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Harnessing the power of bee venom for therapeutic and regenerative medical applications: an updated review

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Honeybees have been helpful insects since ancient centuries, and this benefit is not limited to being a honey producer only. After the bee stings a person, pain, and swelling occur in this place, due to the effects of bee venom (BV). This is not a poison in the total sense of the word because it has many benefits, and this is due to its composition being rich in proteins, peptides, enzymes, and other types of molecules in low concentrations that show promise in the treatment of numerous diseases and conditions. BV has also demonstrated positive effects against various cancers, antimicrobial activity, and wound healing versus the human immunodeficiency virus (HIV). Even though topical BV therapy is used to varying degrees among countries, localized swelling or itching are common side effects that may occur in some patients. This review provides an in-depth analysis of the complex chemical composition of BV, highlighting the diverse range of bioactive compounds and their therapeutic applications, which extend beyond the well-known anti-inflammatory and pain-relieving effects, showcasing the versatility of BV in modern medicine. A specific search strategy was followed across various databases; Web of sciences, Scopus, Medline, and Google Scholar including *in vitro* and *in vivo* clinical studies.to outline an overview of BV composition, methods to use, preparation requirements, and Individual

consumption contraindications. Furthermore, this review addresses safety concerns and emerging approaches, such as the use of nanoparticles, to mitigate adverse effects, demonstrating a balanced and holistic perspective. Importantly, the review also incorporates historical context and traditional uses, as well as a unique focus on veterinary applications, setting it apart from previous works and providing a valuable resource for researchers and practitioners in the field.

KEYWORDS

apitherapy, anti-inflammation, anticancer, antimicrobial, neuroprotection, wound healing

1 Introduction

Bees are commercially beneficial insects that have been around since the Cretaceous age of the Mesozoic Era. They also help fertilize many different crops. Bees are helpful, but their capacity to administer excruciating and poisonous stings constitutes a risk. Thankfully, most honeybees are not hostile to people and only resort to violence if they perceive danger (Pucca et al., 2019). *Apis mellifera* is the most often used honeybee species for agricultural pollination globally. All bee products, particularly venom, and honey, have been used for centuries, and their medicinal properties have been described in holy writings such as the Bible and the Quran (Ali, 2024; Dinu et al., 2024). Bee venom (BV) treatment involves injecting honeybee venom into the human body to cure various ailments. For over 5,000 years, this technique has been used in complementary therapies. It consists of either an indirect implementation, like isolating BV via stimulating electricity and then administering it into the body, or an immediate administration, such as bee stings (Wehbe et al., 2019). Applying BV in medicine stemmed from discovering that beekeepers rarely experience rheumatism or joint discomfort (Ullah et al., 2023). Across different cultures, BV has been employed in ethnomedicine as a natural remedy for a wide range of health conditions. Traditional practices have incorporated BV for its anti-inflammatory effects, pain relief properties, and immune system stimulation. In ethnomedicinal practices, BV has been used to alleviate symptoms of arthritis, rheumatism, and inflammatory conditions. Additionally, BV has been applied for its potential in wound healing, skin conditions, and even as an antimicrobial agent (Bava et al., 2023). BV is a colorless, scentless liquid of numerous molecules with a slightly acidic pH (4.5–5.5), which bees utilize as protection from enemies. A single drop of BV comprises 88% water and only 0.1 g of dry venom (Bellik, 2015). BV consists of several compounds and a significant quantity of water (Farook et al.; Essam Elenany, 2024). BV content has previously been identified via omics and fractionation techniques (Pucca et al., 2019). BV is a biotoxin or api-toxin produced by a gland in the bee's abdomen cavity. It comprises a complicated blend of many physiologically active peptides-incredibly intricate peptide combinations. Melittin, adolapin, apamin, and MCD-peptide are only a few examples. It also has powerful enzymes, like phospholipase A2 (PLA2), hyaluronidase, acid phosphodiesterase, -D-glucosidase, and lysophospholipase are enzymes, and in addition to low-molecular-weight molecules naturally occurring amines (e.g., histamine and epinephrine) and micronutrients (Moreno and Giralt, 2015). Apitoxin formulation is influenced by bee age, where they live, seasonal shifts, and social standing. Melittin, apamin, hyaluronidase, and PLA2 levels are particularly sensitive to change.

Furthermore, the procedures for collecting BV influence the volatile component composition. Electricity that is used to stimulate histamine can vanish during BV extraction (Schmidt, 2018). Many investigations have examined the curative effects of these substances in managing numerous illnesses and conditions (Wehbe et al., 2019). BV possesses anticancer, antimicrobial, and antiviral activities (Gajski et al., 2024).

This article offers an updated and in-depth review of the intricate chemical profile of BV, emphasizing the wide variety of bioactive compounds and their therapeutic potential and clinical applications against various illness. This highlights the adaptability of BV in contemporary medicine.

2 Sources of bee venom

Female honeybees generate venom from a gland situated in their abdomen cavity (Ali, 2024). The gland is attached to a container capsule. Apis social insects rely heavily on their seminiferous system for protection. Bees sting near apiaries to defend their colonies (Piek, 2013). The queen uses stings to eliminate competitors (Portelli, 2020). When many queens are born simultaneously, they escape with a particular number of bees, murder the unborn queens in their cell, or participate in a dying battle. Each hive may only have one queen. BV has the maximum protein concentration in the initial 1–3 days of life, then declines following 7 days. This is critical for killing competitors in the fight for beehive leadership. Honeybee venom's protein concentration decreases when the gland degenerates in subsequent days. Female honeybees do not produce detectable venom at the moment of emergence (Bava et al., 2023). Instead, it swiftly climbs during the next 2 days, stays steady for 14 days, and then decreases. Older honeybees generate less venom than younger bees. The venom's makeup varies with age. Melittin is secreted as a dormant component becomes active during growth and passes into the guardian stage around day 20 of age (Bava et al., 2023). Honeybees withdraw their venom sac and pointed stinger from their abdomen when stinging.

In contrast to similar insects, they are limited to stinging once before dying (Elieh Ali Komi et al., 2018). When a bee strikes a human or an animal, the stinger remains attached under the outer layer of skin, and the honey bee passes away by pulling out its guts, muscles, and nerve center to remove itself. Many of the bees' bodies are lost, leading to death. The stinger's sharp tip has microscopic

hooks that prevent it from being eliminated without causing damage. Once lodged, the venom is pushed into the wound using a separate piston mechanism (Lee et al., 2020). The stinger integrates into the tissue, discharging the components of the venom chamber within a few minutes (Elieh Ali Komi et al., 2018). BV sends an alarm pheromone that stimulates other honeybees to protect the beehive (Elieh Ali Komi et al., 2018). BV can induce localized inflammatory reactions, such as discomfort, warmth, and irritation, as well as systemically triggered allergic responses that can lead to anaphylactic shock and even death (Annila et al., 1996).

BV can be collected using various techniques, with the most common method being the electric shock extraction process. This method involves exposing bees to a low-voltage electric current (20–30 V), which induces them to release venom that is then collected on a glass plate. The bees are not harmed during this process, making it safe for them. Another traditional method involves surgically removing the venom gland from bees or squeezing individual bees until a drop of venom is extracted from the stinger tip. However, this method is less common compared to the electric shock technique. The venom collected through the electric shock process is considered effective and is widely used in clinical applications. The final product has varying properties depending on the extraction process used, with the most effective venom being that which is collected under water to prevent the evaporation of the highly volatile components (Otręba et al., 2021).

After collection, BV undergoes processing to extract its active components for medical use. Techniques such as chromatographic separation and molecular genetic methods are employed to isolate individual BV active ingredients for specialized medical purposes. These processes allow for the extraction of specific compounds like melittin and apamin, which possess unique therapeutic properties (Pucca et al., 2019; Bava et al., 2023).

To ensure the reproducibility and safety of BV-based therapies, it is crucial to accurately identify and measure the components of BV. Standardization of BV is necessary to guarantee the consistency of the final product and its therapeutic efficacy. Factors such as the bee species, season, and geographical location can influence the composition of BV. Therefore, quality control measures, including analysis of moisture content, protein profile, and cytotoxicity, are essential during the processing and extraction stages (El Mehdi et al., 2022).

3 Composition of bee venom

BV is a complex mixture composed primarily of water (88%) and various peptides, enzymes, and other compounds. The main components of BV including (1) peptides; melittin (50%–60% of dry venom), a small peptide with 26 amino acids that causes pore formation in membranes; apamin (2%–3% of dry venom), a neurotoxic peptide mast cell degranulating (MCD) peptide; and adolapin. (2) Enzymes; phospholipase A2 (10%–12% of dry venom) destroys phospholipids in cell membranes, hyaluronidase, phosphatase, α-glucosidase. (3) Biogenic amines; histamine, epinephrine (adrenaline). (4) Other compounds; lipids, carbohydrates, free amino acids, and minerals.

The composition of BV can vary depending on factors like bee species, season, and geographical location. However, melittin and phospholipase A2 are consistently the most abundant components, making up over 80% of dry BV. The complex chemical nature of BV contributes to its wide range of biological activities and therapeutic potential (Sharaf et al., 2024a). Hymenoptera venom includes several active elements, small-molecular-weight compounds, and aliphatic contents (Table 1) (Silva et al., 2015). The makeup is complex, with proteins accounting for 80% of the total. Proteins generally have large molecular weights, while peptides have lower molecular weights. Biogenic amines, such as dopamine, histamine, and serotonin, are crucial low-molecular-weight compounds found in BV. BV peptides, like adolapine, melittin, apamin, and peptide, have been extensively studied for their bioactivities and potential therapeutic applications (Isidorov et al., 2023).

The appropriate collection method is crucial to ensure the highest quality BV. It is essential to collect the venom without impurities from pollen, honey, or other colony byproducts to maintain its purity and efficacy (Essam Elenany, 2024). While there are no formal quality criteria for BV due to its classification outside the regulatory frameworks for medications and food products, researchers have suggested using quantitative analysis of stable components and comprehensive characterization as indirect means of assessing the purity and quality of BV. Additionally, efforts have been made to standardize and manage the quality control of Hymenoptera venom, including BV, to ensure its therapeutic efficacy (Oliveira Orsi et al., 2024).

3.1 Melittin

MEL is BV's primary potent physiological ingredient, representing 40%–50% of the dry mass. It can dissolve in linear, cationic, and hemorrhaging and weighs 2,840 Da. It is made up of 26 amino acids. The molecular structure $C_{131}H_{229}N_{39}O_{31}$, with the N-terminal part predominantly hydrophobic due to +4 charges and little lytic activity. The area located at the C-terminus is hydrophilic due to the +2 protons, responsible for the lytic activity, for a total of +6 charges at physiological Ph (Bava et al., 2023). Due to its amphipathic structure, Melittin is water soluble in monomeric and tetrameric forms. The previous study found that MEL possesses antimicrobial and anti-cancer benefits. It can mechanically and chemically damage many cellular membranes (Shi et al., 2016). MEL binds to the negatively charged membrane surface (Figure 1). As a result, it compromises the functioning of phospholipid bilayers by creating pores, atomic ion, and molecule leaks, and enhanced permeability, ultimately leading to cell lysis (Jamasbi et al., 2016). Melittin connects to membranes as monomers but works across the whole membrane. According to the dosage, this biopeptide might induce transitory or stable holes. Only ions can travel through the membrane when a transient pore is formed. When regular holes emerge, the membrane becomes accessible to big compounds like glucose. Melittin has recently been discovered to activate and sensitize nociceptor cells, resulting in neuronal plastic changes along pain signaling pathways. Similarly, melittin can function as a PLA2 activator. It is also a critical physiologically active component of BV, generating

TABLE 1 The biological significance of bee venom and its constituent ingredients.

