Role of Honeybee Venom in Treatment of Various Diseases and Disorders

Mounika K[1*], Dr.R.Thirumurthy[2], Mohanapriya K[3], R. Kanmani[6], C. Kaviya[7], G. V. Madhumitha[8], P. Monika[9]

1*Associate Professor,Vivekanandha Pharmacy College-Sankari-Salem,Affiliated To Tamilnadu Dr MGR Medical University Chennai.

2.Professor&Hod Vivekanandha Pharmacy College-Sankari-Salem ,Affiliated To Tamilnadu Dr MGR Medical University Chennai.

3.Assistant Professor Vivekanandha Pharmacy College-Sankari-Salem ,Affiliated To Tamilnadu Dr MGR Medical University Chennai.

4,5,6,7.Student (Final year B.Pharm), Vivekanandha Pharmacy College-Sankari-Salem ,Affiliated To Tamilnadu Dr MGR Medical University Chennai.

How to Cite this Article:

K, M., K, M., Kanmani, R., Kaviya, C., Madhumitha, G. V. & Monika, P. (2026). Role of Honeybee Venom in Treatment of Various Diseases and Disorders. International Journal of Creative and Open Research in Engineering and Management, 02(7). https://doi.org/10.55041/ijcope.v2i7.100

https://doi.org/ 10.55041/ijcope.v2i7.100

ABSTRACT:

Apitherapy is an alternate therapy that relies on the usage of honeybee products, most importantly bee venom for the treatment of many human diseases. Venom can be introduced into the human body by manual injection or by direct bee stings. Bee venom contains several active molecules such as peptides and enzymes that have advantageous potential in treating inflammation and central nervous system diseases, such as Parkinson's disease, Alzheimer's disease and sclerosis. Moreover, bee venom has shown promising benefits against different types of cancer as well as anti-viral activity, even against the Arthritis. Many studies described biological activities of bee venom components and launched preclinical trials to improve the potential use of apitoxin and its constituents as the next generation of drugs. The aim of this review is to summarize the main compounds of bee venom, their primary biological properties, mechanisms of action, and their therapeutic values in alternative therapy strategies.

Keywords: Bee venom, apitoxin, apitherapy, Parkinson's disease, Alzheimer's disease, sclerosis, arthritis, cancer

1)INTRODUCTION:

Bees have provided several products to humans, such as honey, beeswax, pollen, royal jelly, and propolis.[1]They also pollinate a wide variety of agricultural crops [2]. Although bees are extremely beneficial to crops and humans, they do present a danger due to their ability to inflict painful and toxic stings [3]. Fortunately, most honeybees are not aggressive towards humans and only attack when they feel threatened. However, due to the human introduction of the Africanized bee, a hybrid with highly aggressive behaviour, massive bee sting attacks have markedly increased and are now endemic in most of the Americas [4]. Standardized medical approaches exist for handling cases, where victims allergic to venom components are stung by bees, or where milder envenoming's are caused by only a few bee stings. Yet, no antivenom exists for treating severe bee envenoming. The underlying reason for this derives from the low immunogenicity of bee venom proteins (e.g., melittin), which hinders successful immunization of production animals to yield high antibody titters in their plasma and, consequently, complicates the development of a bee antivenom significantly [5].

1.1 HONEYBEE VENOM:

Bee venom is a complex mixture of compounds, which include proteins, peptides, amino acids, phospholipids, sugars, biogenic amines, volatile compounds, pheromones, and a high quantity of water (>80%) [6,7,8].

Components of honeybee venom

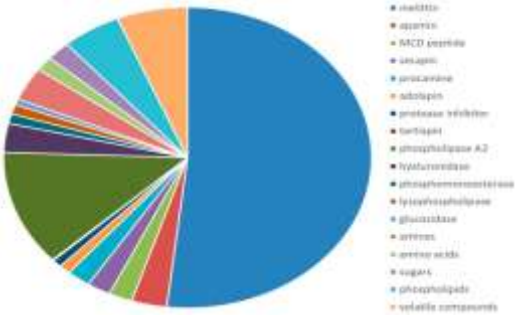
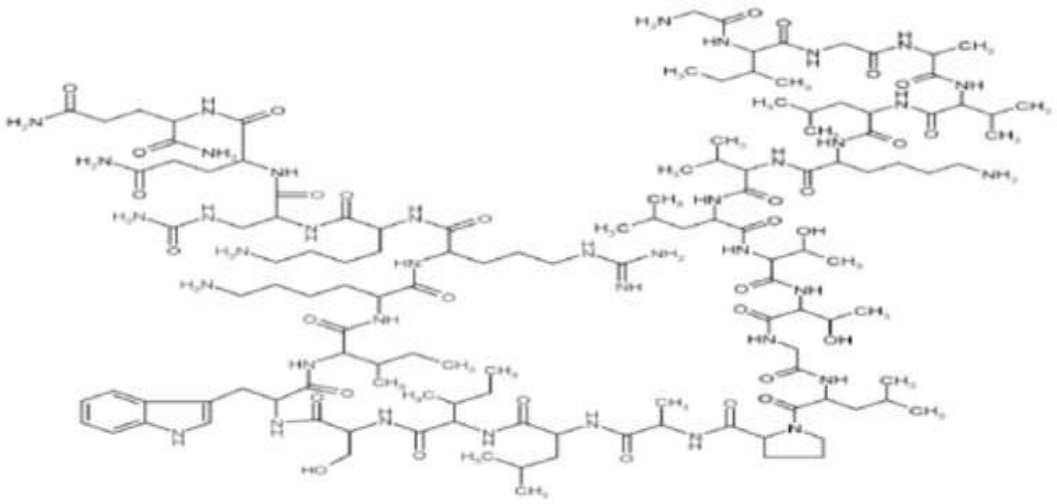


