kim SN, Kim ST, Park JY, Chung SH, Choe BY, et al. Bee venom protects SH-SY5Y human neuroblastoma cells from 1-methyl-4-phenylpyridinium-induced apoptotic cell death. Brain Res. 2012;1429:106-15. doi: 10.1016/j.brainres.2011.10.003. PubMed PMID: 22078207.
80 Doo AR, Kim ST, Kim SN, Moon W, Yin CS, Chae Y, et al. Neuroprotective effects of bee venom pharmaceutical acupuncture in acute 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced mouse model of Parkinson's disease. Neurol Res. 2010;32:88-91. doi: 10.1179/016164109X12537002794282. PubMed PMID: 20034453.
81 Lee SM, Yang EJ, Choi SM, Kim SH, Baek MG, Jiang JH. Effects of bee venom on glutamate-induced toxicity in neuronal and glial cells. Evid Based Complement Alternat Med. 2012;2012:368196. doi: 10.1155/2012/368196. PubMed PMID: 21904562; PubMed Central PMCID: PMCPMC3166716.
82 Kim KH, Lee SY, Shin J, Hwang JT, Jeon HN, Bae H. Dose-Dependent Neuroprotective Effect of Standardized Bee Venom Phospholipase A2 Against MPTP-Induced Parkinson's Disease in Mice. Front Aging Neurosci. 2019;11:80. doi: 10.3389/fnagi.2019.00080. PubMed PMID: 31024294; PubMed Central PMCID: PMCPMC6462482.
83 Ye M, Chung HS, Lee C, Hyun Song J, Shim I, Kim YS, et al. Bee venom phospholipase A2 ameliorates motor dysfunction and modulates microglia activation in Parkinson's disease alpha-synuclein transgenic mice. Exp Mol Med. 2016;48:e244. doi: 10.1038/emm.2016.49. PubMed PMID: 27388550; PubMed Central PMCID: PMCPMC4973312.
84 Chung ES, Lee G, Lee C, Ye M, Chung HS, Kim H, et al. Bee Venom Phospholipase A2, a Novel Foxp3+ Regulatory T Cell Inducer, Protects Dopaminergic Neurons by Modulating Neuroinflammatory Responses in a Mouse Model of Parkinson's Disease. J Immunol. 2015;195:4853-60. doi: 10.4049/jimmunol.1500386. PubMed PMID: 26453752.
85 Liu XD, Zhang JL, Zheng HG, Liu FY, Chen Y. Clinical randomized study of bee-sting therapy for rheumatoid arthritis. Zhen Ci Yan Jiu. 2008;33:197-200. PubMed PMID: 18807725.
86 Lee JD, Park HJ, Chae Y, Lim S. An Overview of Bee Venom Acupuncture in the Treatment of Arthritis. Evid Based Complement Alternat Med. 2005;2:79-84. doi: 10.1093/ecam/neh070. PubMed PMID: 15841281; PubMed Central PMCID: PMCPMC1062163.

87 Castro HJ, Mendez-Lnocencio JI, Omidvar B, Omidvar J, Santilli J, Nielsen HS, Jr., et al. A phase I study of the safety of honeybee venom extract as a possible treatment for patients with progressive forms of multiple sclerosis. Allergy Asthma Proc. 2005;26:470-6. PubMed PMID: 16541972.
88 Shin D, Lee G, Sohn SH, Park S, Jung KH, Lee JM, et al. Regulatory T Cells Contribute to the Inhibition of Radiation-Induced Acute Lung Inflammation via Bee Venom Phospholipase A(2) in Mice. Toxins (Basel). 2016;8. doi: 10.3390/toxins8050131. PubMed PMID: 27144583; PubMed Central PMCID: PMCPMC4885046.
89 Billingham ME, Morley J, Hanson JM, Shipolini RA, Vernon CA. Letter: An anti-inflammatory peptide from bee venom. Nature. 1973;245:163-4. doi: 10.1038/245163a0. PubMed PMID: 4582672.
