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Review Article

Bee Venom and Its Therapeutic Potential

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ABSTRACT

The aim of this review is to evaluate the biological effects of the major components of bee venom (BV), also known as apitoxin, and the implications of these effects in experimental disease models. BV has emerged an important natural agent in modern pharmacology and medicine due to its diverse bioactive constituents, including melittin, apamin, adolapin, phospholipase A2 (PLA2), and hyaluronidase. In neurodegenerative and autoimmune disease models such as Parkinson's disease, Alzheimer's disease, and multiple sclerosis, BV exhibits neuroprotective, anti-inflammatory, and antioxidant effects. However, its toxic potential must be considered, as immune-mediated reactions may cause severe clinical outcomes, particularly in allergic individuals. In conclusion, although BV possesses a broad therapeutic potential, its clinical application requires clearly defined dosing, treatment duration, and targeted delivery strategies. Therefore, further studies are needed to support the development of biotherapeutic approaches aimed at enabling the safe and effective use of BV.

Keywords: *Apitherapy, bee venom, apitoxin*

Arı Zehri ve Terapötik Potansiyeli

ÖZET

Bu derlemenin amacı, arı zehri ya da diğer adıyla apitoksinin başlıca bileşenlerinin biyolojik etkilerini ve bu etkilerin deneysel modellerdeki yansımalarını değerlendirmektir. Arı zehri, melittin, apamin, adolapin, fosfolipaz A2 ve hyaluronidaz gibi çeşitli biyoaktif bileşenleri sayesinde modern farmakoloji ve tıpta önemli bir doğal ajan hâline gelmiştir. Parkinson, Alzheimer ve multipl skleroz gibi nörodejeneratif ve otoimmün hastalık modellerinde, arı zehrinin nöroprotektif, anti-inflamatuar ve antioksidan etkiler sergilediği ortaya konmuştur. Bununla birlikte, özellikle alerjik bireylerde immün aracılı reaksiyonların ciddi klinik sonuçlara yol açabilmesi nedeniyle toksik potansiyelinin de dikkate alınması gerekmektedir. Sonuç olarak, arı zehri geniş bir terapötik potansiyele sahip olmakla birlikte, klinik uygulamasının açık şekilde tanımlanmış dozlama, tedavi süresi ve hedefe yönelik uygulama stratejileri olmaksızın uygun olmadığı değerlendirilmektedir. Bu nedenle, arı zehrinin güvenli ve etkili kullanılabilmesini mümkün kılacak biyoterapötik yaklaşımların geliştirilmesi için daha fazla veriye ihtiyaç vardır.

Anahtar kelimeler: *Apiterapi, apitoksin, arı zehri*

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Introduction

Apitherapy refers to the use of hive products such as honey, propolis, royal jelly, pollen, beeswax, and bee venom (BV) produced by *Apis mellifera*, for the prevention and treatment of various diseases. The increasing prevalence of drug resistance has intensified the search for new pharmacologically active substances. Despite growing scientific interest, BV still lacks standardized extraction and processing methods. Variability in venom composition, together with insufficient toxicological data, limit its integration into evidence-based medical practice. BV has been used for medical purposes since ancient times (Bava et al., 2023). Despite this historical background, modern clinical evidence remains limited, and its medical application lacks global standardization (Sadek et al., 2024).

In recent years, BV has attracted renewed interest as a potential therapeutic option for chronic and autoimmune diseases, with several studies suggesting immunomodulatory effects in conditions such as systemic lupus erythematosus and multiple sclerosis. BV and its components exhibit a wide range of biological activities, including antimicrobial, anti-inflammatory, and anti-arthritic effects, which are primarily attributed to major peptides, such as melittin and apamin. Melittin has demonstrated cytotoxic and pro-apoptotic activities in various tumor models; however, its narrow therapeutic index and the risk of hypersensitivity reactions represent significant limitations to its clinical use (Stela et al., 2024). In addition to its therapeutic benefits, BV may also reduce the adverse effects associated with some conventional treatments (Sadek et al., 2024). Despite these pharmacological properties, BV poses important toxicological risks, particularly hypersensitivity reactions. Furthermore variability in venom composition and the lack of standardized dosing further complicate its clinical applicability (Carli et al., 2025).

This review aims to summarize the major bioactive components of BV, evaluate their pharmacological and toxicological effects, and highlight current gaps that must be addressed to enable its safe and effective clinical use particularly in veterinary medicine.

Major Bioactive Components of Bee Venom

The composition of BV varies depending on factors such as the age of the bee, geographical location, season, social status and subspecies of *Apis mellifera*. The major constituents of BV are peptides, which make up about 48-50% of dry weight. These peptides, which possess significant therapeutic potential, include melittin, apamin, adolapin, and mast cell degranulating (MCD) peptide (Gajski et al., 2024).