Composition	Nature	Effect	Reference
Melittin	Peptide	The peptide has biological action. Melittin inhibits blood coagulation, inhibits pathogens, and protects against radiation. Melittin acts as an anti-inflammatory in tiny doses. It possesses both hemolytic and cytotoxic properties.	Jafari et al. (2024)
Phospholipase A2	Enzyme	Phospholipase is the most allergenic and damaging ingredient in bee venom.	Lee and Bae (2016b)
Hyaluronidase	Enzyme	This enzyme permits venom to enter tissues by widening blood vessels and boosting tissue permeability, increasing blood circulation.	Khan et al. (2018)
Acid phosphatase	Enzyme	Allergen.	Kim and Jin (2016)
Apamin	Peptide	Bioactive polypeptide: a neurotoxin.	Gu et al. (2020)
Mast cell degranulating peptide	Peptide	Causes the release of biogenic amines.	Starkl et al. (2022)
Protease inhibitor	Enzyme	It possesses anti-inflammatory and bleeding-related characteristics and suppresses proteases.	Lee et al. (2023)
Adolapin	Peptide	Anti-inflammatory, antirheumatic, and painkiller.	Bindlish and Sawal (2024)
Histamine	Biologic amine	It expands blood vessels and promotes the permeability of capillaries. It's an allergy.	de Graaf et al. (2021)
Dopamine, noradrenaline	Biologic amine	Neurotransmitters have an impact on sensory perception and function.	Ahmed-Farid et al. (2021)
Alarm pheromone	Peptide	It sets the entire community on heightened alert.	López-Incera et al. (2021)
Secapin	Peptide	-Antibacterial -Anti-elastolytic -Anti-fibrinolytic	Lee et al. (2023)
Procamine A,B	Peptide	Suppresses the action of proteolytic enzymes, hence lowering inflammatory responses.	Răsinar et al. (2023)

numerous biological effects when administered to the patient's acupoint (Wehbe et al., 2019).

3.2 Apamin

Apamin is considered the second most abundant active peptide identified in BV. It represents 1% of all dried BV. This peptide possesses anti-inflammatory and antinociceptive qualities that enhance defensive line capacity. Following crossing across the blood-brain barrier, it enters the brain and affects the neurological system. Apamin suppresses vascular smooth muscle cell migration and growth in the vascular wall by targeting the Akt and Erk signaling pathways. It suppresses Erk1/2 and Akt phosphorylation generated by PDGF-BB. Apamin has been shown to block the G0/G1 cell cycle via the PDGF-BB signaling pathway, making it a possible therapy for atherosclerosis (Kim JungYeon et al., 2015).

Its structure consists of a disulfide bridge between cysteine residues 3 and 15, which is crucial for its biological activity. Apamin is a selective inhibitor of small-conductance calcium-activated potassium (SK) channels, exhibiting nanomolar or even subnanomolar affinity. This specificity allows apamin to modulate SK channel activity without affecting other ion channels or receptors. Apamin has been investigated for its therapeutic potential in various diseases, including ataxia, epilepsy, and inflammatory conditions (Kuzmenkov et al., 2022). The peptide's ability to modulate SK channel activity has been linked to its therapeutic effects, as SK channels play a crucial role in neuronal excitability and synaptic plasticity. Additionally, apamin has been shown to have anti-inflammatory and anti-fibrotic effects, making it a promising candidate for the treatment of chronic diseases. Apamin has been explored for its potential in neuroprotection and neuroregeneration (Kim H. et al., 2021). Studies have demonstrated that apamin can cross the blood-brain barrier and bind to SK channels in the central nervous system, potentially contributing to learning and memory control. Furthermore, apamin has been shown to have neuroprotective effects in models of neurodegenerative diseases, such as Alzheimer's and Parkinson's. Apamin has also been investigated for its potential in cancer treatment (Villa et al., 2020). Studies have suggested that apamin can inhibit the growth of cancer cells by modulating SK channel activity and inducing apoptosis. Additionally, apamin has been shown to have anti-tumor effects in animal models, making it a promising candidate for the development of novel cancer therapies (Gu et al., 2020; Saravanan et al., 2023; Bindlish and Sawal, 2024).

3.3 Mast cell degranulating (MCD) peptide

Mast cell degranulating (MCD) Peptide, or peptide 401, is a BV polypeptide of 22 amino acids equivalent to apamin because it has two disulfide bridges (Răsinar et al., 2023). It makes up around 2%–3% of BV's dry weight. The term MCD alludes to the biological function of mast cells in producing histamine. It is an epileptogenic neurotoxin, a significant antagonist of K+ channels, and may drastically drop rat blood pressure (Gajski et al., 2024). Some MCD biological activity takes different routes and might be an excellent example of the structure-function link (Figure 2). Based on research, MCD is a potent anti-inflammatory drug that might be utilized to investigate the secretion mechanisms of cells associated with inflammation, potentially leading to the creation of medicinal substances (Ullah et al., 2023).

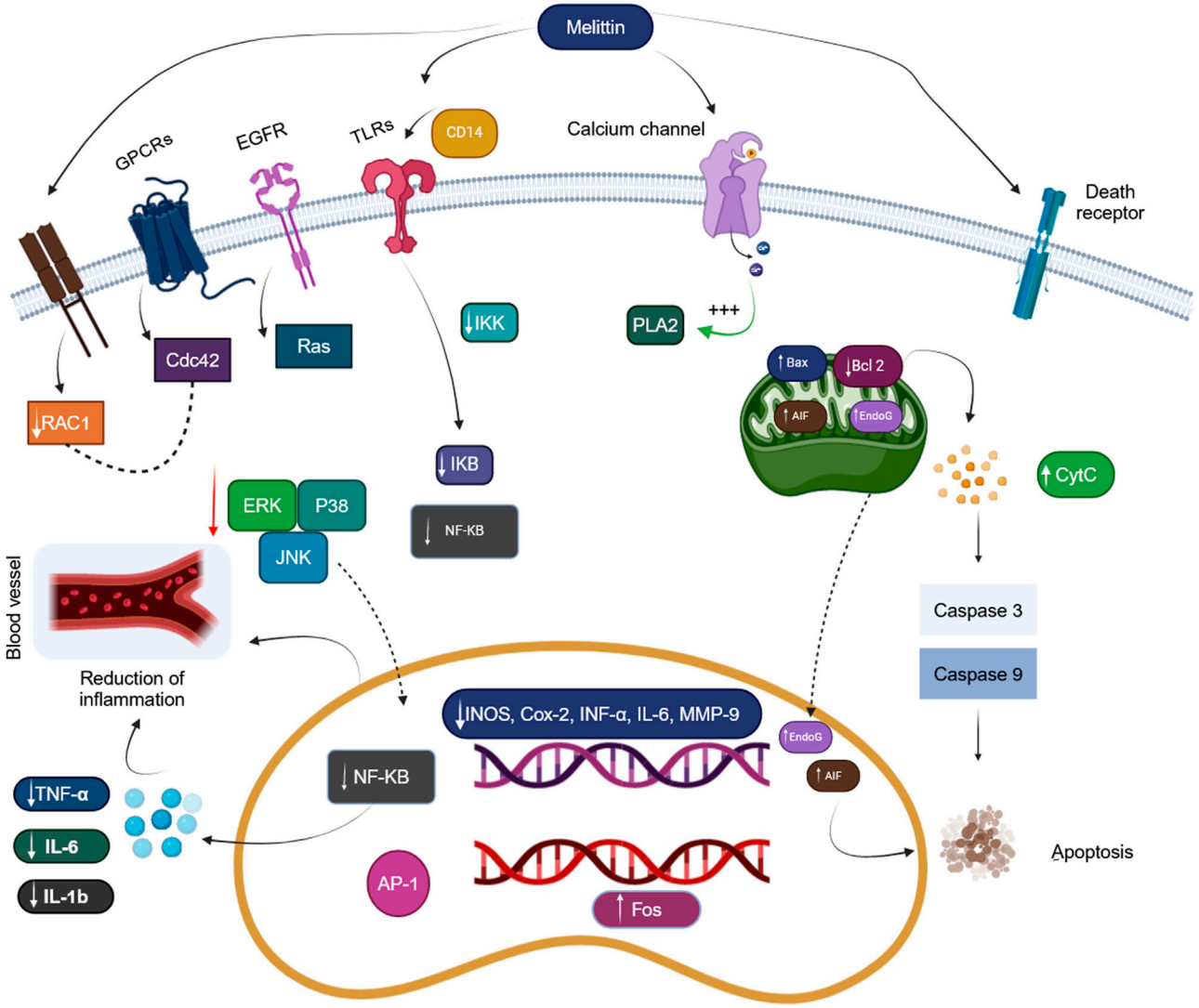

FIGURE 1
Mechanistic actions of bee venom melittin. (Generated by BioRender software).

3.4 Adolapin

Adolapin is a polypeptide with 103 amino acid sequences. It can be identified at 1% dry BV levels. It accounts for 2%–5% of the polypeptides present in BV (Gajski et al., 2024). Adolapin inhibits prostaglandin production and Cyclooxygenase function., providing anti-inflammation, anti-allergic, and fever resolution properties. It suppresses thrombocyte lipoxygenase activity and could possess painkilling characteristics (Sawicka et al., 2024).

3.5 Secapin

Secapin is a 25 amino acid polypeptide with a high proline content and one disulfide bond. It is a non-toxic polypeptide that makes up just 0.5% of dried BV. The Asiatic honey BV contains secapin (AcSecapin-1), which possesses antifibrinolytic, anti-elastolytic, and antibacterial effects (Dinata et al., 2023).

3.6 Procamine and tertiapin

Procamine, a polypeptide isolated from BV, suppresses protease activities, lowering inflammatory responses (Dinata et al., 2023). Tertiapin is a 21 amino acid peptide produced from BV. It has two disulfide bridges and an amidated C-terminal residue. It is a neurotoxic peptide similar to apamin. Tertiapin is a small part of the BV, representing 0.1% of its net content. Tertiapin inhibits the action of potassium gates throughout our bodies. It regulates potassium channels (Świątły-Błaszkiewicz et al., 2020).

