

Bee venom: From venom to medicine - A comprehensive review of composition, envenoming, and therapeutic Potential

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Abstract

Bee venom (BV), a complex secretion of *Apis mellifera* and related species, presents a fascinating duality: a potent threat causing significant morbidity and mortality through envenoming, and a source of promising therapeutic compounds with diverse biological activities. This review synthesizes current knowledge on BV composition, the pathophysiology and management of bee envenoming (particularly mass stinging events and anaphylaxis), and the rapidly evolving field exploring its therapeutic applications. We critically examine traditional uses (apitherapy), modern pharmacological research highlighting anticancer, anti-inflammatory, antimicrobial, and neuroprotective properties, and the challenges in developing specific antivenoms. Recent advances in nanotechnology, molecular biology (e.g., phage display, monoclonal antibodies), and our understanding of venom biology offer unprecedented opportunities to harness BV's potential while mitigating its dangers. Standardization of collection, characterization, and research methodologies is crucial for translating laboratory findings into safe and effective clinical applications.

Keywords: Bee venom, envenoming, apitherapy, therapeutic applications, antivenom development, nanotechnology

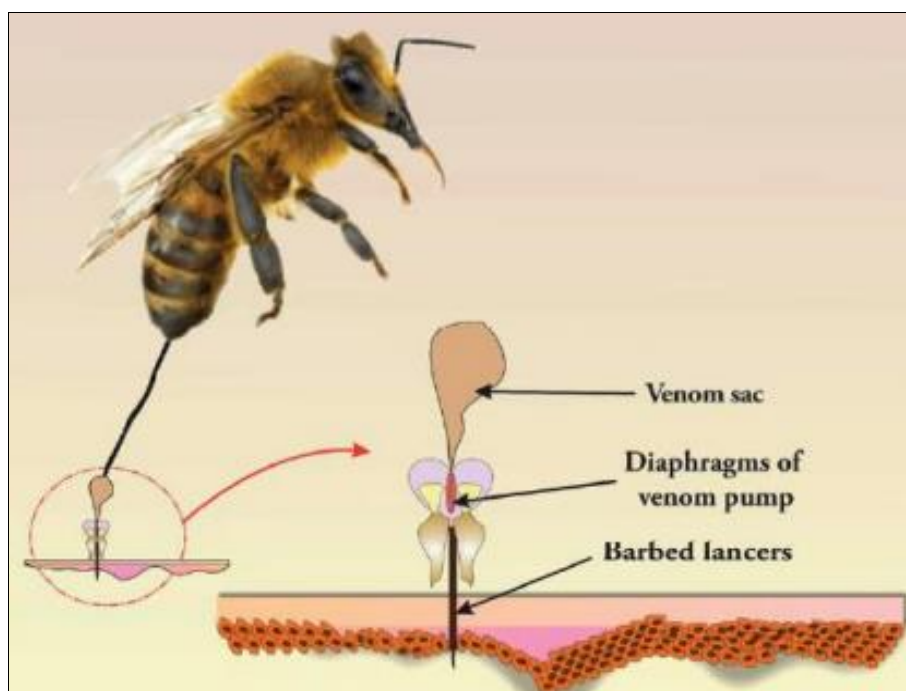
Introduction

Honey bees (*Apis mellifera*) are vital global pollinators, yet their potent defensive mechanism – the injection of venom via a barbed stinger – poses significant health risks to humans. Interactions with bees, particularly the more aggressive Africanized hybrids spreading throughout the Americas since their accidental release in Brazil in 1956, result in millions of stings annually (Pucca *et al.*, 2019) [10]. Consequences range from localized pain and swelling to life-threatening systemic anaphylaxis in sensitized individuals or severe toxic envenoming following massive attacks. Paradoxically, BV and its components, used for

centuries in traditional medicine (apitherapy), are now the focus of intense scientific scrutiny for their diverse pharmacological properties, particularly in oncology. This review aims to comprehensively explore the composition of BV, the clinical challenges and current management of bee envenoming, and the burgeoning evidence supporting its therapeutic potential, highlighting recent advances and future directions.

Composition of Bee Venom

BV is a clear, bitter, aqueous liquid produced in the venom gland of female worker bees



(Fig 1: Venom gland of *Apis mellifera* - Satar, 2023) [11].