Melittin is the predominant peptide component of bee venom and constitutes approximately 52% of its dry mass (Ceremuga et al., 2020). By binding to biological membranes, it leads to the formation of pores in the phospholipid bilayer, resulting in disruption of membrane permeability and cell lysis (Jamasbi et al., 2015). At low doses, melittin exhibits anti-inflammatory effects, whereas at higher doses it induces localized pain, itching, and inflammation. It has also been reported to exert anti-nociceptive, anti-inflammatory, and anti-arthritic effects upon application at acupuncture points (Wehbe et al., 2019).

Apamin constitutes approximately 2-3% of the dry weight of BV and is the smallest neurotoxic peptide present. Its structural stability, provided by two disulfide bonds, enables resistance to degradation and facilitates penetration of the blood–brain barrier. Apamin selectively inhibits calcium-activated potassium channels, thereby modulating neuronal excitability and potentially causing overstimulation (Gu et al., 2020).

Adolapin represents approximately 1% of dried BV and accounts for 2-5% of the peptides in BV (Nitecka-Buchta et al., 2014). Koburova et al. (1985) reported that this peptide has anti-inflammatory, analgesic and antipyretic effects by inhibiting prostaglandin synthesis. Adolapin had significant analgesic activity, suggesting a central mechanism, and an antipyretic activity by reducing experimentally-induced hyperthermia in rats. Adolapin's *in vitro* inhibition of 5-lipoxygenase activity isolated from human platelets was shown by Jung et al. (2015), indicating that it may have analgesic properties.

MCD peptide constitutes approximately 2-3% of the dry weight of BV. At high concentrations, it exerts anti-inflammatory effects, whereas at low concentrations, it functions as a potent mediator of mast cell degranulation and histamine release (Carpena et al., 2020). MCD peptide specifically binds to high-affinity IgE receptors. This interaction inhibits antigen-mediated IgE cross-linking, consequently suppressing mast cell degranulation and histamine release. These effects highlight MCD's potential as a significant anti-allergic agent by modulating mast cell activation and reduce inflammatory responses (Buku et al., 2001).

Phospholipase A2 (PLA2) is an enzyme that plays a central role in inflammatory mediator production through phospholipid hydrolysis. It accounts for about 10-12% of the dry weight of BV. PLA2 is considered a principal allergen in BV, playing a key role in IgE-mediated hypersensitivity (Burzyńska & Piasecka-Kwiatkowska, 2021).

Hyaluronidase, known as the "diffusion factor", and accounts for approximately 1-2% of the dry weight of BV (Lu et al., 2025). Abdel-Monsef et al. (2020) demonstrated that hyaluronidase plays a key role in helping venom spread and boosting its biological effects. In studies on BV, this enzyme was found to efficiently break down hyaluronic acid, a major part of the extracellular matrix, allowing venom components to move more easily into surrounding tissues. In individuals with hypersensitivity to BV, IgE responses to hyaluronidase and other venom components play a significant role. Clinical studies have shown that approximately 78% of individuals allergic

to BV have specific IgE antibodies for hyaluronidase (Burzyńska & Piasecka-Kwiatkowska, 2021). These structural and bioactive characteristics highlight the importance of careful consideration in therapeutic applications.

Therapeutic Effects of Bee Venom

Analgesic Effect

BV injection may induce pain and hyperalgesia. However, antinociceptive effects have been observed in inflammation-related pain conditions. Experimental studies have shown that BV administration significantly reduces pain-related behaviors through both peripheral and central mechanisms (Roh et al., 2006). In inflammatory and burn-induced pain models, BV treatment reduced pain behaviors. Improved motor performance was also observed. These effects have been associated with inhibition of substance P release in the peripheral and central nervous system (Kang et al., 2021). The analgesic potential of BV has also been demonstrated in neuropathic pain models, where repeated administration of diluted BV reduced mechanical allodynia and thermal hyperalgesia. These effects are associated with modulation of noradrenergic activity in the locus coeruleus, downregulation of spinal N-methyl-D-aspartate (NMDA) receptor subunits, and involvement of spinal α-adrenoceptors (Kang et al., 2012). In a recent study by Mau et al. (2024), api-acupuncture significantly increased paw withdrawal latency, indicating that BV elevates pain threshold and enhances resistance to thermal stimuli.

Anti-inflammatory Effect

The anti-inflammatory effects of BV are primarily attributed to melittin, which exhibits potent effects in various experimental inflammation models. Melittin has been shown to reduce oedema and suppress the production of inflammatory mediators, including prostaglandin E_2 (PGE_2), tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), nitric oxide (NO), and other pro-inflammatory cytokines in lipopolysaccharide (LPS)-stimulated macrophages (Chung et al., 2016). In chronic inflammatory conditions such as rheumatoid arthritis, melittin administration resulted in reduced joint swelling and decreased pro-inflammatory cytokine levels (Du et al., 2021). Melittin has also demonstrated protective effects in acute systemic inflammation models. In the LPS-induced sepsis model, melittin treatment reduced inflammation, oxidative stress, and cell death in renal tissue (Kim et al., 2020). Additionally, melittin inhibits ferroptosis in renal cells. Thus, melittin protects renal cells from oxidative damage and ferroptotic cell death (Zan et al., 2024).