3.7 Phospholipase A2

Phospholipase A2 (PLA2), BV's considerably more dangerous enzyme, is a polypeptide chain of 128 amino acids with four disulfide bridges. Its fundamental pH accounts for 12%–15% of BV's dry mass

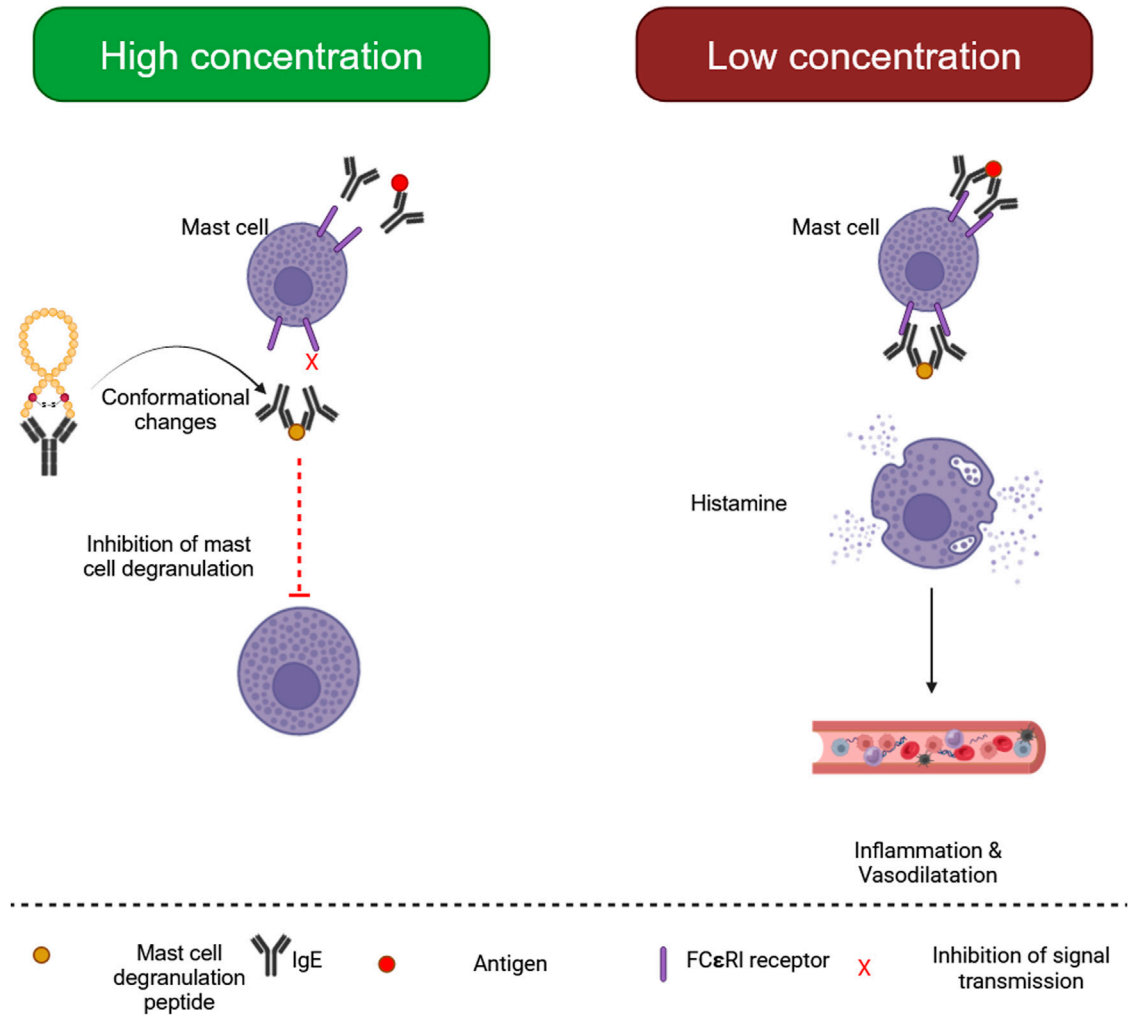

FIGURE 2
Biological processes of mast cell degranulating (MCD) peptide. (Generated by BioRender software).

(Gajski et al., 2024). Melittin, interestingly, can boost its action. This has been proven to occur throughout the red blood cell lysis process, showing synergistic activity between bvPLA2 and melittin (Frangieh et al., 2019). In addition, fresh, experimental results reveal that bvPLA2 has protective immunological reactions against several illnesses (Kim KH. et al., 2019). BvPLA2 causes microglial inactivation and decreases CD4+ T cell recruitment (Figure 3) (Jafarzadeh et al., 2023).

3.8 Hyaluronidase

Hyaluronidase amounts to about 1.5%–2% of BV dry weight and has been shown to break down hyaluronic acid. BV hyaluronidase enables the biologically functioning elements in BV to reach the targeted tissues with greater effectiveness by modifying its architectural durability and improving blood supply in the region. These two activities promote the spread of venom (Bava et al., 2023).

Aside from peptides, BV includes carbohydrates, free amino acids, and minerals. BV contains carbohydrates such as glucose and fructose. The primary components of amino acids are -aminobutyric acid and B-aminoisobutyric acid. BV also includes minerals such as magnesium, calcium, and phosphorus. It also includes volatile chemicals termed pheromones, symbolized by complicated ethers, which warn bees of hazards and trigger stinging responses (Salem and Marzouk, 2024). The RHGXRSP domain distinguishes these acid phosphatases from others. It releases histamine and creates particular IgE, which can be utilized in immunotherapy (Hossen et al., 2016). Dipeptidyl peptidase IV (DPIV) or Api m5 has a molecular mass of 102 kDa (Rzetecka et al., 2024). It is connected to transforming pro-toxins into activated metabolites (Blank et al., 2010; dos Santos-Pinto et al., 2018). Vitellogenin or Api m12 is BV's compound with the most significant molecular weight (200 kDa) (dos Santos-Pinto et al., 2018). Furthermore, it has antibacterial and antioxidant properties (Park HeeGeun et al., 2018).

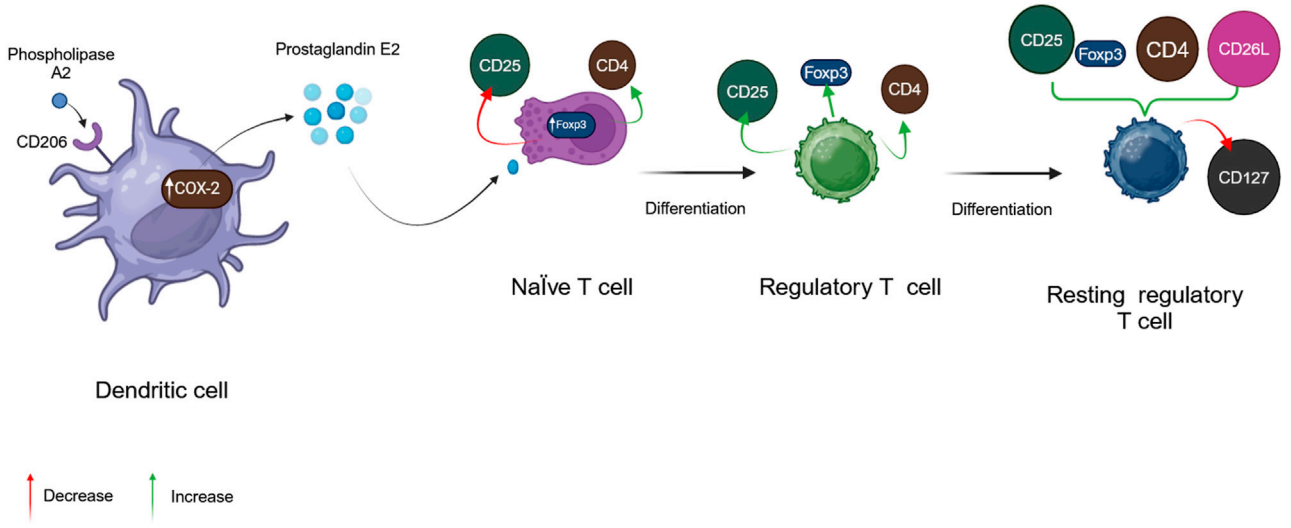

FIGURE 3
Physiological activity of phospholipase A2. (Generated by BioRender software).

4 Delivery approaches of bee venom

Oral delivery is complicated because the protein composition of BV can be degraded by gastrointestinal enzymes (Carpena et al., 2020). However, a study conducted by Meligi and his group, who studied the protective potential of oral administration of BV against liver damage caused by lipopolysaccharide and carbon tetrachloride in rats contradicts other reports (Meligi et al., 2020). BV therapy is usually applied in different ways including bee stings at specified places, injections of pure and sterile Apis homeopathic preparations, BV ointments, lotions, capsules, drops, and phonophoresis. Honeybee sting therapy is considered a classic therapeutic approach. It has several disadvantages, including discomfort. Since melittin's short half-life and the annoyance it gives patients, continuous administration of multiple rounds of stings or injections in the blood requires sting-induced inflammation and trouble maintaining average concentrations (Izhar et al., 2023). Due to BV's short duration of action and the challenge of estimating its dosages, scientists and professionals have promoted and created alternate options, such as mixing polymers or nanoparticles (NPs) (Ojha et al., 2023; Sharma et al., 2024a).

Traditional methods of administering BV therapy have typically involved topical applications, such as intravaginal suppositories or gels containing BV extracts. These methods have been used to target specific areas affected by conditions like bacterial vaginosis (BV). However, advancements in drug delivery have introduced more sophisticated approaches to BV therapy. Controlled drug release systems now allow for precise delivery of the active ingredients, ensuring the right amount reaches the intended site of action. The shift towards advanced drug delivery methods has the potential to enhance the efficacy of BV therapy by improving targeted delivery, increasing bioavailability, and reducing side effects associated with traditional administration routes. For instance, nanotechnology-based delivery systems offer high sensitivity and specificity, allowing for rapid diagnosis and treatment of BV. These modern approaches not only improve the precision of drug delivery but also optimize therapeutic outcomes by ensuring that the active components of BV reach the target tissues more effectively.

5 Therapeutic mechanisms

According to its biological ingredients, BV has a wide variety of medicinal effects. Several studies have discovered the pharmaceutical advancement in one or several features of BV, primarily focusing on pain-relieving (Lee et al., 2005), neuroprotective (Ye et al., 2016b), anti-inflammation (Jeong et al., 2017), enhancing wound recovery (Hozzein et al., 2018), anti-microbial impacts (El-Seedi et al., 2020), and cancer-fighting (Małek et al., 2023). These show that BV has a wide variety of therapeutic uses, which might be due to its multi-target and multi-pathway features (Figure 4). The complex composition of BV, with its mixture of both inflammatory and anti-inflammatory compounds, contributes to its dual nature. While the venom can cause immediate pain and swelling upon a sting, it also has the potential to exert beneficial effects, such as reducing inflammation and providing pain relief, when used in controlled therapeutic settings (Sadek, 2023). The precise mechanisms of action for the various components of BV and their interactions are still being actively investigated. Ongoing research aims to investigate the specific pathways and targets through which BV and its constituents exert their pharmacological effects, both beneficial and detrimental, to optimize its therapeutic potential while minimizing adverse reactions (Pandey et al., 2023a).