It is a complex mixture of pharmacologically active substances, with over 18 identified components (Ali, 2012; Jaafar & Albushabaa, 2025) [7]. The composition is remarkably consistent across *Apis mellifera*, though factors

like bee age, species/subspecies, diet, season, and geography can cause minor variations influencing overall toxicity (Senthilkumaran *et al.*, 2020) [12]. Dry BV primarily consists of peptides, enzymes, and amines

Class of Molecules	Components	% of Dry BV
Enzymes	Phospholipase A ₂	10–12
	Hyaluronidase	1–3
	Acid phosphomonoesterase	1
	Lysophospholipase	1
	α-glucosidase	0.6
Proteins and peptides	Melittin	40–50
	Apamin	1–3
	Mast cell degranulating peptide	1–2
	Secapin	0.5–2
	Procamine	1–2
	Adolapin	1.0
	Protease inhibitor	0.8
	Tertiapin	0.1
	Other small peptides (<5 amino acids)	13–15
	Physiologically active amines	Histamine
Dopamine		0.2–1.0
Noradrenalin		0.1–0.7
Amino acids	Aminobutyric acid	0.5
	α-amino acids	1
Sugars	Glucose and fructose	2
Phospholipids		5
Volatile compounds		4–8

(Fig 2: Composition of dry bee venom expressed as type of molecule, components, and weight percentages - Gajski *et al.*, 2024) [6]

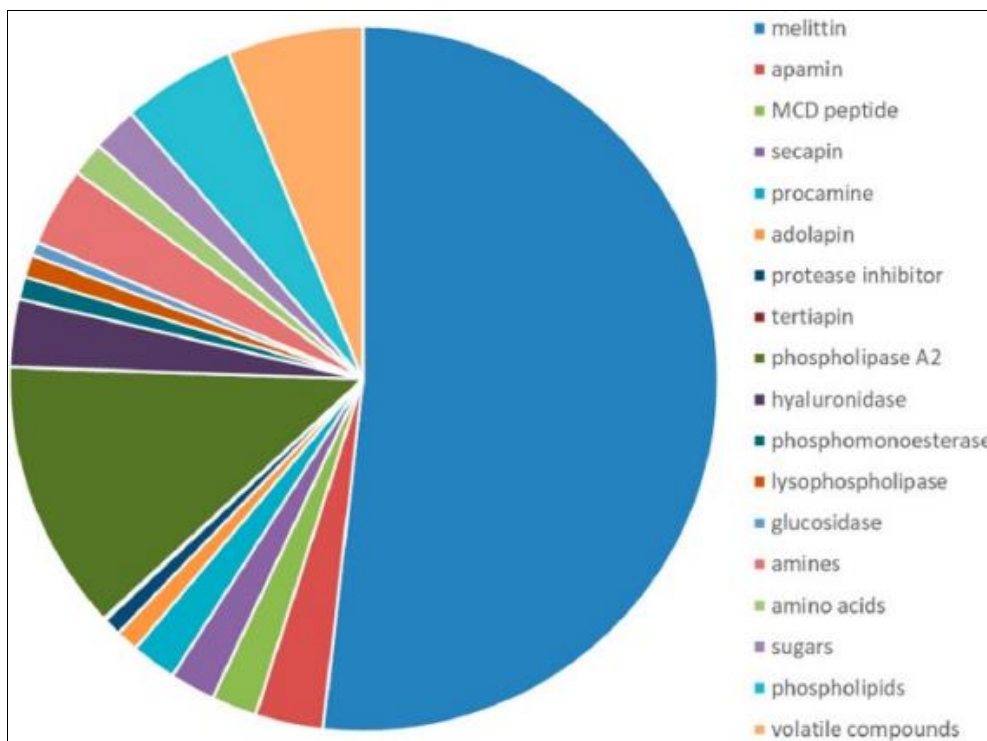


Fig 3: Composition of Honey Bee Venom - Gajski *et al.*, 2024) [6]

Major Peptides

▪ ***Melittin (40-60%):** *The primary cytotoxic component and major pain-inducing substance. It is a 26-amino acid amphipathic peptide that disrupts cell membranes (lysis), activates phospholipase A₂ (PLA₂),

and influences numerous signaling pathways. Its amphipathic nature (hydrophilic N-terminus, hydrophobic C-terminus) is crucial for membrane interaction and anticancer activity (Duffy *et al.*, 2020; Khalil *et al.*, 2021; Gajski *et al.*, 2024) [5, 6, 8].