Fig:1

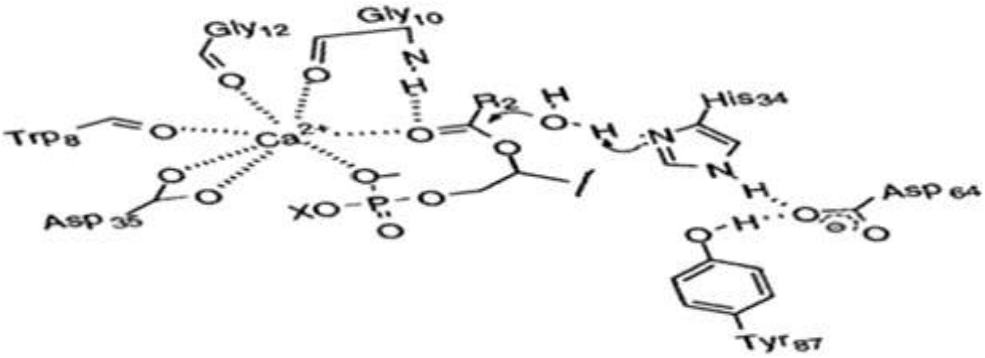
Fig:2

a) Melittin is the main and most toxic compound in bee venom, constituting 50–60% of the whole venom [9]. Melittin only induces minor allergic reactions [10] but causes most of the pain associated with bee stings [3] which is induced through direct and indirect actions on primary nociceptor cells. The direct action is caused by melittin activation of thermal nociceptor transient receptor potential vanilloid 1 (TRPV1) via the PLA_2 cascade pathway, resulting in sensitization of the primary nociceptors [11,12,13]. The indirect action is based on the pore-forming actions of melittin, which allows for the release of pain-inducing substances such as H^+, adenosine triphosphate (ATP), and 5-hydroxytryptamine (5-HT) from mast cells, as well as melittin causes tissue damage, resulting in activation of the pain receptors. Pore formation induced by melittin can also release mediators, such as histamine, bradykinin, and ATP, which activate G-protein-coupled receptors (GPCRs), resulting in the phosphorylation of phospholipase C (PLC). PLC cleaves phosphatidylinositol 4,5-bisphosphateintodiacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP3). DAG is an endogenous activator of transient receptor potential canonical (TRPC) channels, resulting in the indirect excitation of primary nociceptive neurons (i.e., pain) [3].



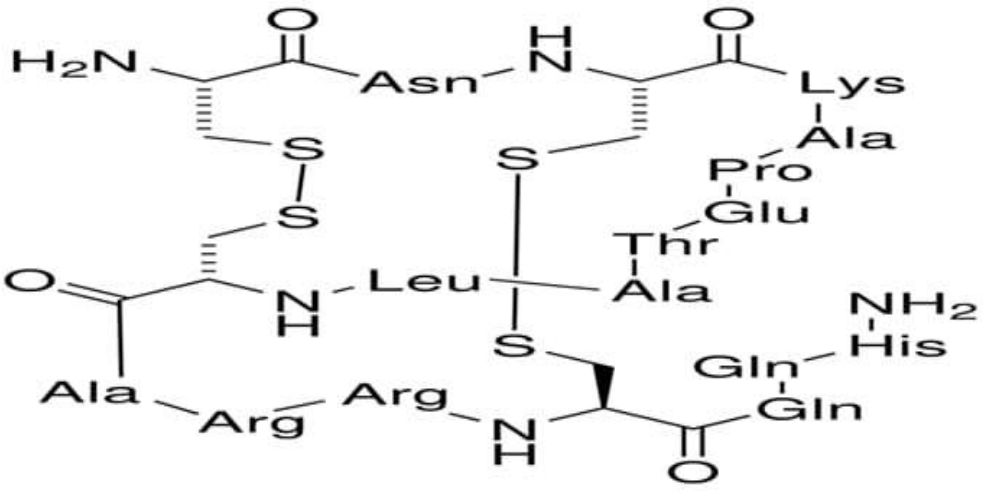
STRUCTURE OF MELITTIN

b) Phospholipase A_2 (PLA_2) is the second most abundant compound (10–12%) and the most allergenic and immunogenic protein in bee venom [14]. Alone, PLA_2 is a non-toxic protein but when PLA_2 forms a complex with melittin, called bee hemolytic factor, it cleaves cellular membrane phospholipids [15]. *In vitro*, bee PLA_2 possesses several activities, such as trypanocidal and antibacterial effects [16,17], neuronal protection caused by prion proteins, and anti-tumor properties [18]. Moreover, bee PLA_2 was able to decrease hepatotoxicity caused by acetaminophen in mice [19]. Phospholipase B (PLB) has also been reported to be present in bee venom [20]. PLB exhibits both PLA_1 and PLA_2 activity, being responsible for cleaving phospholipids on sn-1 and sn-2 position of acyl chains [21], which enhances PLA_2 activity [22].



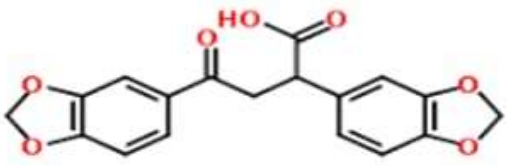
STRUCTURE OF PHOSPHOLIPASE A2

c)Apamin is another important peptide in bee venom, which comprises 1–3% of crude venom and can allosterically and selectively inhibit Ca^{2+}-dependent K^+ channels (SK channels), found in the central nervous system (CNS). Only SK2 and SK3 channels are known to be sensitive to apamin, and when blocked, there is a decrease of the delayed hyperpolarization of cells, which results in increased continuous firing of neurons in the mesencephalon and cerebellum, elevating cell sensitivity to excitatory inputs [23]. Moreover, apamin is able to activate inhibitory muscarinic receptors of motor nerve terminals (i.e., reducing neuromuscular transmission), which has been experimentally explored as a potential treatment against diseases presenting high muscle excitability [24] such as Parkinson's disease, learning deficit disorder and other disabilities [25,26].



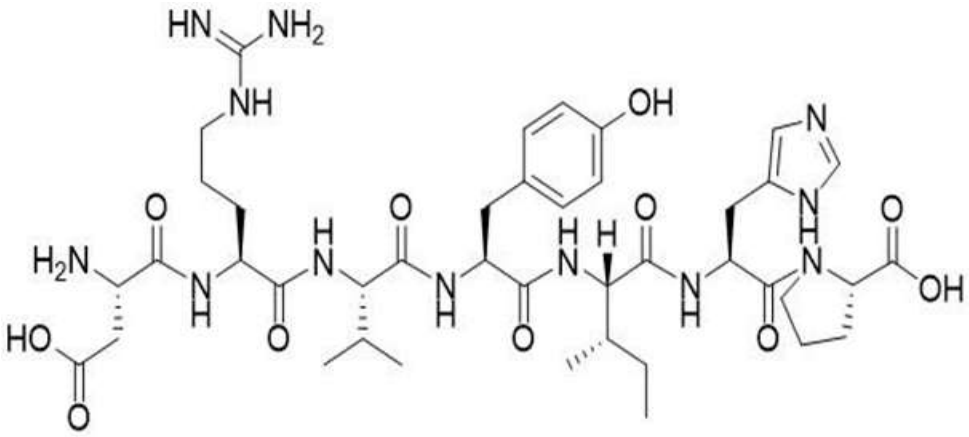
STRUCTURE OF APAMIN

d)Hyaluronidase is an enzyme found in bee venom (1–3%), as well as many other animal venoms [27]. Hyaluronidase is responsible for fast distribution of toxins, also known as the "spreading factor," as this enzyme cleaves hyaluronic acid from the extracellular matrix (ECM) [28,29], leading to a faster and systemic envenoming by disrupting tissues [30]. In addition, hyaluronidase is considered a potent allergen in bee venom [31].