5.1 Antioxidant activity

BV includes compounds with high antioxidant activity (AOA) (Martinello and Mutinelli, 2021). The phenomenon is caused by phospholipases A2, apamin, and melittin. The antioxidant action is based in many ways, such as free radical elimination, proton

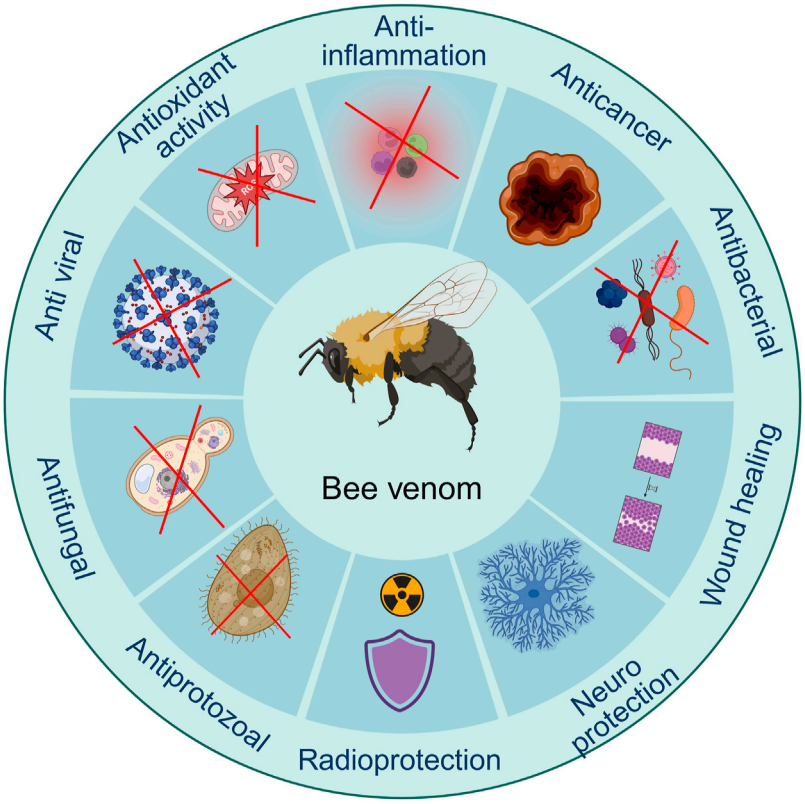

FIGURE 4
Biological activities of bee venom. (Generated by BioRender software).

transfer, metallic ions binding, solitary oxygen suppressing, and serving as a trigger for removing superoxide and hydroxyl radicals (Yaacoub et al., 2023). The antioxidant benefits may be due to the substances' capacity to impede lipid peroxidation and increase superoxide dismutase functionality. Superoxide dismutase is an enzyme that decreases tissue destruction by eliminating the superoxide radical in most cells when subjected to oxygen (Pinmanee et al., 2023).

BV includes extra antioxidants. Vitellogenin is a protective agent in mammalian cells, shielding them from oxidative stress and defending against free radicals. Few studies have employed traditional methods to determine the AOA of BV (Sobral et al., 2016; Somwongin et al., 2018). All samples included antioxidants, unconnected to the elements found and quantified in them. Evidence suggests that melittin alone has lower AOA than BV extracts, perhaps due to other metabolites (Pavel et al., 2014). Other tiny molecules may have a role in BV biological properties, with combinatorial or antagonistic effects at different concentrations resulting in varying consequences.

Previous studies found that honey BV significantly inhibited nonenzymatic lipid peroxidation. It competes with dimethyl sulfoxide for hydroxyl radicals, indicating its high detoxification properties. The findings suggest that honey BV's antioxidant activity contributes to its anti-inflammatory characteristics, particularly its capacity to reduce interleukin-1 synthesis *in vitro* (Değer et al., 2023; Abd El-Aziz et al., 2024; Virk et al., 2024). Additional investigations assessed antioxidant capacity in combination with other criteria. For example, rabbits received 0.1, 0.2, and 0.3 mg Under the skin twice weekly for 20 weeks (El-Hanoun et al., 2020). The study found that treating rabbits boosted glutathione S-transferase (GST) and glutathione (GSH) levels. The readings of malondialdehyde (MDA) and thiobarbituric acid–reactive substances (TBARS) were also lower. These studies confirmed BV's antioxidant capabilities. BV improved reproductive performance and semen antioxidant activity. Elkomy et al. (2021) found delivering BV via subcutaneous injection to rabbits improved total antioxidant capacity (TAC). Kim et al. introduced doses ranging from 10 to 500 μg per kilogram to the standard diet (Kim D-H. et al., 2019). The scientists found that ingesting BV improved the antioxidant properties and altered fatty acid metabolism in broilers.

5.2 Anti-inflammatory activity

Melittin may induce itching, inflammation, and localized discomfort in large dosages, although lower doses of melittin offer widespread anti-inflammatory benefits (Sawicka et al., 2024). Melittin inhibits the Toll-like receptors (TLRs) 2,4, CD14, nuclear factor-κB essential modulator (NEMO), and Platelet-derived growth factor receptor (PDGFR) signaling pathways. This decreases inflammatory reactions in numerous tissues (Lee and Bae, 2016a). BV has anti-nociceptive properties for inflammatory pain. BV has been utilized for decades to treat numerous discomfort reactions, including visceral, inflammatory, and heat (Ullah et al.,

2023). Hypodermic apipuncture with BV decreases thermally and mechanically related hyperplasia Arthritis discomfort is caused by collagen (Elieh Ali Komi et al., 2018). Furthermore, a single ingredient of BV, adolapin, has analgesic effectiveness. Pre-treatment with BV has anti-nociceptive properties against the spinal cord. Fos activity correlates with formalin-generated discomfort in rats (Galante et al., 2023). Apamin is a pain reliever that reduces inflammation and muscle discomfort (Wehbe et al., 2019). Oxaliplatin can cause mechanical allodynia and coldness; however, phospholipase A2 can mitigate these effects (Hossen et al., 2017a). Subcutaneous injection of BV has been demonstrated to offer anti-nociceptive effects in mouse models for both visceral and somatic pain. Additionally, it prevents nociceptive responses in mice caused by acetic acid (Qi et al., 2023). BV is more effective than adjuvants for treating arthritic pain because of its anti-nociceptive properties (Ullah et al., 2023). BV acupuncture effectively alleviated neuritis pain caused by paclitaxel in mouse models (Shen et al., 2020).

5.3 Anticancer activity

Cancer is one of the most severe diseases harming humans and is one of the leading causes of death around the globe. According to current data, around 10 million freshly diagnosed patients with the illness each year, and over 6 million people die from it, accounting for around 12% of all fatalities globally. In 2020, 15 million new cancer cases will be diagnosed (Morgan et al., 2023). Cancer growth and advancement are complex activities. Smoking, pathogenic organisms, environmental contaminants, a lousy diet, and internal variables that include transmitted down anomalies in genes, hormonal changes, and immunological conditions might all contribute to the start of this illness (Golubnitschaja et al., 2016). BV has been frequently used to treat several malignancies (Varol et al., 2022). BV metabolites have received a lot of interest for their possible utility in oncotherapy. Melittin, a powerful antitumor polypeptide, maybe a more practical alternative than the entire BV (Rady et al., 2017).

Melittin has high membrane-perturbing action, which accounts for its anti-inflammatory, anti-microbial, and cancer-fighting abilities (Roversi et al., 2023). When numerous melittin particles enter the cell membrane, they degrade the phospholipids, resulting in cellular fragmentation. It breaks down both phospholipid and synthesized bilayers. It has been found to cause apoptosis and have anticancer properties. Melittin targets several tumor cell types, including kidney, hepatic, pulmonary, prostate, and urinary malignancies, in addition to malignancies of the breast and leukemia (Zarrinnahad et al., 2018).

5.4 Anti-microbial activity

Microbial infections are a challenge, especially with the growth of medication resistance; thus, scientists are seeking Recent discoveries of bioactive potential. Products from nature are considered sources of sustainability with fewer problems that can provide various active substances (Thawabteh et al., 2019).

5.4.1 Anti-bacterial activity

Blending BV with regular medications is effective, helpful, and safe. Against specific microorganisms, but its uses are being carefully considered in both preclinical and clinical studies. BV and melittin have wide-ranging antibacterial properties against Gram-positive and Gram-negative bacteria, with MIC values ranging from 10 to 100 μg/mL and 30 to >500 μg/mL, respectively. BV, melittin, and oxacillin effectively killed Methicillin-resistant *Staphylococcus aureus* (MRSA) ATCC 33591. BV and melittin treatment led to modifications in the bacterial cell membrane due to membrane integrity loss and cellular shape changes involving cellular deformation. And cytoplasm loss (Pereira et al., 2020). Melittin's antibacterial capacity was tested against numerous bacteria (Roversi et al., 2023). Gram-positive bacteria are more sensitive to melittin compared to Gram-negative bacteria due to variations in their cell membrane structures (Gong et al., 2023). Melittin may pass through the peptidoglycan layer of Gram-positive cell membranes more effectively than Gram-negative cell membranes, which are protected by a lipopolysaccharide layer. The proline residue at position 14 has been proven to play a crucial role in melittin's antibacterial action (Sharma et al., 2024b). Melittin can dissolve biofilms generated by *S. aureus* and *Escherichia coli* (Rouhi et al., 2024).

5.4.2 Anti-viral activity

Viral infections have appeared in the previous 10 years. These have jeopardized the lives of millions of people throughout the world, particularly immunocompromised individuals. BV and its constituents have significant antiviral activity against viral infections (Table 2) (Mohanty and Murhekar, 2023). An enhanced understanding of Melittin's processes will help us enhance antiviral approaches. Several antimicrobial peptides (AMPs) primarily disrupt membranes to achieve their effects. Melittin's direct interaction with viral capsid proteins or envelopes in this scenario hinders the binding or absorption of cells capable of producing viruses (Memariani et al., 2020). Furthermore, additional possible antiviral modes of action include inhibiting viral multiplication, reducing viral mRNA expression levels, producing changes in viral genome conformation (Memariani et al., 2020), inhibiting the virus's cytotoxic properties, and inhibiting virally mediated cell fusion (Mohanty and Murhekar, 2023), and inhibit viral bundling (Peng et al., 2023). The possible use of melittin-loaded nanoparticles to eliminate the human immunodeficiency virus while leaving uninfected cells alone suggests a preventative method in which these nanoparticles are employed to make a vaginal lotion that stops HIV transmission. The theoretical underpinning is that Melittin molecules may be discovered on the viral envelope. Pore-like attack complexes develop when nanoparticles fuse (Peng et al., 2023). Another research discovered that bvPLA2 can similarly inhibit viral replication. The same team found the bvPLA2 peptide sequence, suppressing HIV replication (Wehbe et al., 2019).

5.4.3 Anti-fungal activity

Fungal infections harm over a billion people globally and cause about 1.5 million deaths each year (Silva et al., 2019). Antifungal drugs have specific restrictions concerning biocompatibility, spectrum of action, and pharmacological characteristics. These

TABLE 2 Application of bee venom in controlling the viral diseases.

Bee venom/isolated compounds	Model	Technique	Outcome	Reference
Phospholipase A2 (sPLA2)	Hepatitis C virus (HCV)	Plaque assay	PLA2 and its related compounds are promising prospects for the establishment of wide-spectrum antiviral medications targeting viral outer lipid bilayers produced from the endoplasmic reticulum membrane.	Chen et al. (2017)
Melittin	Human immunodeficiency virus (HIV)	Transient transfection Assays	Blocks viral replication. Blocks transcription of genes. Reduces intracellular protein and RNA production. Reduces the long terminal repeat (LTR) activity with an ID50 value. 0.9–1.4 μM after 24 h.	Wachinger et al. (1998)
Bee venom	Herpes simplex virus (HSV)	Plaque assay	Limits viral propagation EC50 1.52 ± 0.11 μg/mL	Uddin et al. (2016)
Bee venom	Papillomaviruses (HPV16 E6)	Reverse transcription assay	Blocks mRNA transcription. Blocks cell proliferation. Reduces protein levels. At 10 μg/mL, it decreases 0.35 ± 0.06-fold after 24 h.	Kim et al. (2015c)

TABLE 3 Applications of bee venom in controlling the fungal infections.