- ***Apamin (~2-3%):*** A neurotoxic 18-amino acid peptide crossing the blood-brain barrier, blocking SK-type Ca²⁺-activated K⁺ channels, potentially modulating CNS excitability.
- ***Mast Cell Degranulating (MCD) Peptide (~1-2%):*** Triggers histamine release from mast cells, contributing to allergic responses but also studied for potential neurotrophic effects.
- ***Adolapin (~0.5-1%):*** Exhibits anti-inflammatory and analgesic effects by inhibiting cyclooxygenase (COX).
- **Major Enzymes**
- ***Phospholipase A2 (PLA2) (10-14%):*** A potent allergen and key enzyme hydrolyzing membrane phospholipids, synergizing with melittin to enhance cell lysis and inflammation. It is a major contributor to venom toxicity and anaphylaxis (Pucca *et al.*, 2019; Shi *et al.*, 2022) ^[10, 13].
- ***Hyaluronidase (1-3%):*** The "spreading factor," breaks down hyaluronic acid in connective tissue, facilitating venom diffusion.

- **Phosphomonoesterase (~1%), Acid Phosphatase (~1%):** Involved in phosphate ester hydrolysis.
- **Biogenic Amines:**
- ***Histamine (0.5-2%):*** Causes vasodilation, increased vascular permeability, itching, and pain.
- **Dopamine, Noradrenaline, Serotonin (<1%):** Contribute to pain sensation, vasoactivity, and neurotransmitter modulation.
- **Other Components:** Small peptides (e.g., secapin, tertiapin), protease inhibitors, carbohydrates, lipids, minerals (including sulfur, implicated in cortisol release - Ali, 2012), and volatile compounds.

This intricate cocktail acts synergistically to produce the immediate pain, inflammation, and potential systemic effects associated with bee stings.

Bee Envenoming: Pathophysiology and Clinical Management

Bee stings present a dual threat: IgE-mediated allergic reactions and direct toxic effects of venom components.



Fig 4

1. **Allergic Reactions (Anaphylaxis):** (Figure 4: *Treatment for bee sting(s) - Green Pathway*)
 - **Pathophysiology:** Sensitization to BV allergens (primarily PLA2, melittin, hyaluronidase, MCD peptide) leads to IgE production. Subsequent stings trigger mast cell and basophil degranulation, releasing histamine, leukotrienes, prostaglandins, and other mediators causing systemic anaphylaxis.
 - **Clinical Presentation:** Rapid onset (minutes) of urticaria, angioedema (especially perilaryngeal, causing airway obstruction), bronchospasm, hypotension, tachycardia, gastrointestinal symptoms, and potentially cardiovascular collapse and death.

- **Risk Factors:** Previous systemic reaction, atopy, family history of insect sting allergy (Senthilkumaran *et al.*, 2020) ^[12].
- **Management:** Immediate administration of intramuscular epinephrine (adrenaline) is lifesaving. Supportive care includes antihistamines (H1 and H2 blockers), corticosteroids, inhaled beta-agonists for bronchospasm, and fluid resuscitation for hypotension. Long-term management involves carrying epinephrine auto-injectors and consideration of venom immunotherapy (VIT) for specific IgE-mediated allergy to prevent future reactions. *No specific antivenom currently exists for allergic reactions.*