STRUCTURE OF HYALURONIDASE

e) Mast cell-degranulating (MCD) peptide is also considered an important component in bee venom based on its capability to induce histamine release from mast cells, which exhibit a central role on inflammation and allergy [32]. In high quantities, however, MCD presents an opposite action, where it inhibits mast cell degranulation (i.e., by inhibiting histamine release). Thus, MCD can also act as an anti-allergic molecule [33]. Indeed, studies have demonstrated that MCD peptide presents anti-inflammatory activity *in vitro* and *in vivo* [34,35].



STRUCTURE OF MCD PEPTIDE

ACID PHOSPHATASE

Venom acid phosphatase is a glycoprotein and a Potent allergen in BV of Apis mellifera. It contains Four possible sites of glycosylation with the Sequence Asn-Xaa-Ser/Thr. The motif RHGXRSP Characterizes its acid phosphatase activity and Distinguishes it from the acid phosphatase enzyme Ofother organism. It responsible for IgE mediated Allergic reactions in humans. It causes the release Of histamine from sensitized basophiles related to Such manifestations has causing urticaria and flare Reactions. Approximately 37% of BV allergic Patients develop Api m 3 (acid phosphatase) Specific IgE, which can be used in immune Therapies. [Acid phosphatase: Molecular weight, 45000-96000 Da][36]

ALPHA- GLUCOSIDASE

Alpha- Glucosidase acts on the alpha-glycosidic Bond at the non- reducing terminal side of a Substrate and liberates alpha – glucose as a product in Apis mellifera Lingustica, alphaglucosidase has three isozymes [I, II, III], Which have different substrate specifications .However, the alpha- glucosidase contained in Honey from the hypopharyngeal gland is alphaglucosidase III, as immunological methods havr Confirmed . [37] The enzymes remain stable at a pH Ranging from 5 to 10 (the optimum pH is 5.5) And is denatured at a pH lower than 4.5. It is Stable at 40 C ,but if it left standing at 60 C for 15 min, it will completely nonfunctional. Its Function is to degrade sucrose in the necterInto glucose and fructose to degrade sucrose in Thenecter into glucose and fructose to produce Honey.[38]

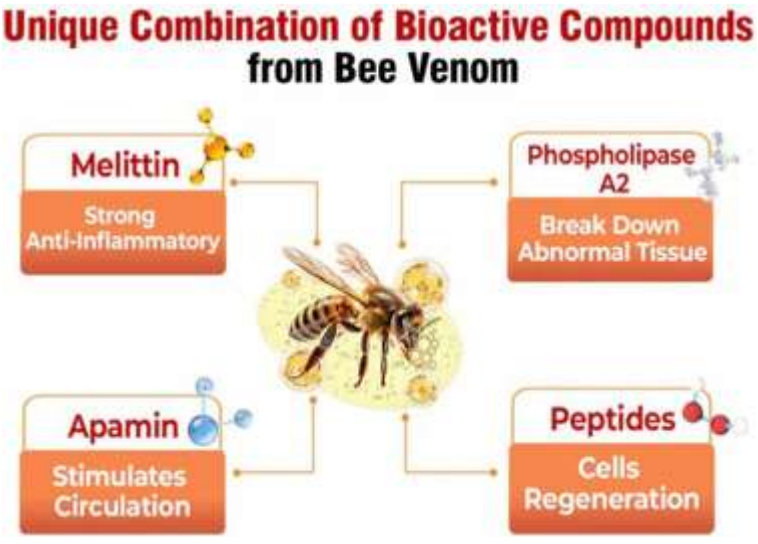


Fig:3

HONEYBEE VENOM ACTIVITES

ANTI-MICROBIAL PROPERTIES OF BEE VENOM

Antifungal activity of bee venom:

It has been documented that melittin possess Anti- fungal activity against Candida albicans By destroying membrane and causing the cell Apoptosis in a capsule or mitochondrial –Dependent way. Also, bee venom is a strong Agent against Trychophytonrubrum ,Trychophyton mentagrophytes and Candida Albicans . It is proved that the effect of bee Venom towards Trychophyton rubrum and Trychophyton mentagrophytes is stronger than of commercially available medicine, Fluconazole.[39]

Furthermore , sweet bee venom (SVB) (Bee Venom without enzymes and histamine) Possesses stronger anti- fungal efficacy Compared to bee venom. Both sweet bee venom And bee venom show anti-fungal capability on 10 experimental Candida albicans strains Isolated from vagina and blood through broth Micro-dilution assay, disk diffusion assay, and Killing- curve assay presented that bee of Apis Cerana has strong inhibitory activity towards Candida albicans as compared to Apis dorsata And Apis florae , respectively.The two constituents of bee venom , apamin And melittin , show inhibitory effect against Aspergillus pillows and Alternaria alternate Which cause inflammatory disease in nasal Cavity. Based on the literature studies, a larger And long –term follow- up trial is needed to Determine the safety and efficacy of bee venom Because its safety is still a strong limiting Consideration during clinical treatment.[40]

Anti-protozoal activity of bee venom :

Studies revealed that bee venom group III sPLA2 has anti- trypanosomiasis properties. The expression of bee venom III sPLA2 in a genetically modified mosquitos midgut has inhibitory action towards plasmodium ookinetes. Additionally, cecropin (a hybrid of melittin) has anti- leishmanial efficacy for Leishmania donavani promastigote via disrupting its plasma membrane. Melittin disrupts themembranes integrity of both prokaryotic and eukaryotic organism which causes lysis of membrane and permeability.This kind of reaction makes melittin an antimicrobial, anti-fungal, and anti- leishmanial agent.[41] According to previous research, PLA2 shows anti- protozoal action towards Trypanosoma brucei brucei in controlled Conditions. Bee venom peptide called Lasioglossins, possesses greater anti- microbial Action because of its membrane interaction ,as Well as DNA binding . It has been reported that ,The peptide melittin possesses anti- protozoal Activity against Toxoplasma gondii, Trypanosoma cruzi, Plasmodium and Leishmania. Furthermore, melittin has been Utilized in vaccine preparation to enhance Immunity to leishmaniasis . Also, melittin shows Killing activity towards Trypanosoma cruzi . As We reviewed , BV possesses anti- protozoal Activities but the exact effect of its compounds Along with mode of action and its Commercialization as a therapeutic medicine Is still unknown.[42]