Antimicrobial Effect

BV exhibits antimicrobial effects primarily due to melittin and PLA2. Melittin penetrates microbial cell membranes, disrupting membrane integrity and inhibiting DNA/RNA function, ultimately leading to cell death (Shi et al., 2016). The PLA2 enzyme hydrolyses phospholipids in bacterial membranes, causing structural damage and bacterial cell death (Lin et al., 2018).

Melittin was tested against *Borrelia burgdorfer*i in spirochete, persister, and biofilm forms. *In vitro* analyses, demonstrated that BV and melittin effectively inhibit antibiotic-resistant forms, highlighting their therapeutic potential. These findings suggest that melittin is a potential therapeutic agent, particularly for resistant bacterial infections (Socarras et al., 2017). Similarly, in a study conducted on *Escherichia coli* and *Pseudomonas species*, the antimicrobial effect of BV was examined. BV demonstrated a strong bactericidal effect especially on *Pseudomonas putida* at appropriate doses and exposure times. These findings suggest that BV primarly targets Gram-negative bacterial membranes (Haktanir et al., 2021).

Antiviral Effect

BV, particularly melittin, exhibits antiviral activity against enveloped viruses by disrupting the viral lipid bilayer and preventing host cell entry. This virucidal mechanism has been demonstrated against viruses such as human immunodeficiency virus (HIV), herpes simplex virus, influenza A virus, and dengue virus. However, the cytotoxicity of melittin toward non-target cells remains a major limitation for its clinical application (Uddin et al., 2016). To reduce cytotoxic effects and improve therapeutic applicability, formulation strategies such as nanoparticle encapsulation have been explored. Hood et al. (2013) evaluated melittin encapsulated in biocompatible nanoparticles and demonstrated that this approach inhibited approximately 98% of HIV-1 infectivity.

Bee venom also exhibits antiviral activity against other enveloped viruses, including Hepatitis C virus (HCV). *In vitro* analyses indicated that crude BV can inhibit HCV infection at remarkably low concentrations. Crude BV inhibits HCV primarily by directly interacting with viral particles. However, there has been no significant inhibition of viral replication or release. These findings suggest that the virucidal activity may result from less-characterized peptides or toxin complexes present in the crude venom, rather than from well-studied components such as melittin, apamin, or MCD peptide (Sarhan et al., 2020). Overall, current data indicate that BV components may have antiviral potential; however, further studies are needed to clarify their mechanisms and practical relevance.

Antitumor Effect

A mortality analysis involving beekeepers reported unexpectedly low death rates from certain types of cancers, particularly lung cancer. This suggests there may be a protective association with bee-related exposures (Cui et al., 2024). A research conducted by Oršolić (2012) suggests that the cytotoxic effects of BV are primarily mediated by melittin. Direct use of melittin is a more

effective option in cancer treatment compared to whole BV. These observations indicate that melittin represents the principal contributor to the cytotoxic properties of BV, which is why many studies have focused on melittin rather than whole venom preparations. Accordingly, studies on various tumor models support this information. In a study on osteosarcoma cell lines, the inhibitory effects of melittin on cell proliferation, migration and invasion were investigated. It has shown significant cytotoxic effects in osteosarcoma cells. In addition, significant reductions in cell migration and invasion have been reported. These findings suggest that melittin may also be a promising agent in the field of veterinary oncology (Pedro et al., 2025). Similarly, in a study conducted with a colorectal cancer model, the antitumor effects of melittin were evaluated both *in vitro* and *in vivo*. In this study, it was reported that melittin promotes tumor cell death by activating mitochondrial apoptosis. Significantly inhibiting both tumor growth and metastasis (Wang et al., 2024). In another lung cancer study, melittin was shown to inhibit tumor growth by inducing apoptosis, inhibiting epithelial-mesenchymal transition, and reducing metastatic potential (Zhang & Chen, 2017). Moreover, novel delivery strategies such as melittin analogs, hydrogels, liposomes, nanoparticles, and adenovirus-based gene therapies have been developed to improve bioavailability, tumor selectivity, and reduce systemic toxicity. Overall, these findings indicate that melittin can influence several biological processes relevant to tumor progression, although the extent to which these mechanisms translate *in vivo* remains to be clarified.