2. Toxic Envenoming (Mass Stinging Events): (Figure 4: Treatment for bee sting(s) - Purple Pathway)

- **Pathophysiology:** The cumulative effects of large venom doses (hundreds or thousands of stings) overwhelm the body's detoxification mechanisms. Melittin and PLA2 cause massive cell membrane damage (hemolysis, rhabdomyolysis), leading to hyperkalemia, acute kidney injury (AKI), hepatic injury, disseminated intravascular coagulation (DIC), and multi-organ failure (MOF). Other components contribute to direct organ toxicity and severe systemic inflammation (Akyıldız *et al.*, 2015; Pucca *et al.*, 2019)^[1, 10]. Kounis syndrome (allergic acute coronary syndrome) and takotsubo cardiomyopathy have also been reported (Senthilkumaran *et al.*, 2020)^[12].
- **Clinical Presentation:** Local reactions at multiple sting sites, nausea, vomiting, diarrhea, dizziness, headache, muscle cramps, hemolysis (dark urine), rhabdomyolysis, hypotension/shock, AKI, hepatic dysfunction, coagulopathy, cardiac arrhythmias, seizures, and coma. The LD50 for humans is estimated at approximately 2.8 mg venom/kg body weight (equivalent to ~560 stings for a 60kg adult, assuming 0.3mg/sting) (Ali, 2012). Deaths in children can occur with far fewer stings (e.g., ~93 stings for a 10kg child).
- **Management:** Focuses on supportive care and removing circulating venom/toxins.
- **Rapid Removal of Stingers:** Critical to limit ongoing venom injection. *Contrary to long-held belief, recent evidence (Lee *et al.*, 2020)^[8] indicates that the method of removal (scraping vs. pinching/pulling) is less important than the speed of removal. * Remove stingers as quickly as possible.
- **Aggressive Supportive Care:** Airway management, oxygenation, fluid resuscitation, vasopressors for shock, electrolyte correction (especially hyperkalemia), renal replacement therapy (hemodialysis) for AKI/rhabdomyolysis, management of coagulopathy and hepatic failure. Plasmapheresis has been used to remove circulating venom components (Akyıldız *et al.*, 2015)^[2].
- **Lack of Specific Antivenom:** A significant therapeutic gap. Current research faces challenges due to the low immunogenicity of key toxins like melittin (Pucca *et al.*, 2019)^[10].

Therapeutic Applications of Bee Venom (Apitherapy and Modern Research)

The use of bee products, including venom, for medicinal purposes (apitherapy) dates back millennia and is referenced in ancient texts (Vedas, Bible, Quran) (Ali, 2012; Bava *et al.*, 2023; Ullah *et al.*, 2023)^[3, 14]. Modern science is now elucidating the mechanisms behind these traditional uses.

1. Traditional Apitherapy (Bee Venom Therapy - BVT):

Involves the deliberate application of live bee stings or injectable venom to treat conditions like:

- Inflammatory arthritis (rheumatoid arthritis, osteoarthritis)
- Multiple Sclerosis (MS)
- Tendonitis (e.g., tennis elbow, golfer's elbow)
- Chronic pain syndromes (low back pain, sciatica)
- Skin conditions (e.g., psoriasis)
- While anecdotal reports exist, robust clinical evidence is largely lacking. A randomized crossover trial on BVT for MS found *no significant benefit* on disease activity (MRI lesions), relapse rate, disability, fatigue, or quality of life compared to no treatment, though it was well-tolerated (Wesselius *et al.*, 2005)^[15].

2. Pharmacological Properties and Mechanisms (Modern Research):

Extensive *in vitro* and *in vivo* (primarily animal model) studies demonstrate diverse bioactivities:

- **Anti-inflammatory:** Inhibition of COX/LOX pathways (Adolapin), suppression of pro-inflammatory cytokines (TNF- α , IL-1 β , IL-6), inhibition of NF- κ B and MAPK signaling pathways (Melittin, whole BV) (Shi *et al.*, 2022; Ullah *et al.*, 2023; Bava *et al.*, 2023)^[3, 13, 14].
- **Analgesic:** Central and peripheral mechanisms, involving modulation of glutamate receptors, adrenergic pathways, and opioid receptors (Adolapin, Apamin) (Shi *et al.*, 2022)^[13].
- **Antimicrobial:** Activity against Gram-positive bacteria (e.g., *Staphylococcus aureus*), viruses (e.g., HIV, influenza), fungi, and protozoa, primarily attributed to melittin's membrane disruption (Ullah *et al.*, 2023; Bava *et al.*, 2023)^[3, 14].
- **Radioprotective:** Mitigation of radiation-induced tissue damage.
- **Neuroprotective:** Potential benefits in models of Parkinson's, Alzheimer's, and stroke (Apamin, MCD peptide - modulating neuroinflammation and ion channels) (Shi *et al.*, 2022; Khalil *et al.*, 2021)^[8, 13].
- **Immunomodulatory:** Complex effects, including potential suppression of autoimmune responses.