NEUROPROTECTIVE ACTIVITY OF BEE VENOM

Parkinson Disease

Parkinson Disease is a degenerative movement disorder that leads to progressive disability in patients. ThePathological hallmarks of the disease are the progressive loss of dopaminergic neurons in the substantiaNigra (a basal ganglia structure found in the human brain), and the presence of Lewy bodies that containsAggregates of alpha-synuclein, a widely distributed protein in the brain [43,44]. Abnormal microglialActivation is also a pathological sign in different neurodegenerative diseases, including PD [45]. ManyPreclinical trials investigated the effect of BV on the migration of leukocytes or microglial activation inAnimal and cellular models. Other tests evaluated the neuroprotective potential of BV acupunctureTherapy (BVA) against rotenone-induced oxidative stress, neuroinflammation, and apoptosis in PDMice models [46]. Rotenone is a pesticide that may affect pathophysiological mechanisms that areImplicated in PD [46]. Interestingly, BV proved its ability to prevent dopamine depletion after theAdministration of rotenone. In

addition, the locomotor activity was re-established after treating PDMice models with BV. The treatment effectively repressed DNA damage and inhibited the expression ofThe apoptotic Bax, Bcl-2, and caspase-3 genes in the brain of PD mice. These findings demonstrate thatBV normalized all the apoptotic and neuroinflammatory markers and restored brain neurochemistryAfter rotenone injury . It has also been shown that BV can protect doparminergic neurons fromDegeneration in experimental PD models. Along with this finding, acupoint stimulation of lower hind Limbs with BV was found to be protective in the MPTP (1-Methyl-4-Phenyl-1,2,3,6-TetrahydroPyridine) Mouse model of PD [47].

Alzheimer's Disease

Alzheimer's Disease is the most common neurodegenerative disease and many pathological processes are involvedIn its emergence [48]. However, the hypothesis of amyloid cascade and the toxicity of amyloid beta(Aβ) peptides have dominated research so far due to advanced studies showing that aggregates of thisPeptide are characteristic signs of the disease [49–51]. Although the etiology of AD remains unknown,The evidences suggest that inflammatory responses may play a crucial role in its pathogenesis [52,53].The current treatments for cognitive loss related to AD rely on the usage of muscarinic or nicotinicReceptor ligands and the acetylcholinesterase (AChE) inhibitor [54]. As an alternative strategy, Ye et al.Showed that bvPLA2 can be used as a treatment to block the progression of AD in transgenic mice.This is due to the ability of bvPLA2 to reduce the accumulation of Aβ and improve cognitive functioningIn mice brains. The same study similarly shows that bvPLA2 can increase glucose brain metabolism andReduce neuroinflammatory responses in the hippocampus, which can limit AD pathogenesis .ARecent study also showed that regulatory T-cells populations could be modulated by bvPLA2 treatment in a rogression of AD by combining bvPLA2 treatment along with Aβ vaccination therapy to prevent itsadverse inflammatory response [55].

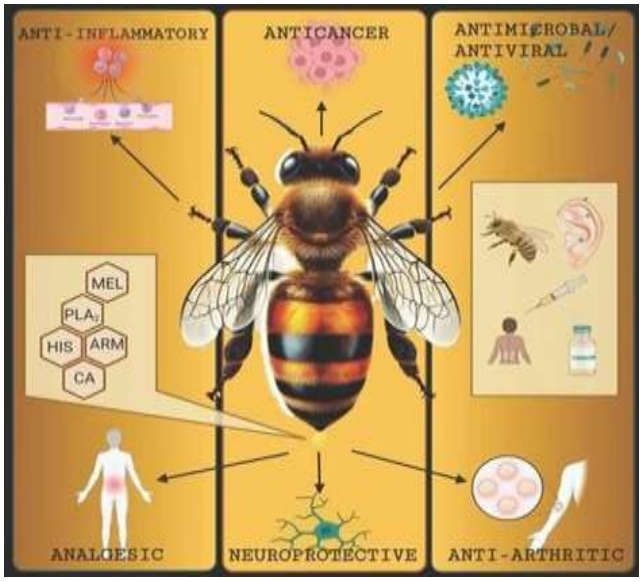


Fig:4

Amyotrophic Lateral Sclerosis

ALS is a CNS disease that causes the death of motor neurons [56]. A significant trait of ALSis the abnormal accumulation of mutant SOD1 (mtSOD1) protein aggregates [57]. A mice modelof ALS carrying the mutated mtSOD1 gene with a Glycine to Alanine substitution (SOD1G93A) wascharacterized by Jaarsma et al., facilitating the understanding of ALS etiology [58]. Both in vitro andin vivo studies using the mutant SOD1 transgenic mice demonstrated various cellular pathogenicevents in motor neurons like protein misfolding, dysfunction of mitochondria, and accumulation ofneurofilament [59]. Interestingly, BV showed some potential for counteracting this disease. In fact, theadministration of BV, at a precise and symptomatic stage

of the progression of ALS, leads to an increasein motor activity in SOD1G93A mutant mice and a prolongation in life expectancy when comparedwith age-matched control mice. This could be caused by the blockage of activated microglia usuallyfound in mice models of ALS [60]. Another study demonstrated that bee venom acupuncture (BVA) atST36 inhibits neuroinflammation in the spinal cord of symptomatic ALS mice by significantly reducing the levels of inflammatory proteins like TLR4, CD14, and TNF-α [61].

ANTI INFLAMMATORY ACTIVITY

Inflammation is protective process for body in response to harmful stimuli. Chronic inflammation led to development of many diseases like diabetes, rheumatoid arthritis, cardiovascular disease, obesity, asthma, skin disease, and CNS related disorders [62]. Melittin, when it is administrated at high doses, causes local pain, itching, and inflammation. However, low doses of bee venom compound can induce wide anti-inflammatory effects. Many reports are investigated the anti-inflammatory mechanisms of melittin in different disease such as rheumatoid arthritis and Alzheimer. In fact, it acts by inhibiting inflammatory cytokines like interlukin-6 (IL-6), IL-8, tumor necrosis factor- alpha (TNF-α) and interferon-γ. Moreover, melittin decreases signaling pathways that activate inflammatory cytokines, including nuclear factor – kappa B, protein kinase Akt, extracellular signal regulated in porphyromonas gingivalis lipopolisaccharide treated human kerationocytes.[63].These findings indicate that, by blocking their primary signaling pathways, melittin inhibits inflammatory cytokines leading to a reduced inflammation in skin, liver, joint and neuronal tissue. Regarding skin diseases, a recent study by Kim et al. showed that BV reduces atopic dermatitis, the most common allergic chronic inflammatory skin disease. In fact, the venom stimulates CD55 production by triggering ERK1/2 pathways, which leads to the alleviation of the disease's symptoms. Interestingly, a previous study by Shin et al. described the anti-inflammatory potential of bvPLA2 in skin diseases by showing that the enzyme attentiates atopic skin inflammation through interaction with CD206[64].