Bee venom/ isolated compounds	Microbe	Technique	Outcome	Reference
Apamin	*Alternaria alternate*	Not reported	Melittin and apamin could prevent the fungal-related synthesis of inflammatory messengers and extracellular matrix (ECM) by nasal fibroblasts.	Shin et al. (2017)
Melittin	Unicellular fungal (UCF) pathogens (*Cryptococcus neoformans*, *Kodamaea ohmeri*, and *Candida albicans*)	automated Vitek2 system	BV/chitosan nanoparticles (CHNPs) inhibited biofilm development and the yeast-to-hyphal transformation of the investigated (UCF) pathogens. These findings demonstrated that BV-chitosan nanoparticles are a potential natural chemical for treating fungal diseases.	El-Didamony et al. (2022b)
Bee venom/melittin	*C. krusei*	Broth microdilution	Bee venom and melittin had intense antifungal action (MIC measures ranging from 30 to 100 μg/mL).	Issam et al. (2015)
Bee venom	*C. albicans*	Disc diffusion	Suppresses fungal dimorphism	Ali (2014)
Bee venom	*Trichophyton rubrum*	Disk diffusion method	The bee venom in its entirety provided a high amount of suppression, and the venom in isolated forms was ineffective. Furthermore, BV-based compounds may serve as promising antifungal treatments.	Park et al. (2018)

concerns are worsened when these medicines can be utilized extensively and inappropriately, hastening the evolution of drug-resistant mutations over time (Smith et al., 2019).

The shortage of novel antifungal drugs under development needs the creation of potent antifungal agents, particularly those derived from natural ingredients. BV is effective against various fungi at micromolar doses (Table 3). Furthermore, emerging evidence suggests that melittin inhibits fungal growth via several processes, such as membrane permeability and apoptotic activation via the ROS-induced mitochondrial/caspase-dependent route, suppression of (1,3)-D-glucan synthase, and alterations in fungus genetic transcription. Animal models should be employed to evaluate melittin's safety and effectiveness in the future. Melittin will likely offer new paths for numerous biological uses, from medicine to agriculture (Memariani et al., 2019).

5.4.4 Anti-protozoal activity

Investigations have shown that BV category III sPLA2 possesses anti-trypanosomiasis—activity BV group III sPLA2 transcription in a genetically engineered mosquito's midgut inhibits Plasmodium ookinetes Cecropin, a melittin hybrid, effectively inhibits Leishmania Donavan promastigote by damaging its plasma membrane (Ullah et al., 2023). Melittin affects membrane integrity in prokaryotic and eukaryotic species, leading to membrane lysis and increased permeability. Melittin exhibits antibacterial, anti-fungal, and antileishmanial properties due to this interaction (Berhe et al., 2024). Previous studies suggest that in controlled circumstances, PLA2 has antiprotozoal activity against *Trypanosoma brucei*. Lasioglossins, a peptide found in BV, have potent antibacterial properties due to their membrane contact and DNA binding (Ullah et al., 2023). The peptide melittin has been shown to have antiprotozoal efficacy versus *Toxoplasma gondii*,

TABLE 4 Application of bee venom in wound healing.

Active component	Action	References
Tertiapin	Anti-inflammatory properties action via inhibiting potassium gates.	Dadar et al. (2019)
Secapin	Anti-fibrinolytic, anti-elastolytic, and antimicrobial properties	Lee et al. (2016a)
Peptide 401 The mast cell degranulation peptide	Benefits include relief from pain, as well as anti-inflammatory and nociceptive effects.	Bellik (2015)
Melittin	Antioxidant, anti-inflammatory, and pro-angiogenic.	Shaik et al. (2023)
Hyaluronidase	Breaks down hyaluronic acid, allowing the venom to penetrate tissue. It causes dilatation and greater blood artery permeation, increasing blood circulation.	Son et al. (2007)
Apamin	Inhibits cyclooxygenase-2 and phospholipase A2.	Kim et al. (2020b)
Adolapin	Antioxidative, anti-apoptotic, and anti-inflammatory.	Han et al. (2011)
Acid phosphatase	Human-sensitized basophils produce a potent histamine releaser. It can be used in anti-BV immunotherapy.	Grunwald et al. (2006)

Trypanosoma cruzi, *Plasmodium*, and *Leishmania*. Melittin has been used in vaccine production to boost protection against leishmaniasis. Melittin can kill *T. cruzi* (Memariani and Memariani, 2021). Although BV has antiprotozoal properties, its specific impact, route of action, and potential for therapeutic use remain unclear.

5.5 Wound healing

The reconstruction of wounds is an intricate mechanism that consists of four concurrent stages: hemostasis, clot formation, inflammation, and division (Duda et al., 2023). The research provided demonstrates that BV treatments have an impact on all stages of the healing process. BV can be used topically or subcutaneously on wounds (Table 4). An animal model study suggests BV might be a viable damage-healing therapy for diabetes patients. BV promotes the initial stage of wound healing (hemostasis) in diabetic mice by increasing the production of Transforming growth factor beta (TGF-β) and Vascular endothelial growth factor (VEGF).

Activating Transcription Factor 3 (ATF3, and inducible nitric oxide synthase (iNOS) has been shown to impact on extracellular matrix biosynthesis through increased collagen synthesis (Wang et al., 2021b). In the Reepithelization stage, BV triggers human epidermal keratinocyte division and migration while decreasing interleukin-8 (IL-8) and Tumor necrosis factor-α (TNF-α). BV affects angiogenesis and neovascularization in diabetic mice by inhibiting caspase-3, -8, and -9 activity while enhancing TGF-β and VEGF levels. TGF-1, fibronectin, and VEGF levels are lowered during remodeling, whereas raising collagen-I mRNA levels reduces the expression of ATF-3 and Inos (Kurek-Górecka et al., 2020).

5.6 Neuroprotection

Neuroinflammation induced by prolonged stimulation of glial cells and microglia is linked to neurodegenerative disorders. Various BV components, such as PLA2 and apamin, have been investigated as anti-neuroinflammation medicines to boost the efficiency of multiple treatments against neurodegenerative illnesses (Mohammadi-Rad et al., 2019). It has been proposed that melittin might help address neurodegenerative disorders linked to stimulation of microglial cells since it substantially inhibits BV2 microglia's pro-inflammatory activities (Zhang et al., 2024). The progressive neurodegenerative illness amyotrophic lateral sclerosis (ALS) damages motor neurons in the brain and spinal cord, resulting in muscle weakening and atrophy (Zarei et al., 2015). Yang et al. found that melittin therapy enhances the anti-inflammatory ability of the proteasome in the central nervous system (CNS) of Amyotrophic Lateral Sclerosis (ALS) model mice (Yang et al., 2011). Melittin-treated mice demonstrate less neuronal loss in the spinal cord and better motor control, which enhances motor performance. In addition, melittin therapy lowers p38 phosphorylation and the microglial cells count in the brainstem and spinal cord. Furthermore, melittin inhibits-synuclein post-transcriptional modification, a critical ALS pathogenic pathway, and activates chaperones to prevent protein misfolding. The findings support melittin's anti-neuroinflammatory properties. Although the CNS is the major issue with ALS, the liver, spleen, and lungs are all impacted. In an animal model of ALS, melittin therapy lowers inflammation while increasing, suggesting cell viability in the spleen and lung (Lee and Bae, 2016a). AD, the most common neurodegenerative disease, comprises several pathogenic mechanisms that contribute to its development (Vickers, 2017). Although the etiology of Alzheimer's disease is still unknown, research suggests that inflammatory reactions may play an important part. In its progression (Cummings et al., 2018). Current therapies for cognitive loss caused by Alzheimer's disease include acetylcholinesterase (AChE) inhibitors and muscarinic or nicotinic receptor ligands. As an alternative strategy, bvPLA2 was shown to be effective in slowing the course of Alzheimer's disease in transgenic mice. This is attributed to. bvPLA2's capacity to minimize accumulation while improving cognitive function in mice brains. It also reveals that bvPLA2 can enhance brain glucose metabolism and lower the hippocampus's neuroinflammatory reactions, potentially inhibiting AD progression (Ye et al., 2016b). Recent research has also shown that bvPLA2 therapy in a 3xTg-AD mouse model might affect regulatory T-cell populations. To prevent AD's unfavorable inflammatory response, scientists developed a novel therapeutic

method that combines bvPLA2 medication with AB vaccine therapy (Baek et al., 2018). In addition to creating protective benefits against inflammatory disorders, bPLA2 possesses anti-inflammatory actions, as previously stated (Palm et al., 2013). A recent study investigated PD in mice using a combination of 78% bPLA2 and 15% melittin (Carpena et al., 2020). bPLA2 reduced inflammation by activating Treg cells. Additionally, bPLA2 activation reduced the loss of dopaminergic cells (Kim KH. et al., 2019).

5.7 Radioprotective activity

Research indicates that BV can protect against the detrimental effects of ionizing radiation. In many evaluation systems, BV protects against gamma and X-ray radiation (Djahonkulovna, 2023). Additionally, BV contains antioxidant properties that neutralize free radicals while shielding the body from harmful radiation ()Shaaban et al., 2019. BV protects bone marrow cells from chromosomal mutations (aberrations) in the Wistar mouse model (Yu et al., 2023). It promotes hematopoiesis, induces the production of histamine from MCD, and lowers blood oxygen pressure through phospholipase A2 (Gajski et al., 2024). PLA2, a BV component, contains a forkhead box P3 (Foxp3), + CD4, + CD25, + Treg cell that protects against radiotherapy-induced extensive pulmonary inflammation (Hossen et al., 2017b). BV therapy significantly lowers levels of IL-6 and TNF-a following gamma radiation therapy (Hasan et al., 2023). BV decreases serum Aspartate transaminase (AST), Lactate Dehydrogenase (LDH), Creatine Kinase MB (CK-MB), Cardiac Troponin I (cTnI), and Alanine aminotransferase (ALT) concentrations in Wistar mice via decreasing hepatic NF-kB transcription. However, the amounts rose following gamma radiation (Salimo et al., 2023). According to investigations, BV exhibits radioprotective properties against oxidative and basal DNA damage (Montoro et al., 2023). Administering melittin a day before being subjected to the radiation (8.5 Gy) dramatically improves survival rates in mice (Duché and Sanderson, 2024). BV shields human peripheral blood lymphocytes against damaging gamma radiation (Yu et al., 2023). In an analogous study, BV was shown to protect blood cells against radiation (3–4 Gy) when administered 24 h beforehand (Khateeb and Taha, 2024). Contemporary technologies and non-ionizing radiation have become more prevalent daily, leading to detrimental consequences on the body. BV has demonstrated radioprotection, making it a potential non-toxic and efficient radioprotector agent for the future.

6 Medical applications

BV is a well-known pharmacologically active product of the hive synthesized by the venom glands associated with the sting apparatus of workers and queens, stored in the venom reservoir, and injected through the sting apparatus during the stinging process (Aparna, 2020). Due to its anti-oxidants, anti-coagulants, anti-inflammatory properties, and bioactive substances like melittin and phospholipase BV is mainly used to treat many inflammatory disorders such as arthritis, cancer, diseases of the nervous system, heart and blood system abnormalities, skin diseases, and others (Khalil et al., 2021). Furthermore, therapeutic application of BV includes their use in the management of bursitis, tendonitis, dissolving scar tissue, in the management of post herpetic neuralgia, Lyme disease, rheumatoid arthritis, osteoarthritis, multiple sclerosis, TMDs, and more (Table 5) (Kurek-Górecka et al., 2020).