3. Anticancer Effects:

This area holds immense promise and is a major focus of current research.

- **Key Agent: Melittin.** Its ability to lyse cell membranes shows selectivity towards cancer cells compared to normal cells, potentially due to differences in membrane composition (higher negative charge on cancer cells) (Gajski *et al.*, 2024; Duffy *et al.*, 2020; Khalil *et al.*, 2021)^[5, 6, 8].
- **Mechanisms:** Beyond direct cytolysis, BV and melittin induce apoptosis in cancer cells via multiple pathways:
 - Activation of caspases through mitochondrial or death receptor pathways.
 - Inhibition of cancer cell proliferation, migration, and invasion.
 - Suppression of angiogenesis.
 - Induction of cell cycle arrest.

- **Crucial Finding:** Duffy *et al.* (2020) [5] demonstrated that BV and melittin potently suppress growth factor receptor activation (EGFR/HER2) specifically in HER2-enriched and triple-negative breast cancer (TNBC) subtypes, interfering with receptor phosphorylation at the plasma membrane. The positively charged C-terminus of melittin mediates this interaction. Engineering melittin with an RGD motif

enhanced tumor targeting and reduced toxicity to normal cells. Melittin also synergized with docetaxel in suppressing breast tumor growth *in vivo*.

- **Activity has been shown against various cancer types *in vitro* and *in vivo*:** breast, lung, liver, prostate, bladder, kidney, leukemia, melanoma, glioblastoma (Gajski *et al.*, 2024; Khalil *et al.*, 2021; Ullah *et al.*, 2023) [6, 8, 14].

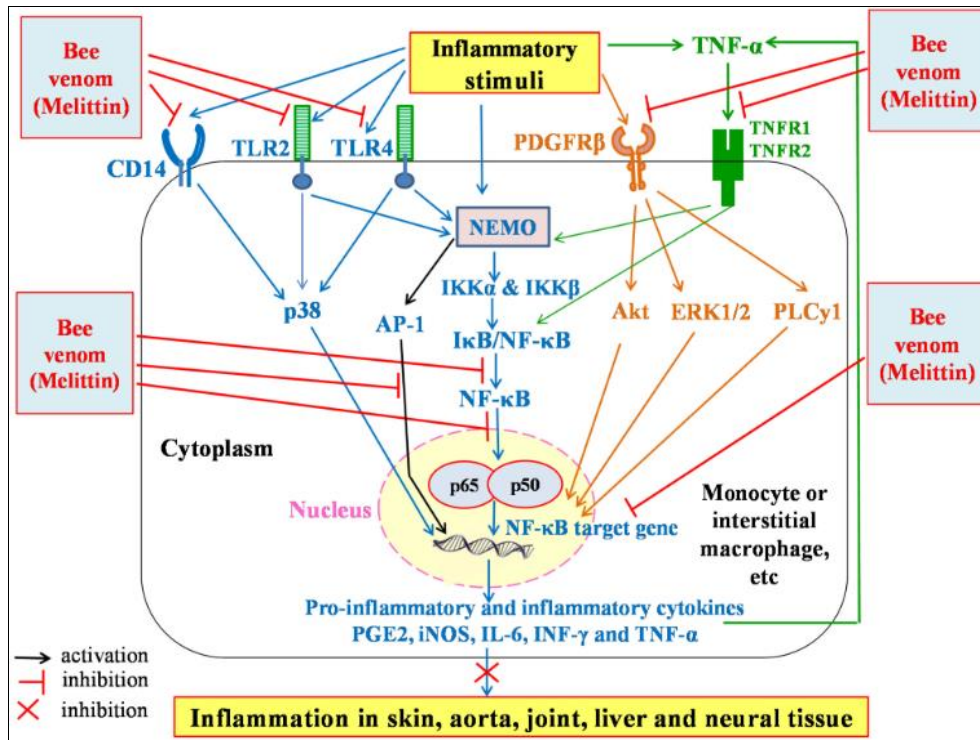


Fig 5: Mechanisms of Bee Venom and Melittin in Cancer Therapy (Khalil *et al.*, 2021) [8] illustrates key pathways.