ANTIVIRAL ACTIVITY

Bee venom (BV) and its two main components, melittin and phospholipase A2 (PLA2), are well known for their antimicrobial properties and can be used as complementary agents to fight bacteria. These compounds work by creating pores in bacterial membranes, which leads to their breakdown and ultimately causes the bacteria to burst. However, their antiviral effects haven't been explored as much in the scientific literature. A recent study shed light on the antiviral potential of BV, with promising results both in lab experiments and live animal tests [65]. The research showed that BV and melittin have strong antiviral effects against a variety of viruses, including enveloped ones like the vesicular stomatitis virus, influenza A virus, and herpes simplex virus, as well as non-enveloped viruses such as enterovirus71 and coxsackie virus. Impressively, melittin was able to protect mice from lethal doses of the influenza A H1N1 virus. While the exact way BV and melittin fight viruses isn't fully understood yet, it's clear that BV interacts directly with the virus's outer surface [66]. Additionally, BV and its components can trigger the body's production of type I interferon, a crucial part of the immune response that helps block viral replication inside Infected cells. Research at Washington University School of Medicine in St. Louis has even explored using nano particles loaded with melittin to specifically target and destroy HIV particles without harming healthy cells. This innovative approach aims to develop a vaginal gel containing these nanoparticles to prevent the spread of HIV. The idea is that the melittin on the nanoparticle's merges with the virus's envelope, forming porelike structures that break it open [67].

IMMUNO MODULATORY ACTIVITY

Bee venom, a complex substance produced by honeybees, contains several bioactive compounds that have garnered increasing interest for their potential immunomodulatory effects. The major components of bee venom include melittin, phospholipase A2, hyaluronidase, apamin, and several peptides, enzymes, and proteins. These compounds interact with various components of the immune system, triggering both innate and adaptive immune responses. Melittin, one of the primary peptides in bee venom, has been shown to

exhibit anti-inflammatory and antimicrobial properties. It can induce the release of proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukins (IL-1, IL-6), which play crucial roles in immune system regulation [68]. Furthermore, melittin can activate macrophages and dendritic cells, key players in the body's defense against pathogens. Phospholipase A2* in bee venom also has potent immunomodulatory effects, particularly through the breakdown of phospholipids in cell membranes, which generates arachidonic acid and subsequent inflammatory mediators like prostaglandins and leukotrienes. This action contributes to both local and systemic inflammatory responses, which can be beneficial in cases of immune dysregulation. Additionally, bee venom's hyaluronidase promotes the spread of other active components, enhancing tissue penetration and increasing the venom's efficacy in modulating immune responses. The venom's ability to modulate immune activity extends to its potential therapeutic applications [69]. For instance, studies suggest that bee venom might help in the treatment of autoimmune diseases, where the immune system mistakenly attacks the body's own tissues, by regulating T-cell responses and promoting a more balanced immune activity. It is also proposed that bee venom could improve circulation and stimulate the lymphatic system, which aids in the removal of toxins and enhances the body's natural defense mechanisms. In conditions involving chronic inflammation, bee venom's capacity to down regulate overactive immune responses and reduce inflammatory cytokine production may offer relief. Moreover, bee venom's anti-cancer potential has been explored, as some studies suggest that it can inhibit the growth of cancer cells through immune system activation and direct cytotoxic effects. However, despite the promising findings, much of the research is still in early stages, and more clinical trials are required to fully understand the therapeutic potential, safety, and optimal usage of bee venom for immune system modulation [70].

PROPERTIES OF BEE VENOM

Bee venom is an odorless, translucent fluid with pungent scent. It has an unpleasant taste and pH from 4.5 to 5.5. It is dissolvable in water and insoluble in ammonium sulfate as well as alcohol. Due to the oxidation of BV protein, the dehydrated BV becomes light pale, while some variants available on the market are brown. Also, BV contains about 88 % of water. Additionally, the venom contents like phospholipid, fructose and glucose are similar to the contents present in bee hemolymph. Due to its components, in direct contact with eyes or mucous membranes, BV causes mechanical damage[71].

STABILITY OF BEE VENOM

A study found that diluting BV 3000 and 4000 times can keep it stable for 12 months at ambient temperature and refrigerator temperature. However, in the same investigation, diluted BV maintained at ambient temperature for 12 months did not demonstrate antibacterial action against Staphylococcus aureus, although diluted BV stored in a refrigerator did. Impact of the component responsible for the antibacterial activity of BV reduces at room temperature, according to this study[72].Another study, conducted in 2021, assessed stability of melittin, a component of BV known to be responsible for several biological effects such as anticancer, antiviral, and anti-inflammatory. Melittin concentration of identical BV held at ambient temperature and in the refrigerator for 6 months was quantified using a reversed phase high performance liquid chromatography (HPLC) technique with a photodiode array (PDA) detector in this study, and no significant difference was found. Melittin's remarkable stability, even at room temperature, lowers the storage costs for BV makers [73].

CONCLUSION

Honey bee venom is a complex and biologically active natural substance consist of various compositions such as melittin, apamin, adolapin, phospholipase A2, secabin, hyalurodinase, acid phosphatase. These compositions exhibitsa vast pharmacological activity inflammatory, immunomodulatory anti-viral, and such as antianti-cancer, neuroprotective properties. It also applicable for the treatment of neurodegenerative disorders like Alzheimer's disease, Parkinson's disease. The bioactivities in bee venom also treat for various conditions such as chronic pain disorders, arthritis and cancer. The clinical application of bee venom is

limited due to the potential allergic reactions. Although the bee venom therapeutic applications explained in the current research, but in ancient times apitherapy, bee venom therapy and bee venom acupuncture are evolved. In summary, with the responsive scientific exploration and various advancement in technology, bee venom may become a valuable compound of conventional medicine in the future.