In addition to melittin, PLA2 also contributes to the antitumor effects of BV. PLA2 hydrolyses membrane phospholipids, induces apoptosis and necrosis, and modulates the tumor microenvironment by regulating inflammatory mediators. PLA2 also improves antigen presentation and T-cell activation which may help overcome tumor-associated immune tolerance. Recent studies demonstrate that melittin inhibits key signaling pathways, including PI3K/Akt and NF-κB (Rizkallah et al., 2025). It also exerts synergistic effects with reactive oxygen species to promote cancer cell death. These findings highlight that BV exerts multifaceted antitumor activity, combining direct cytotoxicity, immune modulation, and advanced delivery strategies. They support its potential application in various cancer treatment strategies (Cui et al., 2024). However, most of these mechanisms have been characterized in controlled experimental settings, and their relevance to veterinary oncology requires further investigation.

Neuroprotective Effect

Effects on Parkinson's Disease: BV treatment suppressed inflammatory microglia activation in the Parkinson's disease model, resulting in protection of dopaminergic neurons in the substantia nigra (Kim et al., 2011). In another Parkinson's disease model, the combination of BV and dopamine-loaded nanoparticles improved motor symptoms and significantly reduced oxidative stress markers. In addition, neuronal damage was reduced in parallel with increased dopamine levels (Ahmed-Farid et al., 2021). The neuroprotective effect of apamin was examined in a mouse model of Parkinson's disease. Apamin treatment significantly reduced neuronal loss in the substantia nigra compared with untreated mice. The findings suggest that apamin may help protect against Parkinson's disease–related neurodegeneration (Alvarez-Fischer et al., 2013).

Effects on Alzheimer's Disease: An amnesia-like Alzheimer's model was created on rats and BV was applied. Following this, BV has been reported to promote memory improvement and increase neurogenesis activity in the hippocampus. BV's bioactive components are responsible for these neuroprotective effects. Furthermore, observed improvements in behavioral tests have been reported to be associated with reduced oxidative stress and increased neuronal plasticity (Khleifat et al., 2023).

Effects on Multiple Sclerosis: In their study on an experimental model of autoimmune encephalomyelitis (EAE) in mice, Jelodar et al. (2021) reported that BV administration relieved clinical symptoms. IL-27 levels increased significantly in the BV group, and this increase was evaluated as an anti-inflammatory indicator in the context of the EAE model. In histopathological evaluations, it was observed that inflammatory infiltration in brain tissue was significantly reduced. These findings may provide a foundation for exploring BV's potential applications in veterinary neurology, although clinical validation in animal patients is required.

Antioxidant Effect

BV has been reported to exhibit antioxidant properties in both *in vitro* and *in vivo* experimental models (Hanafi et al., 2018; Somwongin et al., 2018). An *in vitro* study has evaluated the free radical scavenging capacity of BV through various methods, including 2,2-diphenyl-1-picrylhydrazyl (DPPH), ferric reducing/antioxidant power (FRAP), 2,2'-azinobis-3-ethylbenzothiazolin-6-sulfonic acid (ABTS), thiobarbituric acid reactive substances (TBARS), and β-carotene bleaching inhibition assays. This effect is thought to be due to the overall composition of the venom, rather than to the specific component that makes up the BV (Somwongin et al., 2018). Similarly, an *in vivo* study has demonstrated that BV administration in rats with non-alcoholic fatty liver (NAFL) improved antioxidant parameters, including glutathione (GSH) levels, GSH/GSSG ratio, glutathione reductase (GR), glutathione S-transferase (GST) and glutathione peroxidase (GPx) activities. Additionally, levels of malondialdehyde (MDA) and TNFα were significantly reduced (Hanafi et al., 2018). These findings suggest potential applications in veterinary oxidative stress-related disorders, although clinical validation is necessary.