- **Challenges:** Delivery (non-specific cytotoxicity), stability, dosage, and potential allergic reactions. Nanotechnology (e.g., nanoparticles, liposomes) is being explored to target melittin specifically to tumors and mitigate side effects (Khalil *et al.*, 2021; Shi *et al.*, 2022) [8, 13].

Venom Collection, Standardization, and Safety

1. **Collection Methods:** Critical for obtaining pure, high-quality venom for research and therapeutics.
 - **Electrical Stimulation:** The primary commercial method. A mild electric current applied to a grid placed at the hive entrance stimulates bees to sting a glass or plastic surface beneath the grid, depositing venom which dries quickly. Devices are designed to minimize bee mortality and contamination (Satar, 2023; de Graaf *et al.*, 2021) [4, 10].
 - **Manual Extraction:** Less common, involves dissecting venom sacs/glands.
 - **Factors Affecting Quality:** Bee health, colony strength, environmental conditions, collection frequency, storage.
2. **Standardization and Characterization:** Essential for research reproducibility and therapeutic product quality control (de Graaf *et al.*, 2021) [4].

- **Physical/Chemical:** Protein content (e.g., Bradford assay), moisture content, UV spectroscopy, HPLC profiling (melittin/PLA2 content), SDS-PAGE.
- **Biological:** PLA2 enzymatic activity, hemolytic activity (melittin), lethal dose (LD50) determination, allergenicity testing (IgE binding assays).
- **Assigning Allergens:** Standardized procedures exist for identifying and naming new BV allergens (e.g., Api m 1 = PLA2).
- 3. **Storage:** Dried BV is relatively stable. Should be stored in dark-colored bottles, protected from light, moisture, and oxygen, preferably frozen (-20°C or lower) for long-term stability (Jaafar & Albushabaa, 2025; de Graaf *et al.*, 2021) [4, 7].
- 4. **Safety and Toxicity**
 - **Acute Toxicity:** As described for envenoming. The primary risk for therapeutic use is IgE-mediated anaphylaxis. Rigorous patient screening (history, skin tests, sIgE) is mandatory before any BV-based treatment.
 - **Therapeutic Window:** While the LD50 provides a toxicity baseline, the therapeutic dose for conditions like cancer is still under investigation and likely requires targeted delivery systems to achieve efficacy without systemic toxicity.

- **Other Considerations:** Potential for non-allergic adverse reactions (local inflammation, pain), batch-to-batch variability, contamination.

Current Challenges and Future Directions

1. Bee Envenoming:

- **Specific Antivenom Development:** The most critical unmet need, especially for mass envenoming. Overcoming the low immunogenicity of key toxins (melittin) is paramount. Strategies include:
 - **Recombinant Technologies:** Phage display libraries to identify high-affinity human antibodies or antibody fragments (scFv, Fab) against melittin, PLA2, and other major toxins (Pucca *et al.*, 2019) [10].
 - **Monoclonal Antibodies (mAbs):** Engineering neutralizing mAbs.
 - **Adjuvants and Carrier Design:** Enhancing the immune response to weakly immunogenic toxins during antivenom production.
 - **Cross-Reactivity:** Exploring potential cross-reactivity with antivenoms against other hymenopteran venoms.
 - **Improved Biomarkers:** Diagnostic tests to stratify envenoming severity (allergic vs. toxic, prediction of organ involvement) for better treatment decisions (Senthilkumaran *et al.*, 2020) [12].

- **Climate Change Impact:** Understanding how environmental changes affect bee behavior, venom composition, and toxicity (Senthilkumaran *et al.*, 2020) [12].