REFERENCE:

1. Mizrahi A, Lensky Y. Bee Products: Properties, Applications, and Apitherapy. Tel Aviv: Springer Science & Business Media; (2013). [Google Scholar]

2. Hoover SE, Ovinge LP. Pollen collection, honey production, and pollination services: managing honey bees in an agricultural setting. J Econ Entomol. (2018) 111:1509–16. 10.1093/jee/toy125 [DOI] [PMC free article] [PubMed] [Google Scholar]

3. Chen J, Guan S-M, Sun W, Fu H. Melittin, the major pain-producing substance of bee venom. Neurosci Bull. (2016) 32:265–72. 10.1007/s12264-016-0024-y [DOI] [PMC free article] [PubMed] [Google Scholar]

4. Schumacher MJ, Egen NB. Significance of Africanized bees for public health: a review. Arch Intern Med. (1995) 155:2038–43. 10.1001/archinte.155.19.2038 [DOI] [PubMed] [Google Scholar]

5. King TP, Coscia MR, Kochoumian L. Structure-immunogenicity relationship of melittin and its N-terminal truncated analogs. Biochemistry. (1993) 32:3506–10. 10.1021/bi00064a039 [DOI] [PubMed] [Google Scholar]

6. Abd El-Wahed AA, Khalifa SAM, Sheikh BY, Farag MA, Saeed A, Larik FA, et al. Chapter 13–bee venom composition: from Chemistry to biological activity. In Atta-ur-Rahman editor. Studies in Natural Products Chemistry. Oxford: Elsevier; (2017). p. 459–84. [Google Scholar]

7. Szókán G, Horváth J, Almás M, Saftics G, Palócz A. Liquid chromatographic analysis and separation of polypeptide components from honey bee venoms. J Liq Chromatogr. (1994) 17:3333–49. 10.1080/10826079408013516 [DOI] [Google Scholar]

8. Hossen MS, Shapla UM, Gan SH, Khalil MI. Impact of bee venom enzymes on diseases and immune responses. Molecules. (2016) 22:1–16. 10.3390/molecules22010025 [DOI] [PMC free article] [PubMed] [Google Scholar]

9. Raghuraman H, Chattopadhyay A. Melittin: a membrane-active peptide with diverse functions. Biosci Rep. (2007) 27:189–223. 10.1007/s10540-006-9030-z [DOI] [PubMed] [Google Scholar]

10. Paull BR, Yunginger JW, Gleich GJ. Melittin: an allergen of honeybee venom. J Allergy Clin Immunol. (1977) 59:334–8. 10.1016/0091-6749(77)90056-2 [DOI] [PubMed] [Google Scholar]

11. Ding J, Xiao Y, Lu D, Du Y-R, Cui X-Y, Chen J. Effects of SKF-96365, a TRPC inhibitor, on melittin-induced inward current and intracellular Ca2+ rise in primary sensory cells. Neurosci Bull. (2011) 27:135–42. 10.1007/s12264-011-1018-4 [DOI] [PMC free article] [PubMed] [Google Scholar]

12. Hao J, Liu M-G, Yu Y-Q, Cao F-L, Li Z, Lu Z-M, et al. Roles of peripheral mitogen-activated protein kinases in melittin-induced nociception and hyperalgesia. Neuroscience. (2008) 152:1067–75. 10.1016/j.neuroscience.2007.12.038 [DOI] [PubMed] [Google Scholar]

13. Ding J, Zhang J-R, Wang Y, Li C-L, Lu D, Guan S-M, et al. Effects of a non-selective TRPC channel blocker, SKF-96365, on melittininduced spontaneous persistent nociception and inflammatory pain

hypersensitivity. Neurosci Bull. (2012) 28:173–81. 10.1007/s12264-012-1213-y [DOI] [PMC free article] [PubMed] [Google Scholar]

14. Elieh Ali Komi D, Shafaghat F, Zwiener RD. Immunology of bee venom. Clin Rev Allergy Immunol. (2018) 54:386–96. 10.1007/s12016-017-8597-4 [DOI] [PubMed] [Google Scholar]
15. .Mingarro I, Pérez-Payá E, Pinilla C, Appel JR, Houghten RA, Blondelle SE. Activation of bee venom phospholipase A_2 through a peptide-enzyme complex. FEBS Lett. (1995) 372:131–4. 10.1016/0014-5793(95)00964-B [DOI] [PubMed] [Google Scholar
16. Boutrin M-CF, Foster HA, Pentreath VW. The effects of bee (*Apis mellifera*) venom phospholipase A_2 on *Trypanosoma brucei* brucei and enterobacteria. Exp Parasitol. (2008) 119:246–51. 10.1016/j.exppara.2008.02.002 [DOI] [PubMed] [Google Scholar]
17. Leandro LF, Mendes CA, Casemiro LA, Vinholis AHC, Cunha WR, de Almeida R, et al. Antimicrobial activity of apitoxin, melittin and phospholipase A_2 of honey bee (*Apis mellifera*) venom against oral pathogens. An Acad Bras Cienc. (2015) 87:147–55. 10.1590/0001-3765201520130511 [DOI] [PubMed] [Google Scholar
18. 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. 10.1016/j.pharmthera.2007.04.004 [DOI] [PubMed] [Google Scholar]
19. .Kim H, Keum DJ, Kwak J won, Chung H-S, Bae H. Bee venom phospholipase A_2 protects against acetaminophen-induced acute liver injury by modulating regulatory T cellsandIL-10 in mice. PLoS ONE. (2014) 9:e114726. 10.1371/journal.pone.0114726 [DOI] [PMC free article] [PubMed] [Google Scholar]
20. .Doery HM, Pearson JE. Phospholipase B in snake venoms and bee venom. Biochem J. (1964) 92:599–602. 10.1042/bj0920599 [DOI] [PMC free article] [PubMed] [Google Scholar]
21. .Abusabbah M, Lau WH, Mahmoud ME, Salih AM, Omar D. Prospects of using carbohydrates as supplemented-diets and protein rich mixture as alternative-diet to improve the quality of venom produced by *Apis cerana* L. J EntomolZool Stud. (2016) 4:23–6. [Google Scholar]
22. .Hossen MS, Shapla UM, Gan SH, Khalil MI. Impact of bee venom enzymes on diseases and immune responses. Molecules. (2016) 22:1–16. 10.3390/molecules22010025 [DOI] [PMC free article] [PubMed] [Google Scholar]
23. .Lamy C, Goodchild SJ, Weatherall KL, Jane DE, Liégeois J-F, Seutin V, et al. Allosteric block of KCa2 channels by apamin. J Biol Chem. (2010) 285:27067–77. 10.1074/jbc.M110.110072 [DOI] [PMC free article] [PubMed] [Google Scholar]
24. .de Matos Silva LFC, de Paula Ramos ER, Ambiel CR, Correia-de-SáP, Alves-Do-Prado W. Apamin reduces neuromuscular transmission by activating inhibitory muscarinic M(2) receptors on motor nerve terminals. Eur J Pharmacol. (2010) 626:239–43. 10.1016/j.ejphar.2009.09.064 [DOI] [PubMed] [Google Scholar]
25. .Moreno M, Giralt E. Three valuable peptides from bee and wasp venoms for therapeutic and biotechnological use: melittin, apamin and mastoparan. Toxins. (2015) 7:1126–50. 10.3390/toxins7041126 [DOI] [PMC free article] [PubMed] [Google Scholar]
26. .Chase TN, Oh-Lee JD. Composition for Treating Parkinson's Disease (2013). Available online at: https://patents.google.com/patent/WO2013083574A1/en?oq=Thomas%2c+N.C.;+Justin%2c+D.O.L.+Composition+for+Treatins+Parkinsin%E2%80%99s+Disease.+WO2013083574+A1%2c+13+June+2013+ (accessed April 14, 2019).