Adverse Effects of Bee Venom

Although BV can be used for therapeutic purposes, its safety is still an important issue to consider. BV components exhibit anti-inflammatory and other beneficial effects at low doses, whereas at higher concentrations they disrupt cell membranes and produce toxic effects such as inflammation, haemolysis, and allergic or anaphylactic reactions. In anaphylactic reactions after BV exposure, the IgE-mediated inflammatory response induced by the major allergens in BV causes an increase in vascular permeability and damage to the vessel wall. This situation paves the way for intravascular haemorrhages and episodic haemorrhages in the tissues. In addition, histamine, proteases and other mediators released as a result of systemic mast cell degranulation create an imbalance on coagulation and fibrinolytic systems, thereby increasing the risk of bleeding (Mingomataj & Bakiri, 2012; Sorucu, 2019). The major allergens responsible for these reactions include PLA2, melittin, and hyaluronidase. In sensitive individuals, BV exposure can lead to serious symptoms such as limb paralysis, pain, dyspnoea, nausea, unconsciousness, and lymphocyte instability. The severity of these adverse reactions depends on factors such as body weight, age, number of stings, immune status, and prior sensitization. BV application can cause local reactions such as redness, swelling, and oedema at the sting site. It can also lead to systemic effects such as angioedema, urticaria, vomiting, pruritus, and diarrhoea; peripheral neuritis, optic neuropathy, bilateral empyema, septicaemia, and acute inflammatory polyradiculoneuropathy. Isolated BV components exhibit toxic effects when administered at concentrations 20 to 50 times the therapeutic dose, while whole venom has a much wider safety margin. Toxicity appears at extremely high doses, approximately 200-500 times the therapeutic level. In line with these pharmacodynamic characteristics, whole BV can be considered a safer option for general therapeutic applications. However, for targeted and specific interventions, isolated components may be preferred due to their distinct pharmacological activities; in such cases, the narrow safety range must be taken into careful consideration (Ullah et al., 2023). In the study conducted by Han et al. (2012), BV was applied dermally to rats. No serious toxic reactions were observed at low doses, while high doses induced local adverse reactions including skin inflammation, redness and swelling. In studies on beekeepers, nearly all participants (97%) had detectable anti-PLA2 IgE antibodies in their serum, and higher levels of these antibodies were associated with more pronounced allergic reactions after bee stings. These findings suggest that PLA2 induces mast cell and basophil activation, leading to histamine release and the manifestation of allergic symptoms. Consequently, while BV holds therapeutic promise, its allergenic components, particularly PLA2, are a major factor in adverse immune responses and should be carefully considered in clinical applications (Lee & Bae, 2016). Taken together, these findings suggest that BV does not induce severe toxicity at therapeutic doses in non-allergic individuals. However, allergic individuals may experience serious systemic reactions mediated by immune mechanisms. These observations highlight the importance of dose management and careful monitoring in clinical applications particularly in individuals with known hypersensitivity.

Conclusion

BV is a compound with versatile therapeutic potential in traditional and modern medicine. Thanks to bioactive components such as melittin, apamine, adolapin, PLA2 and hyaluronidase, it has been investigated for its potential roles in various disease models by different mechanisms. These bioactive substances stand out for their anti-inflammatory, analgesic, antimicrobial, antiviral, antioxidant and antitumor activities. Therefore, BV is a promising resource for biotechnological and pharmaceutical research.

Despite this therapeutic potential offered by BV, there are important points to be considered in its use. The risk of allergic reactions, dose-dependent limitations, safety considerations, and potential toxic effects are important limiting factors in the clinical applications of BV-based treatments. However, ongoing scientific research to overcome these problems may make safer and more effective uses possible.

In conclusion, BV occupies an important place at the point where traditional knowledge and modern science are combined. In the future, BV–based approaches may find broader applicability in both human and veterinary medicine as supporting evidence continues to accumulate.

Author contribution

This review was written by BSD with support from HSŞ. Both authors, BSD and HSŞ, contributed to the final version of this manuscript.

Conflict of interest

The author declares no conflict of interest.

References

Abdel-Monsef, M.M., Zidan, H.A., Darwish, D.A., Masoud, H.M., Helmy, M.S., & Ibrahim, M.A. (2020). Biochemical isolation and characterization of hyaluronidase enzyme from venom of Egyptian honeybee Apis mellifera Lamarckii. *Journal of Apicultural Science*, 64(1), 153–164. https://doi.org/10.2478/jas-2020-0015

Ahmed-Farid, O.A., Taha, M., Bakeer, R.M., Radwan, O.K., Hendawy, H.A.M., Soliman, A. S., & Yousef, E. (2021). Effects of bee venom and dopamine-loaded nanoparticles on reserpine-induced Parkinson's disease rat model. *Scientific Reports*, 11(1), 21141. https://doi.org/10.1038/s41598-021-00764-y

Alvarez-Fischer, D., Noelker, C., Vulinović, F., Grünewald, A., Chevarin, C., Klein, C., … Hartmann, A. (2013). Bee venom and its component apamin as neuroprotective agents in a Parkinson disease mouse model. *PLoS ONE*, 8(4), e61700. https://doi.org/10.1371/journal.pone.0061700

Bava, R., Castagna, F., Musella, V., Lupia, C., Palma, E., & Britti, D. (2023). Therapeutic use of bee venom and potential applications in veterinary medicine. *Veterinary Sciences*, 10(2), 119. https://doi.

org/10.3390/vetsci10020119

Buku, A., Price, J. A., Mendlowitz, M., & Masur, S. (2001). Mast cell degranulating peptide binds to RBL-2H3 mast cell receptors and inhibits IgE binding. *Peptides*, 22(12), 1993–1998. https://doi.org/10.1016/S0196-9781(01)00542-3

Burzyńska, M., & Piasecka-Kwiatkowska, D. (2021). A review of honeybee venom allergens and allergenicity. *International Journal of Molecular Sciences*, 22(16), 8371. https://doi.org/10.3390/ijms22168371