90 Im EJ, Kim SJ, Hong SB, Park JK, Rhee MH. Anti-Inflammatory Activity of Bee Venom in BV2 Microglial Cells: Mediation of MyD88-Dependent NF-kappaB Signaling Pathway. Evid Based Complement Alternat Med. 2016;2016:3704764. doi: 10.1155/2016/3704764. PubMed PMID: 27563334; PubMed Central PMCID: PMCPMC4987476.
91 Kim H, Lee H, Lee G, Jang H, Kim SS, Yoon H, et al. Phospholipase A2 inhibits cisplatin-induced acute kidney injury by modulating regulatory T cells by the CD206 mannose receptor. Kidney Int. 2015;88:550-9. doi: 10.1038/ki.2015.147. PubMed PMID: 25993317.
92 Hossen MS, Shapla UM, Gan SH, Khalil MI. Impact of Bee Venom Enzymes on Diseases and Immune Responses. Molecules. 2016;22. doi: 10.3390/molecules22010025. PubMed PMID: 28035985; PubMed Central PMCID: PMCPMC6155781.
93 Lee G, Kang G-H, Bae H. Bee venom phospholipase A2 suppression of experimental autoimmune encephalomyelitis is dependent on its enzymatic activity. Molecular & Cellular Toxicology. 2019;15:307-13. doi: 10.1007/s13273-019-0034-8.
94 Geha RS. Regulation of IgE synthesis in humans. J Allergy Clin Immunol. 1992;90:143-50. doi: 10.1016/0091-6749(92)90064-9. PubMed PMID: 1500620.
95 Chung KF, Barnes PJ. Cytokines in asthma. Thorax. 1999;54:825-57. doi: 10.1136/thx.54.9.825. PubMed PMID: 10456976; PubMed Central PMCID: PMCPMC1745579.
96 Mucida DS, de Castro Keller A, Fernvik EC, Russo M. Unconventional strategies for the suppression of allergic asthma. Curr Drug Targets Inflamm Allergy. 2003;2:187-95. doi: 10.2174/1568010033484223. PubMed PMID: 14561172.
97 Park S, Baek H, Jung KH, Lee G, Lee H, Kang GH, et al. Bee venom phospholipase A2 suppresses allergic airway inflammation in an ovalbumin-induced asthma model through the induction of regulatory T cells. Immun Inflamm Dis. 2015;3:386-97. doi: 10.1002/iid3.76. PubMed PMID: 26734460; PubMed Central PMCID: PMCPMC4693726.
98 Kim KH, Kim M, Lee J, Jeon HN, Kim SH, Bae H. Comparison of the Protective Effects of Bee Venom Extracts with Varying PLA2 Compositions in a Mouse Model of Parkinson's Disease. Toxins (Basel). 2019;11. doi: 10.3390/toxins11060358. PubMed PMID: 31248167; PubMed Central PMCID: PMCPMC6628630.
99 Baek H, Lee CJ, Choi DB, Kim NS, Kim YS, Ye YJ, et al. Bee venom phospholipase A2 ameliorates Alzheimer's disease pathology in Abeta vaccination treatment without inducing neuro-inflammation in a 3xTg-AD mouse model. Sci Rep. 2018;8:17369. doi: 10.1038/s41598-018-35030-1. PubMed PMID: 30478329; PubMed Central PMCID: PMCPMC6255868.
100 Chen CH, Zhou W, Liu S, Deng Y, Cai F, Tone M, et al. Increased NF-kappaB signalling up-regulates BACE1 expression and its therapeutic potential in Alzheimer's disease. Int J Neuropsychopharmacol. 2012;15:77-90. doi: 10.1017/S1461145711000149. PubMed PMID: 21329555.
101 Ham HJ, Han SB, Yun J, Yeo IJ, Ham YW, Kim SH, et al. Bee venom phospholipase A2 ameliorates amyloidogenesis and neuroinflammation through inhibition of signal transducer and activator of transcription-3 pathway in Tg2576 mice. Transl Neurodegener. 2019;8:26. doi: 10.1186/s40035-019-0167-7. PubMed PMID: 31592103; PubMed Central PMCID: PMCPMC6774221.