27. .Fox JW. A brief review of the scientific history of several lesser-known snake venom proteins: l-amino acid oxidases, hyaluronidases and phosphodiesterases. Toxicon. (2013) 62:75–82. 10.1016/j.toxicon.2012.09.009 [DOI] [PubMed] [Google Scholar]

28. Kreil G. Hyaluronidases–a group of neglected enzymes. Protein Sci. (1995) 4:1666–9. 10.1002/pro.5560040902 [DOI] [PMC free article] [PubMed] [Google Scholar]

29. Marković-Housley Z, Miglierini G, Soldatova L, Rizkallah PJ, Müller U, Schirmer T. Crystal structure of hyaluronidase, a major allergen of bee venom. Structure. (2000) 8:1025–35. 10.1016/S0969-2126(00)00511-6 [DOI] [PubMed] [Google Scholar]

30. Girish KS, Kemparaju K. The magic glue hyaluronan and its eraser hyaluronidase: a biological overview. Life Sci. (2007) 80:1921–43. 10.1016/j.lfs.2007.02.037 [DOI] [PubMed] [Google Scholar]

31. Clinton PM, Kemeny DM, Youlten LJ, Lessof MH. Histamine release from peripheral blood leukocytes with purified bee venom allergens: effect of hyperimmune beekeeper plasma. Int Arch Allergy Appl Immunol. (1989) 89:43–8. 10.1159/000234921 [DOI] [PubMed] [Google Scholar]

32. Habermann E. Bee and wasp venoms. Science. (1972) 177:314–22. 10.1126/science.177.4046.314 [DOI] [PubMed] [Google Scholar]

33. Birr C, Wengert-Müller M. Molecular perspectives of synthetic mast cell-degranulating peptide. In: Eberle AN, Wieland T, Geiger R, editors. Perspectives in Peptide Chemistry. Basel: Karger; (1981). p. 372–80. [Google Scholar]

34. Banks BE, Dempsey CE, Vernon CA, Warner JA, Yamey J. Anti-inflammatory activity of bee venom peptide 401 (mast cell degranulating peptide) and compound 48/80 results from mast cell degranulation *in vivo*. Br J Pharmacol. (1990) 99:350–4. 10.1111/j.1476-5381.1990.tb14707.x [DOI] [PMC free article] [PubMed] [Google Scholar]

35. .Ziai MR, Russek S, Wang H-C, Beer B, Blume AJ. Mast cell degranulating peptide: a multi-functional neurotoxin. J Pharm Pharmacol. (1990) 42:457–61. 10.1111/j.2042-7158.1990.tb06595.x [DOI] [PubMed] [Google Scholar]

36. Shi P, Xie S, Yang J, Zhang Y, Han S, Su S, Yao H. Pharmacological effects andMechanisms of bee venom and its main Components: Recent progress and perspective. Frontiers in pharmacology. 2022 Sep 27;13:1001553.

37. Alcalá-Escamilla KI, Moguel-Ordóñez YB.Main bioactive components and therapeutic properties of bee (Apis mellifera L.) venom.Review. Revista mexicana de cienciaspecuarias. 2024 Mar;15(1):230-48

38. Itzél Alcalá-Escamilla K, Beatriz MoguelOrdóñez Y. Main bioactive components and therapeutic properties of bee (Apis mellifera L.) venom. Review. Revista Mexicana de CienciasPecuarias. 2024 Jan 1;15(1).

39. Maitip J, Mookhploy W, Khorndork S, Chantawannakul P. Comparative study of Antimicrobial properties of bee venom extracts And melittins of honey bees. Antibiotics. 2021 Dec 8;10(12):1503.

40. Isidorov V, Zalewski A, Zambrowski G, Swiecicka I. Chemical composition and Antimicrobial properties of honey bee venom. Molecules. 2023 May 17;28(10):4135.

41. Sekar M, Lum PT, Bonam SR, Hua Gan S. Medicinal Benefits of Bee Venom. Honey: Composition and Health Benefits. 2023 Mar 24:302-13.

42. Abacı N, Orhan İE. Bee venom and its Biological effects. Current Perspectives on Medicinal and Aromatic Plants. 2022;5(1):86-105

43. Goldman, J.G.; Williams-Gray, C.; Barker, R.A.; Duda, J.E.; Galvin, J.E. The spectrum of cognitive impairmentIn Lewy body diseases. Mov. Disord. 2014, 29, 217–231. [CrossRef]

44. Aarsland, D.; Creese, B.; Politis, M.; Chaudhuri, K.R.; Ffytche, D.H.; Weintraub, D.; Ballard, C. Cognitive Decline in Parkinson disease. Nat. Rev. Neurol. 2017, 13, 217–231. [CrossRef]

45. Iakovakis, D.; Hadjidimitriou, S.; Charisis, V.; Bostantzopoulou, S.; Katsarou, Z.; Hadjileontiadis, L.J.Touchscreen typing-pattern analysis for detecting fine motor skills decline in early-stage Parkinson's disease.Sci. Rep. 2018. [CrossRef]

46. Tanner, C.M.; Kamel, F.; Ross, G.W.; Hoppin, J.A.; Goldman, S.M.; Korell, M.; Marras, C.; Bhudhikanok, G.S.;Kasten, M.; Chade, A.R.; et al. Rotenone, paraquat, and Parkinson's disease. Environ. Health Perspect. 2011119, 866–872. [CrossRef]

47. Khalil, W.K.B.; Assaf, N.; ElShebiney, S.A.; Salem, N.A. Neuroprotective effects of bee venom acupunctureTherapy against rotenone-induced oxidative stress and apoptosis. Neurochem. Int. 2015, 80, 79–86. [CrossRef]

48. Alvarez-Fischer, D.; Noelker, C.; Vulinovi´c, F.; Grünewald, A.; Chevarin, C.; Klein, C.; Oertel, W.H.;Hirsch, E.C.; Michel, P.P.; Hartmann, A. Bee Venom and Its Component Apamin as Neuroprotective AgentsIn a Parkinson Disease Mouse Model. PLoS ONE 2013, 8. [CrossRef]

49. Aksoz, E.; Gocmez, S.; Sahin, T.D.; Aksit, D.; Aksit, H.; Utkan, T. The protective effect of metformin in

50. Scopolamine-induced learning and memory impairment in rats. Pharm. Rep. 2019, 71, 818–825. [CrossRef]

51. Sabri, O.; Sabbagh, M.N.; Seibyl, J.; Barthel, H.; Akatsu, H.; Ouchi, Y.; Senda, K.; Murayama, S.; Ishii, K.;Takao, M.; et al. Florbetaben PET imaging to detect amyloid beta plaques in Alzheimer's disease: Phase 3Study. Alzheimers Dement. 2015, 11, 964–974. [CrossRef]