Carli, T., Locatelli, I., Košnik, M., Bevk, D., & Kukec, A. (2025). Epidemiology and risk factor analysis of systemic allergic reaction to bee venom in the Slovenian population of beekeepers. *Slovenian Journal of Public Health*, 64(1), 40–48. https://doi.org/10.2478/sjph-2025-0006

Carpena, M., Nuñez-Estevez, B., Soria-Lopez, A., & Simal-Gandara, J. (2020). Bee venom: an updating review of ıts bioactive molecules and ıts health applications. *Nutrients*, 12(11), 3360. https://doi.org/10.3390/nu12113360

Ceremuga, M., Stela, M., Janik, E., Gorniak, L., Synowiec, E., Sliwinski, T., … Bijak, M. (2020). Melittin-a natural peptide from bee venom which ınduces apoptosis in human leukaemia cells. *Biomolecules*, 10(2), 247. https://doi.org/10.3390/biom10020247

Chung, H.J., Lee, J., Shin, J.S., Kim, M.R., Koh, W., Kim, M.J., … Ha, I.H. (2016). In vitro and in vivo anti-allergic and anti-inflammatory effects of eBV, a newly developed derivative of bee venom, through modulation of IRF3 signaling pathway in a carrageenan-induced edema model. *PloS One*, 11(12), e0168120. https://doi.org/10.1371/journal.pone.0168120

Cui, Z., Zhou, Z., Sun, Z., Duan, J., Liu, R., Qi, C., & Yan, C. (2024). Melittin and phospholipase A2: promising anti-cancer candidates from bee venom. *Biomedicine & Pharmacotherapy*, 179, 117385. https://doi.org/10.1016/j.biopha.2024.117385

Du, G., He, P., Zhao, J., He, C., Jiang, M., Zhang, Z., … Sun, X. (2021). Polymeric microneedle-mediated transdermal delivery of melittin for rheumatoid arthritis treatment. *Journal of Controlled Release: Official Journal of the Controlled Release Society*, 336, 537–548. https://doi.org/10.1016/j.jconrel.2021.07.005

Gajski, G., Leonova, E., & Sjakste, N. (2024). Bee venom: composition and anticancer properties. *Toxins*, 16(3), 117. https://doi.org/10.3390/toxins16030117

Gu, H., Han, S.M., & Park, K.K. (2020). Therapeutic effects of apamin as a bee venom component for non-neoplastic disease. *Toxins*, 12(3), 195. https://doi.org/10.3390/toxins12030195

Haktanir, I., Masoura, M., Mantzouridou, F.T., & Gkatzionis, K. (2021). Mechanism of antimicrobial activity of honeybee (Apis mellifera) venom on Gram-negative bacteria: Escherichia coli and Pseudomonas spp. *AMB Express*, 11(1), 54. https://doi.org/10.1186/s13568-021-01214-8

Han, S.M., Lee, G.G., & Park, K.K. (2012). Acute dermal toxicity study of bee venom (Apis mellifera L.) in rats. *Toxicological Research*, 28(2), 99–102. https://doi.org/10.5487/TR.2012.28.2.099

Hanafi, M.Y., Zaher, E.L.M., El-Adely, S.E.M., Sakr, A., Ghobashi, A.H.M., Hemly, M.H., … Kamel, M.A. (2018). The therapeutic effects of bee venom on some metabolic and antioxidant parameters associated with HFD-induced non-alcoholic fatty liver in rats. *Experimental and Therapeutic Medicine*, 15(6), 5091–5099. https://doi.org/10.3892/etm.2018.6028

Hood, J.L., Jallouk, A.P., Campbell, N., Ratner, L., & Wickline, S.A. (2013). Cytolytic nanoparticles attenuate HIV-1 infectivity. *Antiviral Therapy*, 18(1), 95–103. https://doi.org/10.3851/IMP2346

Jamasbi, E., Mularski, A., & Separovic, F. (2015). Model membrane and cell studies of antimicrobial activity of melittin analogues. *Current Topics in Medicinal Chemistry*, 16(1), 40–45. https://doi.org/10.2174/1568026615666150703115919

Jelodar, S., Zare Mirakabadi, A., Oryan, S., & Mohammadnejad, L. (2021). Effect of honey bee venom on experimental autoimmune encephalomyelitis (EAE) as a model for multiple sclerosis (MS). *Archives of Razi Institute*, 76(6), 1727–1733. https://doi.org/10.22092/ARI.2021.126291.1342

Jung, S.Y., Lee, K.W., Choi, S.M., & Yang, E.J. (2015). Bee venom protects against rotenone-induced cell death in NSC34 motor neuron cells. *Toxins*, 7(9), 3715–3726. https://doi.org/10.3390/toxins7093715