102 Arany I, Safirstein RL. Cisplatin nephrotoxicity. Semin Nephrol. 2003;23:460-4. doi: 10.1016/s0270-9295(03)00089-5. PubMed PMID: 13680535.
103 Kim H, Keum DJ, Kwak J, Chung HS, Bae H. Bee venom phospholipase A2 protects against acetaminophen-induced acute liver injury by modulating regulatory T cells and IL-10 in mice. PLoS One. 2014;9:e114726. doi: 10.1371/journal.pone.0114726. PubMed PMID: 25478691; PubMed Central PMCID: PMCPMC4257707.
104 Kang GH, Lee S, Choi DB, Shin D, Kim J,

Yang H, et al. Bee Venom Phospholipase A2 Ameliorates Atherosclerosis by Modulating Regulatory T Cells. Toxins (Basel). 2020;12. doi: 10.3390/toxins12100609. PubMed PMID: 32977607; PubMed Central PMCID: PMCPMC7598180.
105 Chen J, Lariviere WR. The nociceptive and anti-nociceptive effects of bee venom injection and therapy: a double-edged sword. Prog Neurobiol. 2010;92:151-83. doi: 10.1016/j.pneurobio.2010.06.006. PubMed PMID: 20558236; PubMed Central PMCID: PMCPMC2946189.
106 Lee JH, Kwon YB, Han HJ, Mar WC, Lee HJ, Yang IS, et al. Bee venom pretreatment has both an antinociceptive and anti-inflammatory effect on carrageenan-induced inflammation. J Vet Med Sci. 2001;63:251-9. doi: 10.1292/jvms.63.251. PubMed PMID: 11307924.
107 Alcindor T, Beauger N. Oxaliplatin: a review in the era of molecularly targeted therapy. Curr Oncol. 2011;18:18-25. doi: 10.3747/co.v18i1.708. PubMed PMID: 21331278; PubMed Central PMCID: PMCPMC3031353.
108 Muggia FM. Recent updates in the clinical use of platinum compounds for the treatment of gynecologic cancers. Semin Oncol. 2004;31:17-24. doi: 10.1053/j.seminoncol.2004.11.007. PubMed PMID: 15726530.
109 Petit T, Benider A, Yovine A, Bougnoux P, Spaeth D, Maindrault-Goebel F, et al. Phase II study of an oxaliplatin/vinorelbine combination in patients with anthracycline- and taxane-pre-treated metastatic breast cancer. Anticancer Drugs. 2006;17:337-43. doi: 10.1097/00001813-200603000-00013. PubMed PMID: 16520663.
110 Li D, Kim W, Shin D, Jung Y, Bae H, Kim SK. Preventive Effects of Bee Venom Derived Phospholipase A(2) on Oxaliplatin-Induced Neuropathic Pain in Mice. Toxins (Basel). 2016;8. doi: 10.3390/toxins8010027. PubMed PMID: 26797636; PubMed Central PMCID: PMCPMC4728549.
111 Nakashima A, Tomono S, Yamazaki T, Inui M, Morita N, Ichimonji I, et al. Phospholipase A2 from bee venom increases poly(I:C)-induced activation in human keratinocytes. Int Immunol. 2020;32:371-83. doi: 10.1093/intimm/dxaa005. PubMed PMID: 31957789.
112 Brown S, Reynolds NJ. Atopic and non-atopic eczema. BMJ. 2006;332:584-8. doi: 10.1136/bmj.332.7541.584. PubMed PMID: 16528081; PubMed Central PMCID: PMCPMC1397720.
113 Jung KH, Baek H, Kang M, Kim N, Lee SY, Bae H. Bee Venom Phospholipase A2 Ameliorates House Dust Mite Extract Induced Atopic Dermatitis Like Skin Lesions in Mice. Toxins (Basel). 2017;9. doi: 10.3390/toxins9020068. PubMed PMID: 28218721; PubMed Central PMCID: PMCPMC5331447.