6.1 Liver diseases

Chronic liver disease (CLD) is a significant source of death and disability globally, with 2 million people dying from it every year (Younossi et al., 2023). In this sense, CLD is the 10th reason for mortality globally (Younossi and Henry, 2016; Heron, 2021). Besides death, CLD causes severe damage to patients' quality of life, as well as substantial medical and economic costs (Stepanova et al., 2017). Nevertheless, various socioeconomic and medical shifts have happened worldwide during the previous 2 decades, potentially altering the impact of each CLD. BV has been demonstrated to help minimize hepatic damage, inflammation, and fibrosis (Table 6). Melittin reduces TNF release and IL-1 and IL-6 transcription in TNF-treated hepatic stellate cells (HSCs). Melittin suppresses inflammation and fibrosis in thioacetamide-induced liver fibrosis by blocking the NF-κB signaling pathway. Furthermore, they postulated that the controlled inflammatory response may impact melittin's anti-fibrotic action in activated HSCs. They then demonstrate that melittin prevents liver failure in the D-galactosamine/LPS-induced mice liver failure model via suppressing NF-B signaling and apoptosis (Li et al., 2023). Melittin lowers the high mortality rate, alleviates hepatic pathological damage, suppresses hepatocyte apoptosis, and suppresses hepatic inflammatory responses (Jafari et al., 2024). They also observed that melittin inhibits NF-B transcription in TNF-induced liver injury. Melittin suppresses NF-κB DNA binding and promoter activity in TNF-treated hepatocytes, demonstrating that melittin prevents hepatocyte death by decreasing NF-κB activation. Recently, researchers observed that giving melittin decreased bile duct inflammation and fibrosis (Kim et al., 2015a).

6.2 Cancer treatment

At the beginning of the 1950s, apitoxin's influence on the colchicine-induced carcinogenic pathway was documented (Gajski et al., 2024). In turn, the study's findings of reasons for mortality among qualified beekeepers compared with most of humanity revealed that BV had oncoprotective potential, particularly in the case of lung malignancy (Małek et al., 2023; Ali, 2024). Starting in the early 1980s, papers detailing the findings of studies on the cancer-fighting potential of BV began to appear (Table 7).

MEL from *A. mellifera* is the most often used pharmacological peptide in cancer investigations. MEL may impact signaling and regulatory routes, resulting in numerous cancer-related death processes, including a decrease in the division, stimulation of the death of cells, limitation of vascular development, interruption of the cell cycle, and restriction of malignant tumor circulation, movement, the spread of cancer cells and invading forces according to available literature (Rady et al., 2017). How melittin antitumor activity has

TABLE 5 Physiochemical properties, doses, and benefits of bee venom, and its components in numerous medical applications.

Bee venom/ Metabolites	Physiochemical properties	Disease	Model	Method of application	Dosage of use	Outcomes	References
Bee venom	Anti-inflammation and damaging effects on cells on several kinds of tumour cells.	Liver carcinoma Breast cancer Cervical cancer	Liver (Hep-G2), breast (MCF-7), and cervical (HPV-18 infected HeLa cells)] and two normal cells (splenocytes and macrophages (MQ		NA	Having an effect on IL-10, TNF-α, and IFN-γ. Increased Cas3 levels.	Salama et al. (2021)
	Inhibiting cervical-cancer tumorigenesis	Cervical cancer	HPV-positive cervical-cancer cell lines, such as Caski and HeLa cells, and not to HPV-negative cervical-cancer cells (C33A)		0, 0.625, 1.25, 2.5, 5, and 10 μg/mL of BV for 24 h	Cyclin A, cyclin B, Bcl-2, and Bcl-XL levels decreased. Effects on caspases and intercellular signaling pathways.	Kim et al. (2020a)
	Small conductance K+ (SK) channel inhibition may be effective in managing Parkinson's disease in both short and long term.	Parkinson's disease	Human	Injection	s.c. bee venom injections (100 μg)	Delayed disease progression.	Hartmann et al. (2016)
	Significant decrease in muscle tonus.The VAS scale decrease was statistically significant.	Temporoma ndibular disorder (RDC/TMD Ia and RDC/TMD Ib)	Human	Local dermal massage to the area of masseter muscle	0.0005% bee venom ointment	Relived masticatory muscles myalgia	Nitecka-Buchta et al. (2014)
	Increase locomotor velocity. ↑ Parkinson's Disease Quality of Life Questionnaire. ↑ Motor manifestations	Parkinson's disease (PD)	Human trial	Acupuncture	0.1 mL, diluted to 0.005% twice a week for 12 weeks.	significant improvements in gait speed	Doo et al. (2015)
	(RLPP) ↓ TNF-α	Recalcitrant localized plaque psoriasis (RLPP)	Human trial	Intradermal injection	Inject 0.05–0.1 mL of commercial BV (Epivac®) once a week for 3 months.	↓ Recalcitrant localized plaque psoriasis	Eltaher et al. (2015)
	(i) Lower blood glucose levels (ii). Reduced blood cholesterol concentrations, reduced low density lipoproteins, and boosted high density lipoproteins.	Diabetes	Rabbits	A bee sting	Includes 0.2–0.5mL of BV for 14 days.	Management of hyperglycemia and hyperlipidemia	Khulan et al. (2015)
	Remarkable improvement in blood levels of TNFα (−14%), IL1β (−52%), IL-6 (−53%), NFKB (−32.6%), and ESR (−39.8%).	Chronic Low Back Pain	Human trial	Bee stinging at GV14 acupuncture sites.		Effectively managed low back pain.	El Gendy et al. (2017)
	Destructive and apoptosis outcomes.	Breast cancer	MCF-7		2.5, 5, 7.5, 10, 12.5 (μg/mL)	CBV (in a dose-related fashion). NO generation, caspase-3 stimulation, MCF-7 survival, functioning of catalase, and glutathione level. CBV caused destruction of DNA in MCF-7 cells in a dosage-dependent way.	Kamran et al. (2020)
Melittin	Reduced amino acids in the proline/ glutamine/arginine system. Reduced amounts of carnitines, polyamines, ATP, and NAD+.	Ovarian cancer	Human ovarian cancer cell lines A2780 (cisplatin-sensitive) and A2780CR (cisplatin-resistant)		4.5, and 6.8 μg/mL	Anti-cancer activity	Alonezi et al. (2016)
	Increased apoptosis. Ca2+ is released from the endoplasmic reticulum and accumulates in the mitochondria.	Leukemia	Acute lymphoblastic leukaemia (CCRF-CEM) and chronic myelogenous leukaemia (K-562)		0.001–100 μM	Disruption in mitochondrial membrane potential, annexin V binding, and caspase 3/7 activation.	Ceremuga et al. (2020)
	Anti-angiogenic, and anti-inflammatory.	Lung carcinoma	Mouse		0.1–5 mg/kg	Reduced the number of macrophages in the tumor environment and reduce VEGF and CD206 transcription in bone marrow-derived M2 macrophages.	Lee et al. (2017)

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TABLE 5 (*Continued*) Physiochemical properties, doses, and benefits of bee venom, and its components in numerous medical applications.

Bee venom/ Metabolites	Physiochemical properties	Disease	Model	Method of application	Dosage of use	Outcomes	References
	Anti-inflammatory.	Liver inflammation	Mouse	i.p. injection, twice a week for 12 weeks	0.1 mg/kg	Reduced inflammation, fibrosis, and the production of VCAM-1, IL-6, and TNF-α in the liver.	Park et al. (2011)
	Anti-inflammatory	Neuro inflammation	*In vitro*		0.5–2 μg/mL	Reduced NO and iNOS levels Repressed NF-κB activity by inhibiting IκBα degradation and JNK and Akt phosphorylation.	Moon et al. (2007)
	Antitumor activity, and anti-angiogenic ations.	Non-small cell lung cancer	Human non-small cell lung cancer cell line, A549	subcutaneous	1 and 10 mg/kg	Lowering of HIF-1α and VEGF levels.	Zhang and Chen (2017)
	Anticancer	Malignant melanoma	Human malignant melanoma (A375) cells		3, 4 and 6 μg/mL	Increased expression of cytochrome c leads to its translocation to the cytosol, as well as Cas3 and Cas9. Decline in EGFR transcription.	Sangboonruang et al. (2020)
	Anti-cancer effects	Gastric cancer Colon cancer	AGS, COLO205 and HCT-15 cell lines		10–20 μg/mL	Membrane damage.	Soliman et al. (2019)
	Anti-inflammatory properties 100 times more potent than hydrocortisone Antimicrobial properties antinociceptive effect Antitumor activities Radioprotection	Atopic dermatitis	Mouse	TNF-α/IFN-γ stimulated human keratinocytes	(100, 200, and 500 g mixed with normal saline) was applied 5 times/week for 4 weeks	Reduced ad skin lesions. BV and melittin inhibited the generation of chemokines (e.g., CCL17 and CCL22) and cytokines associated with inflammation (e.g., IL-1β, IL-6, and IFN-γ) generated by 2,4-dinitrochlorobenzene.	An et al. (2018)
		Arthritis	raw 264.7 and synoviocytes obtained from patients with rheumatoid arthritis, *in vitro*		5–10 μg/mL	Blocked the transcription of LPS-induced COX-2, PGE2, cPLA2, NO, and iNOS Reduced JUK and NF-κB activation, IκB release, and nuclear translocation of the p50 subunit.	Park et al. (2004)
		Amyotrophic lateral sclerosis	Mouse, s.c. injection at ST36 acupoint three times a week		0.1 μg/g	Microglia and phospo-p38 levels have decreased in the spinal cord and brainstem. Improves motor abilities and prevents neuronal death in the spinal cord. Inhibited a-synuclein misfolding. Reduced transcription of Iba-1 and CD14 in the lung Obliterated expressed CD14 and COX-2 in the spleen. Elevated pERK and Bcl-2 in the spleen	Lee et al. (2014b)
	Anticancer activity	Osteosarcoma	Human MG63 osteosarcoma cells		1 μM	Stimulation of phospholipase A2 leads to cell death and Ca^{2+} influx, whereas inhibition of cell proliferation occurs via the stimulation of inositol-requiring protein-1a and Xbox-binding protein 1.	Chu et al. (2007)
Apamin	Anti- apoptosis, and anti-inflammatory actions	Atherosclerosis	THP-1 cell treated with oxLDL - LPS injection with high fat diet		0.5, 1 and 2 μg/mL	Reduced NF-κB signaling pathway.	Kim et al. (2012)
	SK channel blockage. Increased the action potential duration	Heart failure	Pacing induced heart failure	Rabbit	(100 nmol/L) infusion	Reduce reduced ventricular fibrillation (VF) vulnerability.	Yin et al. (2017)

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TABLE 5 (*Continued*) Physiochemical properties, doses, and benefits of bee venom, and its components in numerous medical applications.