52. Baek, H.; Lee, C.; Choi, D.B.; Kim, N.S.; Kim, Y.S.; Ye, Y.J.; Kim, Y.S.; Kim, J.S.; Shim, I.; Bae, H. Bee venomPhospholipase A2 ameliorates Alzheimer's disease pathology in Aβ vaccination treatment without inducingNeuro-inflammation in a 3xTg-AD mouse model. Sci. Rep. 2018, 8. [CrossRef]

53. Kakuda, N.; Miyasaka, T.; Iwasaki, N.; Nirasawa, T.; Wada-Kakuda, S.; Takahashi-Fujigasaki, J.; Murayama, S.;Ihara, Y.; Ikegawa, M. Distinct deposition of amyloid-β species in brains with Alzheimer's disease pathologyVisualized with MALDI imaging mass spectrometry. Acta Neuropathol. Commun. 2017, 5. [CrossRef]

54. Van Eldik, L.J.; Carrillo, M.C.; Cole, P.E.; Feuerbach, D.; Greenberg, B.; Hendrix, J.A.; Kennedy, M.; Kozauer, N.Margolin, R.A.; Molinuevo, J.L.; et al. The roles of inflammation and immune mechanisms in Alzheimer'sDisease. Alzheimers Dement. 2016, 2, 99–109. [CrossRef]

55. Kinney, J.W.; Bemiller, S.M.; Murtishaw, A.S.; Leisgang, A.M.; Salazar, A.M.; Lamb, B.T. Inflammation as aCentral mechanism in Alzheimer's disease. Alzheimers Dement. 2018, 4, 575–590. [CrossRef]

56. Terry, A.V.; Buccafusco, J.J. The Cholinergic Hypothesis of Age and Alzheimer's Disease-Related CognitiveDeficits: Recent Challenges and TheirImplications for Novel Drug Development. J. Pharm. Exp. Ther. 2003,306, 821–827. [CrossRef]

57. Rajagopalan, V.; Pioro, E.P. Unbiased MRI analyses identify micropathologic differences between upperMotor neuron-predominant ALS phenotypes. Front. Neurosci. 2019, 13. [CrossRef]

58. Boillée, S.; Yamanaka, K.; Lobsiger, C.S.; Copeland, N.G.; Jenkins, N.A.; Kassiotis, G.; Kollias, G.;Cleveland, D.W. Onset and progression in inherited ALS determined by motor neurons and microglia.Science 2006, 312, 1389–1392. [CrossRef]

59. Jaarsma, D.; Haasdijk, E.D.; Grashorn, J.A.C.; Hawkins, R.; Van Duijn, W.; Verspaget, W.H.; London, J.;Holstege, J.C. Human Cu/Zn Superoxide Dismutase (SOD1) Overexpression in Mice Causes MitochondrialVacuolization, Axonal Degeneration, and Premature Motoneuron Death and Accelerates MotoneuronDiseaseIn Mice Expressing a Familial AmyotrophicLateral Sclerosis Mutant SOD1. Neurobiol. Dis. 2000, 7, 623–643[CrossRef]

60. Yang, E.J.; Jiang, J.H.; Lee, S.M.; Yang, S.C.; Hwang, H.S.; Lee, M.S.; Choi, S.M. Bee venom attenuatesNeuroinflammatory events and extends survival in amyotrophic lateral sclerosis models. J. Neuroinflamm.2010, 7. [CrossRef]

61. Cai, M.D.; Choi, S.M.; Yang, E.J. The effects of bee venom acupuncture on the central nervous system andMuscle in an animal hSOD1G93A mutant. Toxins 2015, 7, 846–858. [CrossRef]

62. Maitip J, Mookhploy W, Khorndork S, Chantawannakul P. Comparative study of antimicrobial properties of bee venom extracts and melittins of honey bees. Antibiotics. 2021 Dec 8;10(12):1503.

63. Isidorov V, Zalewski A, Zambrowski G, Swiecicka I. Chemical composition and antimicrobial properties of honey bee venom. Molecules. 2023 May 17;28(10):4135.

64. Sekar M, Lum PT, Bonam SR, Hua Gan S. Medicinal Benefits of Bee Venom. Honey: Composition and Health Benefits. 2023 Mar 24:302-13.

65. Abacı N, Orhan İE. Bee venom and its biological effects. Current Perspectives on Medicinal and Aromatic Plants. 2022;5(1):86105.

66. Zhang, S.; Liu, Y.; Ye, Y.; Wang, X.R.; Lin, L.T.; Xiao, L.Y.; Zhou, P.; Shi, G.X.; Liu, C.Z. Bee venom therapy: Potential mechanisms and therapeutic applications. Toxicon 2018, 148, 64–73. [Google Scholar] [CrossRef]

67. Wehbe, R.; Frangieh, J.; Rima, M.; El Obeid, D.; Sabatier, J.M.; Fajloun, Z. Bee Venom: Overview of Main Compounds and Bioactivities for Therapeutic Interests. Molecules 2019, 24, 2997. [Google Scholar] [CrossRef] [PubMed] [Green Version]

68. Carpena, M.; Nuñez-Estevez, B.; Soria-Lopez, A.; Simal-Gandara, J. Bee Venom: An Updating Review of Its Bioactive Molecules and Its Health Applications. Nutrients 2020, 12, 3360. [Google Scholar] [CrossRef]

69. Ali M. Studies on bee venom and its medical uses. Int J Adv Res Technol 2012;1(2):1-15. [Links]

70. 7. Faux CM. Honey bee anatomy. In: Kane TR, Faux CM editors. Honey bee medicine for the veterinary parctitioner. Wiley Blackwell. 2021:33-40. [Links]

71. Azam, M. N. K., Ahmed, M. N., Biswas, S., Ara, N., Rahman, M. M., Hirashima, A., & Hasan, M. N. (2018). A review on bioactivities of honey bee venom. Annual Research & Review in Biology, 1-13. https://doi.org/10.9734/ARRB/2018/45028 5. Babaie, M., Mehrabi, Z., & Mollaei, A. (2020). Partial purification and characterization of antiScholar] [CrossRef]

72. Münstedt, K. Bee products—An overview of their pharmacological properties and medicinal applications. Bee Prod. Their Appl. Food Pharm. Ind. 2022, 1–23. [Google Scholar]

73. Gokulakrishnaa, R.; Thirunavukkarasu, S. Apitherapy: A valuable gift from honey bee. J. Entomol. Zool. Stud. 2020, 8, 2317–2323. [Google Scholar]