114 Shin D, Choi W, Bae H. Bee Venom Phospholipase A2 Alleviate House Dust Mite-Induced Atopic Dermatitis-Like Skin Lesions by the CD206 Mannose Receptor. Toxins (Basel). 2018;10. doi: 10.3390/toxins10040146. PubMed PMID: 29614845; PubMed Central PMCID: PMCPMC5923312.
115 Hewawaduge C, Lee B-H, Kim T-H, Uddin MB, Kim J-H, Kim CG, et al. Phospholipase A2 isolated from the venom of honey bees prevents viral attachment in mammalian cells. Journal of Biomedical and Translational Research. 2016;17:75-8. doi: 10.12729/jbtr.2016.17.3.075.
116 Fenard D, Lambeau G, Maurin T, Lefebvre JC, Doglio A. A peptide derived from bee venom-secreted phospholipase A2 inhibits replication of T-cell tropic HIV-1 strains via interaction with the CXCR4 chemokine receptor. Mol Pharmacol. 2001;60:341-7. doi: 10.1124/mol.60.2.341. PubMed PMID: 11455021.
117 Boulanger N, Brun R, Ehret-Sabatier L, Kunz C, Bulet P. Immunopeptides in the defense reactions of Glossina morsitans to bacterial and Trypanosoma brucei brucei infections. Insect Biochem Mol Biol. 2002;32:369-75. doi: 10.1016/s0965-1748(02)00029-2. PubMed PMID: 11886771.
118 Boutrin MC, Foster HA, Pentreath VW. The effects of bee (Apis mellifera) venom phospholipase A2 on Trypanosoma brucei brucei and enterobacteria. Exp Parasitol. 2008;119:246-51. doi: 10.1016/j.exppara.2008.02.002. PubMed PMID: 18343372.
119 Perumal Samy R, Gopalakrishnakone P, Thwin MM, Chow TK, Bow H, Yap EH, et al. Antibacterial activity of snake, scorpion and bee venoms: a comparison with purified venom phospholipase A2 enzymes. J Appl Microbiol. 2007;102:650-9. doi: 10.1111/j.1365-2672.2006.03161.x. PubMed PMID: 17309613.
120 Moreira LA, Ito J, Ghosh A, Devenport M, Zieler H, Abraham EG, et al. Bee venom phospholipase inhibits malaria parasite development in transgenic mosquitoes. J Biol Chem. 2002;277:40839-43. doi: 10.1074/jbc.M206647200. PubMed PMID: 12167627.
121 Deregnaucourt C, Schrevel J. Bee venom phospholipase A2 induces stage-specific growth arrest of the intraerythrocytic Plasmodium falciparum via modifications of human serum components. J Biol Chem.

2000;275:39973-80. doi: 10.1074/jbc.M006712200. PubMed PMID: 10988294.
122 Hirsch EC, Breidert T, Rousselet E, Hunot S, Hartmann A, Michel PP. The role of glial reaction and inflammation in Parkinson's disease. Ann N Y Acad Sci. 2003;991:214-28. doi: 10.1111/j.1749-6632.2003.tb07478.x. PubMed PMID: 12846989.
123 Incamnoi P, Patramanon R, Thammasirirak S, Chaveerach A, Uawonggul N, Sukprasert S, et al. Heteromtoxin (HmTx), a novel heterodimeric phospholipase A(2) from Heterometrus laoticus scorpion venom. Toxicon. 2013;61:62-71. doi: 10.1016/j.toxicon.2012.10.012. PubMed PMID: 23142507.
124 Jridi I, Catacchio I, Majdoub H, Shahbazeddah D, El Ayeb M, Frassanito MA, et al. Hemilipin, a novel Hemiscorpius lepturus venom heterodimeric phospholipase A2, which inhibits angiogenesis in vitro and in vivo. Toxicon. 2015;105:34-44. doi: 10.1016/j.toxicon.2015.08.022. PubMed PMID: 26335363.