Kang, D.W., Choi, J.G., Kim, J., Park, J.B., Lee, J.H., & Kim, H.W. (2021). Bee venom reduces burn-induced pain via the suppression of peripheral and central substance P expression in mice. *Journal of Veterinary Science*, 22(1), e9. https://doi.org/10.4142/jvs.2021.22.e9

Kang, S.Y., Roh, D.H., Yoon, S.Y., Moon, J.Y., Kim, H.W., Lee, H.J., … Lee, J.H. (2012). Repetitive treatment with diluted bee venom reduces neuropathic pain via potentiation of locus coeruleus noradrenergic neuronal activity and modulation of spinal NR1 phosphorylation in rats. *The Journal of Pain*, 13(2), 155–166. https://doi.org/10.1016/j.jpain.2011.10.012

Khleifat, K.M., Al-Tawarah, N.M., Al-Kafaween, M.A., Al-Ksasbeh, W., Qaralleh, H., Alqaraleh, M., … Mohd Hilmi, A.B. (2023). Memory enhancing and neurogenesis activity of honey bee venom in the symptoms of amnesia: using rats with amnesia-like Alzheimer's disease as a model. *Current Alzheimer Research*, 20(3), 190–201. https://doi.org/10.2174/1567205020666230614143027

Kim, J.I., Yang, E.J., Lee, M.S., Kim, Y.S., Huh, Y., Cho, I.H., … Koh, H.K. (2011). Bee venom reduces neuroinflammation in the MPTP-induced model of Parkinson's disease. *International Journal of Neuroscience*, 121(4), 209–217. https://doi.org/10.3109/00207454.2010.548613

Kim, J.Y., Leem, J., & Park, K.K. (2020). Antioxidative, antiapoptotic, and anti-inflammatory effects of apamin in a murine model of lipopolysaccharide-induced acute kidney injury. *Molecules*, 25(23), 5717. https://doi.org/10.3390/molecules25235717

Koburova, K.L., Michailova, S.G., & Shkenderov, S.V. (1985). Further investigation on the antiinflammatory properties of adolapin—bee venom polypeptide. *Acta Physiologica Et Pharmacologica Bulgarica*, 11(2), 50–55.

Lee, G., & Bae, H. (2016). Bee venom phospholipase a2: yesterday's enemy becomes today's friend. *Toxins*, 8(2), 48. https://doi.org/10.3390/toxins8020048

Lin, Y., Bogdanov, M., Lu, S., Guan, Z., Margolin, W., Weiss, J., & Zheng, L. (2018). The phospholipid-repair system LplT/Aas in Gram-negative bacteria protects the bacterial membrane envelope from host phospholipase A2 attack. *The Journal of Biological Chemistry*, 293(9), 3386–3398. https://doi.org/10.1074/jbc.RA117.001231

Lu, J., Zhao, Z., Pan, L., Wu, H., Wang, S., Tong, X., & Wu, S. (2025). Hyaluronidase: structure, mechanism of action, diseases and therapeutic targets. *Molecular Biomedicine*, 6, 50. https://doi.org/10.1186/s43556-025-00299-y

Mau, N.N., Quan, L.V., Du, P.V., Thanh, T.V., Thanh, N.H., Quang, N.B., … Mao, C.V. (2024). Anti-inflammatory, analgesic, and motor improvement effects of bee venom acupuncture on Freund's complete adjuvant-induced spinal degeneration in rats. *Tropical Journal of Natural Product Research (TJNPR)*, 8(11), 9166–9173. https://doi.org/10.26538/tjnpr/v8i11.27

Mingomataj, E.C., & Bakiri, A.H. (2012). Episodic hemorrhage during honeybee venom anaphylaxis: potential mechanisms. *Journal of Investigational Allergology & Clinical Immunology*, 22(4), 237–244.

Nitecka-Buchta, A., Buchta, P., Tabeńska-Bosakowska, E., Walczyńska-Dragoń, K., & Baron, S. (2014). Myorelaxant effect of bee venom topical skin application in patients with RDC/TMD Ia and RDC/TMD Ib: a randomized, double blinded study. *BioMed Research International*, 2014, 1–9. https://doi.org/10.1155/2014/296053

Oršolić, N. (2012). Bee venom in cancer therapy. *Cancer and Metastasis Reviews*, 31(1–2), 173–194. https://doi.org/10.1007/s10555-011-9339-3

Pedro, G., Brasileiro, F.C. da S., Ferreira, R.S., Bráz, A.M.M., & Laufer-Amorim, R. (2025). Melittin inhibits proliferation, migration, and invasion in osteosarcoma cell lines using 2D and 3D models. *The Journal of Venomous Animals and Toxins Including Tropical Diseases*, 31(40), e20240053. https://doi.org/10.1590/1678-9199-JVATITD-2024-0053