Bee venom/ Metabolites	Physiochemical properties	Disease	Model	Method of application	Dosage of use	Outcomes	References
	Blocked MAPK, Smad, and TGF-_1 signalling pathways.	Liver fibrosis	HSC-T6 cells, an immortalized rat hepatic stellate cell line		0.5, 1 and 2 μg/mL	Suppressed hepatic fibrosis	Kim et al. (2017)
	Improved memory acquisition	Alzheimer's disease	Transgenic mouse			Enhanced efficiency of nicotinic signaling	Proulx et al. (2020)
	Increased membrane potential in postsynaptic cell	Neurofibromatosis	Heterozygous Nf1+/mouse model			SK channel blockage.	Kallarackal et al. (2013)
Mast-Cell Degranulating (MCD) Peptide (Peptide 401)	Anti-inflammatoryactivity	Edema	Carrageenin-induced swelling of the Rathin paw		10 mg/kg	Suppressed edema	Banks et al. (1990)
Adolapin	Analgesic, and anti-inflammatory actions	Brain, and spleen inflammations	Rat spleen and brain		40 μg/kg	Inhibited cyclooxygenase. Elevation of c-GMP level. Decrease of c-AMP.	Koburova et al. (1985)
Phospholipase A_2	Neural protective effect	Multiple sclerosis (Experimental autoimmune encephalomyelitis)	C57BL/6 mouse	Injection	(0.2 mg/kg, i.p., daily for a period of 10 days)	bvPLA2 reduces limb paralysis and CD4+ cell invasion, but loses its benefits when Tregs are reduced.	Lee et al. (2019b)
	Anti-inflammatory and anti-arthritic activities	Rheumatoid arthritis	Male DBA/1 mouse	Intraperitoneal injections	(0.1, 0.5, 1.0 mg/kg, i.p., for 5 weeks)	Prevent bodily weight reduction. Reduce squeaking score. Paw thickness and arthritis index.	Choi et al. (2021)
	Alleviated atopic skin inflammation	Atopic dermatitis (AD)	Male C57BL/6 mouse	Alleviates atopic skin inflammation	(80 ng/ear, topical application, four times a week for 3 weeks)	Reduce atopic dermatitis-related skin edema, optimize ear thickness, reduce Th1 and Th2 cytokine expression, promote Treg, reduce epidermal and dermal thickness and macrophage invasion, and inhibit mast cell penetration.	Shin et al. (2018)
Hyaluronidase	Sperm like structure	Male Infertility	*In vitro*			Substantial homology with PH-20, a membrane protein of guinea pig sperm that regulates sperm-egg attachment.	Gmachl and Kreil (1993)
Acid phosphatase	Densensitization	Allergy	*Trichoplusia ni* cells			Optimized component-resolved strategy for honeybee venom allergic reactions, with a focus on developing improved diagnostic methods and improving allergenic immunotherapy.	(Stahelin, 2016; Murakami et al., 2017)

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TABLE 6 Application of bee venom in controlling the liver diseases.

Active component	Model	Outcome	Reference
Apamin	Cholestatic liver fibrosis in mice	Apamin therapy has reduced liver damage and pro-inflammatory cytokines concentrations.	Kim et al. (2017)
Bee venom	High-fat diet (HFD)-induced nonalcoholic fatty liver (NAFL) in rats	BV-treated rats had considerably decreased levels of all hepatic enzymes. Treatment resulted in the correction of adiponectin levels and substantial reductions in hepatic triglyceride and cholesterol levels.	Hanafi et al. (2018)
PLA2	Liver injury induced by acetaminophen in mice	PLA2 protects against hepatic impairment and stimulates anti-inflammatory cytokines to be generated in acetaminophen-injected rats.	Kim et al. (2014)
MEL	Acute liver failure (ALF) in mice	MEL lowered total bilirubin, ALT, AST, TNF-α, and IL-1β levels in acute liver failure mice, improving survival rates, reducing symptoms, and relieving hepatic inflammation. MEL demonstrated antioxidant and anti-inflammatory properties in LPS-stimulated RAW264.7 macrophages.	Fan et al. (2021)
phospholipase A2 (bvPLA2)	Cholestatic liver injury and fibrosis in a murine model	BvPLA2 treatment prevented hepatocyte death. Furthermore, bvPLA2 lowered cytokine production and inhibited the nuclear factor kappa-B pathway.	Kim et al. (2021b)

TABLE 7 Application of bee venom in cancer therapy.

Active component	Model	Action	Outcome	Reference
Bee venom	Human Lung cancer	Regulation of genetic transcription: Poly (ADP-ribose) polymerase (PARP), caspase-9, p53, BCL2, Box.	Apoptosis and cellular suppression.	Hwang et al. (2022)
Bee venom	Human Glioblastoma	Reduction in inflammation-promoting cytokines concentrations.	Insufficient toxic effects.	Sevin et al. (2023)
Bee venom	Pancreatic Cancer Human	Cyclin and Cyclin-dependent kinase (CDK) transcription and p53-p21 system activity can be modified.	Cell death and cellular arrest.	Zhao et al. (2022)
Melittin	Leukemia Human	Melittin-triggered decrease in mitochondria energy metabolism	Cytotoxic	Gasanoff et al. (2021)
Melittin	Gastric cancer Human	Inhibiting MMP2 and MMP9 activity leads to decreased activity in the Wnt/BMP and MMP-2 signaling pathways. Suppression of molecular adhesion.	Cytotoxicity, attachment, and infiltration suppression.	Huang et al. (2021)
Bee venom	Head and neck squamous cell carcinoma Human	Increased expression of Bax leads to reduced levels of Bcl2 and Epidermal growth factor receptor (EGFR), affecting the cell cycle.	Cisplatin has cytotoxic properties, arrests the cell cycle, and increases activity.	Grawish et al. (2020)
Bee venom, melittin	Malignant melanoma Human	Inhibits Phosphoinositide 3-kinases (PI3Ks)/AKT/mammalian target of rapamycin (mTOR) and mitogen-activated protein kinase (MAPK) processes. Increased transcription of Casp3 and Casp9	Cell death inhibits motility and colonization.	Lim et al. (2019)
Melittin	Ovarian cancer Human	Reduced amino acids in the proline/glutamine/arginine pathway. Decreasing amounts of carnitines, polyamines, ATP, and NAD+.	Cytotoxic	Alonezi et al. (2016)

been studied, and it has been found that melittin may increase the death of hepatocellular carcinoma cells (HCC) through the CAMKII-TAK1-JNK/p38 system. In addition, melittin has been found to encourage TRAIL-resistant HCC cells to TRAIL-induced cell death, probably through stimulating the CAMKII-TAK1-JNK/p38 route and blocking the IKK-NFB signaling. The outcomes are consistent with melittin activating calcium channels, increasing Ca^{2+} concentrations inside the cells, and calcium-responsive CaMKII (Balasubramani et al., 2023). It has also been reported that BV and melittin inhibit the malignant expansion of cells by triggering caspases (3 and 9) and suppressing NF-B signaling (Ghadiri et al., 2024). It has been proven that BV inhibits proliferation and causes

apoptotic cell death by activating death receptors (DR4 and DR5) (Khaliq et al., 2022). The primary reasons for cancer progression are metastasis and the infiltration of malignant cells. As a result, cancer researchers emphasize identifying the biological processes that drive cancerous cells to migrate and potential strategies to inhibit metastasis (Zuazo-Gaztelu and Casanovas, 2018).

In this context, melittin has been shown to impede *in vitro* and *in vivo* HCC cell movement via lowering Rac1-dependent processes (Haque et al., 2023). In contrast, a recent study demonstrated that combining melittin with anticancer drugs, such as temozolomide (TMZ), dramatically lowers melanoma cell growth and invasion compared to circumstances where TMZ or melittin was provided alone (Lim et al., 2019). Although MEL's promise as a carcinoma treatment modality has long been identified, its fast breakdown in circulation and unexpected cellular lysis activities provide substantial obstacles. To address these concerns, current optimization strategies rely on nanoparticle-based melittin delivery. Nanotechnology has enabled the creation and practical testing of melittin conjugates against a variety of tumors of human kinds in preliminary studies (Singh et al., 2023; Jafari et al., 2024). To develop an effective and safe melittin delivery method that can lower hemolytic activity while maintaining cytotoxic properties. Consequently, a dual-secured nano-sting (DSNS) was created by combining zwitterionic glycol chitosan and disulfide links. At low concentrations, melittin-loaded DSNS displayed a virtually complete cytotoxic impact on numerous cancer cell types, including undamaged red blood cells (Giribaldi et al., 2021).

Only one study on cell cultivation found no statistically noteworthy cytotoxic impact on cancer cells (human glioblastoma). BV and melittin influence several intracellular pathways, and their blockage triggers apoptosis., melittin inhibits the PI3K/Akt/mTOR pathway in breast cancer cells (Pandey et al., 2023b), or liver cancer cells (Lv et al., 2023). Lim et al. found that BV and melittin suppress the PI3K/Akt/mTOR and MAPK pathways in cancerous melanoma cells (Lim et al., 2019). In two investigations on ovarian carcinoma cells, Alonezi et al. reveal a new explanation of melittin activity where compounds in the tricarboxylic acid cycle, oxidative phosphorylation, purine, and pyrimidine metabolic rate, and the arginine/proline pathways are decreased. In addition, the investigators discovered that melittin reduced carnitines, polyamines, adenosine triphosphate (ATP), and nicotinamide adenine dinucleotide (NAD+) (Alonezi et al., 2017). Erkoc et al. found that melittin induces calcium signaling apoptosis and inhibits Cyclic adenosine monophosphate (Camp) in breast cancer cells, resulting in cell death and an anti-division effect (Erkoc et al., 2022). BV also alters cell shape, resulting in DNA and protein disintegration (Jung et al., 2018). Li et al.'s study on lung cancer cells indicates that melittin boosts the generation of reactive oxygen species (ROS) and the formation of intracellular iron while affecting the activity of glutathione peroxidase 4 (GPX4); it causes mitochondrial dysfunction and death, a condition called ferroptosis (Li et al., 2022). In the past few years, some research has concentrated on the influence of BV. on cancer cell migration. The tumor mass grows complexly, with proteolytic enzymes gradually destroying the stromal tissue. Matrix metalloproteinases (MMPs) play a significant part in this process. BV inhibits the expression of MMP-2 and MMP-9 in glioblastoma cells in a dose-responsive way, but not in healthy hippocampus cells (Małek et al., 2022). It is important to note that, unlike several other pharmaceutical chemicals, BV active ingredients possess the ability to cross the blood-brain barrier, making them a potentially feasible approach for the management of CNS disorders in coming years. Additionally, research on gastric cancer cells show that melittin inhibits MMP-2 and MMP-9 function. BV and melittin have comparable effects on hepatocarcinoma cells (Mansour et al., 2021). Inhibiting angiogenesis is also linked to reduced tumor invasion. Shin et al. revealed that melittin suppresses hypoxia-inducible factor 1-alpha (HIF-1α), an element that controls the production of (VEGF), a strong amplifier of vascular development. Zhang et al. found similar outcomes in non-small cell lung cancer (Zhang et al., 2015).