125 Jridi I, Catacchio I, Majdoub H, Shahbazzadeh D, El Ayeb M, Frassanito MA, et al. The small subunit of Hemilipin2, a new heterodimeric phospholipase A2 from Hemiscorpius lepturus scorpion venom, mediates the antiangiogenic effect of the whole protein. Toxicon. 2017;126:38-46. doi: 10.1016/j.toxicon.2016.12.001. PubMed PMID: 27940138.
126 Zamudio FZ, Conde R, Arevalo C, Becerril B, Martin BM, Valdivia HH, et al. The mechanism of inhibition of ryanodine receptor channels by imperatoxin I, a heterodimeric protein from the scorpion Pandinus imperator. J Biol Chem. 1997;272:11886-94. doi: 10.1074/jbc.272.18.11886. PubMed PMID: 9115249.
127 Conde R, Zamudio FZ, Becerril B, Possani LD. Phospholipin, a novel heterodimeric phospholipase A2 from Pandinus imperator scp6pion venom. FEBS Lett. 1999;460:447-50. doi: 10.1016/s0014-5793(99)01392-7. PubMed PMID: 10556514.
128 Valdez-Cruz NA, Batista CV, Possani LD. Phaiodactylipin, a glycosylated heterodimeric phospholipase A from the venom of the scorpion Anuroctonus phaiodactylus. Eur J Biochem. 2004;271:1453-64. doi: 10.1111/j.1432-1033.2004.04047.x. PubMed PMID: 15066171.
129 Louati H, Krayem N, Fendri A, Aissa I, Sellami M, Bezzine S, et al. A thermoactive secreted phospholipase A(2) purified from the venom glands of Scorpio maurus: relation between the kinetic properties and the hemolytic activity. Toxicon. 2013;72:133-42. doi: 10.1016/j.toxicon.2013.06.017. PubMed PMID: 23831286.
130 Ramanaiah M, Parthasarathy PR, Venkaiah B. Purification and properties of phospholipase A2 from the venom of scorpion, (Heterometrus fulvipes). Biochem Int. 1990;20:931-40. PubMed PMID: 2112384.
131 Iruela-Arispe ML, Zovein A. 8 - Angiogenesis. In: Polin RA, Abman SH, Rowitch DH, Benitz WE, Fox WW, editors. Fetal and Neonatal Physiology. 5th ed. Amsterdam: Elsevier; 2017. p. 85-9.e2. doi: 10.1016/B978-0-323-35214-7.00008-1.
132 Krayem N, Abdelkefi-Koubaa Z, Marrakchi N, Luis J, Gargouri Y. Anti-angiogenic effect of phospholipases A2 from Scorpio maurus venom glands on Human Umbilical Vein Endothelial Cells. Toxicon. 2018;145:6-14. doi: 10.1016/j.toxicon.2018.02.042. PubMed PMID: 29486161.
133 Lee YS, Kim YH, Shin EK, Kim DH, Lim SS, Lee JY, et al. Anti-angiogenic activity of methanol extract of Phellinus linteus and its fractions. J Ethnopharmacol. 2010;131:56-62. doi: 10.1016/j.jep.2010.05.064. PubMed PMID: 20554007.
134 Krayem N, Abdelkefi-Koubaa Z, Marrakchi N, Gargouri Y, Luis J. Native and recombinant phospholipases A2 of Scorpio maurus venom glands impair angiogenesis by targeting integrins alpha5beta1 and alphavbeta3. Int J Biol Macromol. 2018;116:305-15. doi: 10.1016/j.ijbiomac.2018.04.141. PubMed PMID: 29715557.
135 Vetter RS, Visscher PK. Bites and stings of medically important venomous arthropods. Int J Dermatol. 1998;37:481-96. doi: 10.1046/j.1365-4362.1998.00455.x. PubMed PMID: 9679688.