2. Therapeutic Applications:

- **Clinical Translation:** Moving promising *in vitro* and animal data into well-designed human clinical trials, particularly for cancer and inflammatory diseases. Defining safe and effective dosing regimens is crucial.
 - **Delivery Systems:** Advancing nanotechnology (nanoparticles, liposomes, hydrogels) for targeted delivery of melittin and other components to disease sites (e.g., tumors, inflamed joints) while minimizing systemic exposure and toxicity (Khalil *et al.*, 2021; Shi *et al.*, 2022) [8, 13]. RGD-engineered melittin (Duffy *et al.*, 2020) [5] is a prime example.
 - **Synthetic Analogues:** Designing modified melittin or other peptide analogues with enhanced stability, selectivity, and reduced toxicity.
 - **Mechanistic Elucidation:** Deeper understanding of the molecular targets and signaling pathways (e.g., PI3K/Akt, MAPK, NF-κB, JAK/STAT) modulated by BV components using omics technologies and bioinformatics (Shi *et al.*, 2022) [13].

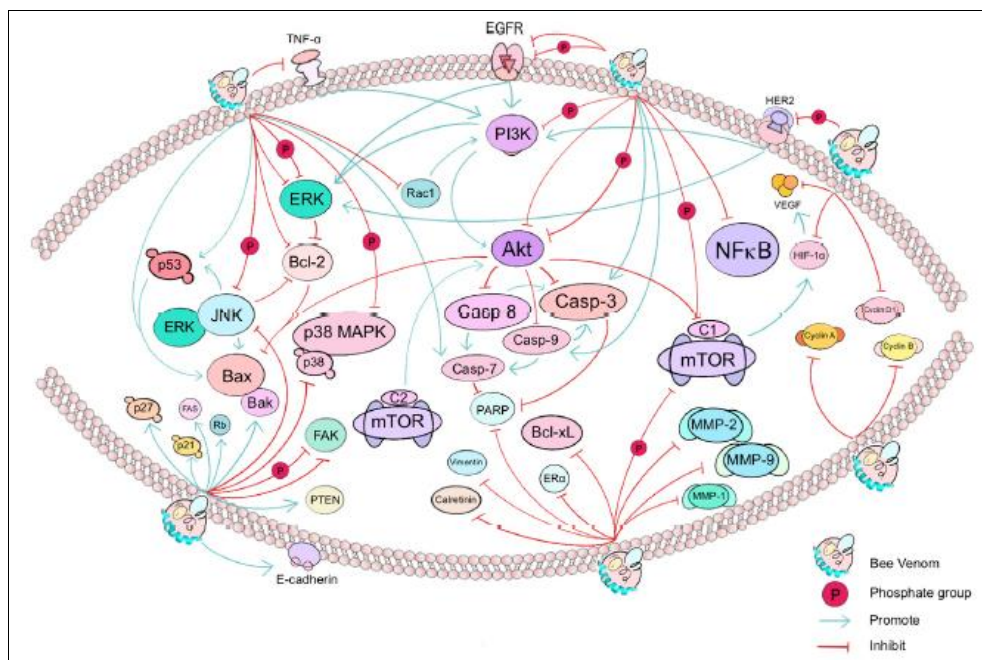


Fig 6: Key Signaling Pathways Targeted by Bee Venom Components (Shi *et al.*, 2022) [13].

- **Veterinary Applications:** Expanding research beyond rodent models into veterinary species for conditions like arthritis or mastitis (Bava *et al.*, 2023) [3].
- **Standardization and Regulation:** Ensuring consistent quality, purity, and potency of BV products used in research and therapy (de Graaf *et al.*, 2021) [4].

Conclusion

Bee venom embodies a remarkable paradox: a potent natural weapon capable of causing severe envenoming and death,

yet also a rich source of bioactive molecules with significant therapeutic potential. While the management of allergic reactions relies on established emergency protocols (epinephrine) and immunotherapy, the absence of a specific antivenom for toxic envenoming remains a major healthcare challenge, driving innovative research using recombinant antibody technologies. Simultaneously, the pharmacological prowess of BV, particularly melittin, is being unlocked through modern science. Its potent anticancer, anti-inflammatory, and antimicrobial activities, demonstrated in numerous preclinical studies, offer exciting avenues for

drug development, especially against aggressive cancers like TNBC. The future lies in overcoming delivery challenges through nanotechnology and engineering, rigorously testing safety and efficacy in clinical trials, standardizing venom products, and continuously improving our understanding of its complex biology and mechanisms of action. As research progresses, the translation of bee venom components from feared toxins into valuable therapeutic agents holds immense promise for improving human and animal health.

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