Rizkallah, J., Charbel, N., Yassine, A., El Masri, A., Raffoul, C., El Sardouk, O., … Kreidieh, F. (2025). Melittin-based nanoparticles for cancer therapy: mechanisms, applications, and future perspectives. *Pharmaceutics*, 17(8), 1019. https://doi.org/10.3390/pharmaceutics17081019

Roh, D.H., Kim, H.W., Yoon, S.Y., Kang, S.Y., Kwon, Y.B., Cho, K.H., … Lee, J.H. (2006). Bee venom injection significantly reduces

nociceptive behavior in the mouse formalin test via capsaicin-insensitive afferents. *The Journal of Pain*, 7(7), 500–512. https://doi.org/10.1016/j.jpain.2006.02.002

Sadek, K.M., Shib, N.A., Taher, E.S., Rashed, F., Shukry, M., Atia, G.A., … Abdeen, A. (2024). Harnessing the power of bee venom for therapeutic and regenerative medical applications: an updated review. *Frontiers in Pharmacology*, 15. https://doi.org/10.3389/fphar.2024.1412245

Sarhan, M., El-Bitar, A.M.H., & Hotta, H. (2020). Potent virucidal activity of honeybee "Apis mellifera" venom against hepatitis C virus. *Toxicon: Official Journal of the International Society on Toxinology*, 188, 55–64. https://doi.org/10.1016/j.toxicon.2020.10.014

Shi, W., Li, C., Li, M., Zong, X., Han, D., & Chen, Y. (2016). Antimicrobial peptide melittin against Xanthomonas oryzae pv. oryzae, the bacterial leaf blight pathogen in rice. *Applied Microbiology and Biotechnology*, 100(11), 5059–5067. https://doi.org/10.1007/s00253-016-7400-4

Socarras, K.M., Theophilus, P.A.S., Torres, J.P., Gupta, K., & Sapi, E. (2017). Antimicrobial activity of bee venom and melittin against Borrelia burgdorferi. *Antibiotics*, 6(4), 31. https://doi.org/10.3390/antibiotics6040031

Somwongin, S., Chantawannakul, P., & Chaiyana, W. (2018). Antioxidant activity and irritation property of venoms from Apis species. *Toxicon*, 145, 32–39. https://doi.org/10.1016/j.toxicon.2018.02.049

Sorucu, A. (2019). Arı ürünleri ve apiterapi. *Veteriner Farmakoloji ve Toksikoloji Derneği Bülteni, 10*(1), 1–15.

Stela, M., Cichon, N., Spławska, A., Szyposzynska, M., & Bijak, M. (2024). Therapeutic potential and mechanisms of bee venom therapy: a comprehensive review of apitoxin applications and safety enhancement strategies. *Pharmaceuticals*, 17(9), 1211. https://doi.org/10.3390/ph17091211

Uddin, M.B., Lee, B.H., Nikapitiya, C., Kim, J.H., Kim, T.H., Lee, H.C., … Kim, C.J. (2016). Inhibitory effects of bee venom and its components against viruses in vitro and in vivo. *Journal of Microbiology (Seoul, Korea)*, 54(12), 853–866. https://doi.org/10.1007/s12275-016-6376-1

Ullah, A., Aldakheel, F.M., Anjum, S.I., Raza, G., Khan, S.A., & Tlak Gajger, I. (2023). Pharmacological properties and therapeutic potential of honey bee venom. *Saudi Pharmaceutical Journal : SPJ*, 31(1), 96–109. https://doi.org/10.1016/j.jsps.2022.11.008

Wang, K., Tao, L., Zhu, M., Yu, X., Lu, Y., Yuan, B., & Hu, F. (2024). Melittin ınhibits colorectal cancer growth and metastasis by ac-tivating the mitochondrial apoptotic pathway and suppressing epithelial–mesenchymal transition and angiogenesis. *International Journal of Molecular Sciences*, 25(21), 11686. https://doi.org/10.3390/ijms252111686

Wehbe, R., Frangieh, J., Rima, M., El Obeid, D., Sabatier, J.M., & Fajloun, Z. (2019). Bee venom: overview of main compounds and bioactivities for therapeutic interests. *Molecules*, 24(16), 2997. https://doi.org/10.3390/molecules24162997

Zan, H., Liu, J., Yang, M., Zhao, H., Gao, C., Dai, Y., … Zhang, Y. (2024). Melittin alleviates sepsis-induced acute kidney injury by promoting GPX4 expression to inhibit ferroptosis. *Redox Report: Communications in Free Radical Research*, 29(1), 2290864. https://doi.org/10.1080/13510002.2023.2290864

Zhang, S.F., & Chen, Z. (2017). Melittin exerts an antitumor effect on non-small cell lung cancer cells. *Molecular Medicine Reports*, 16(3), 3581–3586. https://doi.org/10.3892/mmr.2017.6970