In another investigation on the U87 human glioblastoma line, significant cytotoxic properties began at a 5 μg/mL dose. The investigation skipped over the influence of venom on native cells. Gajski et al. found that BV had a cytotoxic impact on glioblastoma A1235 cells at 20 μg/mL (Gajski et al., 2016). However, 2 μg/mL of the crude BV caused a considerable reduction in cell survival (above 60%) in human colon cancer HCT116 cells. Another research employing the same colon cancer cell line confirmed the cytotoxic impact of BV at 1 μg/mL. Furthermore, BV had no harmful effects on FHC colon epithelial normal cells, even at a dosage of 10 μg/mL (Małek et al., 2023). The discovered BV levels that inhibit cancer cells may be inadequate to be considered in systemic-therapy without substantial adverse effects. Melittin's great tendency to trigger hemolysis and quick metabolism might represent a hurdle to employing BV. BV has a cytotoxic impact on tumor cells at concentrations higher than 1 μg/mL (Based on the cellular lineage). To get such a BV concentration in the bodily fluids of a 75 kg individual, around 75 mg of venom would need to be administered. Nonetheless, in animal studies, a venom dosage between 0.5 and 1.0 mg/kg bw had been effectively implemented (Małek et al., 2023). Other disadvantages of systemic therapy might be eliminated by administering BV directly into the tumor. This approach has little toxicity and an excellent therapeutic index (El Bakary et al., 2020). Other disadvantages of systemic therapy might be eliminated by administering BV directly into the tumor. This approach has little toxicity and an excellent therapeutic index (Xing et al., 2003). Cell culture investigations provide for the evaluation of the molecular processes of a drug's activity. Still, they do not answer how cancer behaves in the host's natural environment. As a result, animal models can examine tumor growth in the body's circumstances and the propensity to produce distant metastases. There has been significantly less animal research than *in vitro* studies on the anticancer properties of BV. In the Ehrlich ascites carcinoma mouse model, BV has been found to lower MMP-2 and MMP-9, as well as VEGF, TNF-α, and nitric oxide (NO) levels, hence decreasing tumor growth and preventing angiogenesis (El Bakary et al., 2020). Lee et al. discovered that melittin reduced VEGF levels in animals with lung cancer (Lee et al., 2017). Rocha et al. reported that melittin inhibited the formation of colorectal cancer metastases in a mouse model (Rocha et al., 2022). El-Beltagy et al. found that restoring histological abnormalities in ovarian and breast cancer rat models decreased serum MMP-1, NF-κB, and TNF-α levels (El-Beltagy et al., 2021).

Both *in vitro* and animal investigations show that BV and melittin have anticancer properties. The findings thus far put us

closer to conducting clinical studies on using BV in cancer in the future (Jafari et al., 2024). Maybe additional proof of BV's favorable benefits will lead to the initiation of human studies. As previously stated, the influence of BV on the body is multidirectional, and determining the effect of its different components on the complete human body takes extensive investigation. It is unclear if BV may achieve therapeutic quantities in tumor tissue without eliciting unpleasant consequences. It should be emphasized that in addition to the anti-cancer action, the venom has additional systemic properties that may contribute to the anticancer activity of BV.

6.3 In periodontal therapy

Periodontitis is a bacterial illness that damages tooth-supporting tissue, destroying ligaments and bones. Periodontitis can lead to loss of teeth, cardiovascular problems, and rheumatoid arthritis (Alkhursani et al., 2022; Atia et al., 2022; Nasser Atia et al., 2022; Atia GaN. et al., 2023). In individuals with periodontitis, osteoclasts stimulate bone resorption (Atia GaN. et al., 2023). Periodontitis is commonly treated with mechanical techniques and antibiotics. Nevertheless, there is a shortage of therapies addressing the disease's immunological elements (Nasser Atia et al., 2022). *Porphyromonas gingivalis* is a crucial bacterium linked to chronic periodontitis commonly found in periodontal disease locations (How et al., 2016). *P. gingivalis* produces virulence-related substances to survive in the oral environment (Jia et al., 2019). These contaminants stimulate host cells, including gingival macrophages and fibroblasts, leading to inflammation in periodontal tissue and alveolar bone resorption (Xu et al., 2020; Atia GA. et al., 2023). Periodontal infection triggers inflammation that increases host immune cells and promotes the breakdown of bones through cytokines, chemokines, and attachment molecules (Cekici et al., 2014). BV inhibits *P. gingivalis*-triggered proinflammatory alveolar bone destruction *in vivo* and RANKL-associated osteoclasts development, stimulation, and metabolism *in vitro* (Gu et al., 2019).

6.4 Management of autoimmune diseases

Autoimmune illnesses that include rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis have long been thought to be T helper cells (Th cells) 1-dominant; nevertheless, the importance of Th17 cells and Tregs in autoimmune diseases has only recently been discovered (Rosenblum et al., 2015). Rheumatoid arthritis is a prevalent autoimmune condition, although current treatment options are not always practical (Guo et al., 2018). BV has been utilized for decades for the management of chronic inflammatory conditions, such as rheumatoid arthritis (Wang et al., 2021a). BV's anti-rheumatic and anti-inflammatory properties have been known for almost a century (Nainu et al., 2021).

6.4.1 Rheumatoid arthritis

Rheumatoid arthritis is an autoimmune condition characterized by synovial growth and cellular penetration. It can cause joint damage, malformation, incapacity, swelling, and pain in numerous joints (Sharif et al., 2018). Low-dose methotrexate is the most frequent therapy for rheumatoid arthritis. Methotrexate can cause hepatotoxicity, leading to insufficient drug tolerance (Wang et al., 2018). As a result, patients are more prone to pursue alternative therapies. Previous research suggests that BV injection may reduce inflammation and pain in animals with rheumatoid arthritis (Figure 5) (El-Tedawy et al., 2020). Li et al. employed Freund's adjuvant-induced animal model to study arthritis. They discovered that treatment with BV at ST-36 inhibited Fos transcription in the superficial layer of the lumbar spinal cord, resulting in reduced paw edema and nociceptive behaviors on the injected side (Li et al., 2010). In a type II collagen-induced arthritis (CIA) model, Lee et al. discovered that BV injection treatment inhibits immunological responses. TNF-α production decreased significantly in the BV group compared to the control group, whereas IL-1β levels remained constant (Lee JaeDong et al., 2004). Another study found that rats with Cytosolic Iron-Sulfur Cluster Assembly (CIA) had much higher amounts of free radicals and protease activity than normal rats. BV injection (0.25 mg/kg) effectively modulated rheumatoid arthritis by reducing protease activity and eliminating ROS (Petronek et al., 2021). In conjunction with methotrexate, BV could boost effectiveness and have antiarthritic properties (Darwish et al., 2013).

BV injection has been shown to provide antiarthritic and antinociceptive effects in rats with arthritis, making it a potential alternative treatment for rheumatoid arthritis (RA) (El-Tedawy et al., 2020). Melittin treatment in arthritis decreases LPS-induced p50 redistribution into the nucleus, lowering inflammatory gene expression (Zhang et al., 2024). Melittin binds to p50 with high affinity (Kd = 1.2 108 M). They also looked at melittin's anti-inflammatory properties through its associations with IKKs. Melittin suppresses TNF/LPS-induced NO and PGE2 generation in a mouse macrophage cell line and synoviocytes of rheumatoid arthritis patients (Yang et al., 2023). Additionally, they found that melittin suppresses inflammatory target gene expression and NF-κB activation through the JNK pathway (Xing et al., 2024).

6.4.2 Multiple sclerosis

Multiple sclerosis is an inflammatory illness that can cause brain and spinal cord damage through inflammation of the central nervous system. The cause of multiple sclerosis is uncertain. It might be caused by a viral infection, environmental causes, or hereditary factors (Ghasemi et al., 2017). After 2000, numerous alternatives have been employed for the management of multiple sclerosis, including BV and cannabis-derived substances. The preliminary therapy with decreased nerve degeneration and glial stimulation, and cytokine production, including IFN-γ, IL-17, IL-17A, TNF-α, IL-1β, and chemokines (MCP-1 and MIP-1α). BV treatment can decrease CD4+, CD4+/Interferon-gamma (IFN-γ+), and CD4+/IL-17 + T cells while raising CD4+/Foxp3+ T cells in the nervous system and lymphatic systems of rats with acute experimental autoimmune encephalomyelitis (EAE) (Lee MJ. et al., 2016).

6.5 Management of neurological conditions

Among these neurological problems, neurodegenerative ailments have a substantial influence on not only people but also

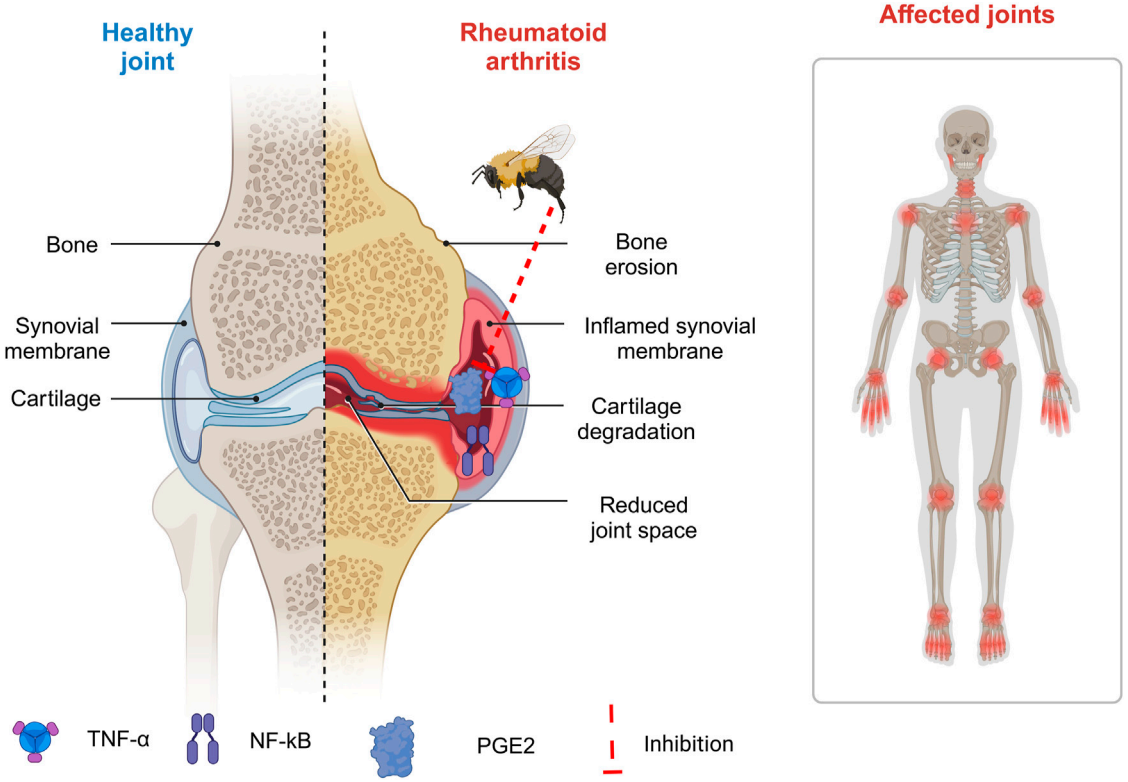

FIGURE 5
Implementation of bee venom in management of rheumatoid arthritis. (Generated by BioRender software).

carers and society. The most common neurological illness is Alzheimer's, followed by Parkinson's and epilepsy (Nassan and Videnovic, 2022). They are a varied group with unrelenting progression, and aging is a crucial risk factor in their development. Regardless of their differences, all of these disorders are associated with intellectual disability, motor abnormalities, and behavioral abnormalities. The particular cause of neuronal degeneration and protein accumulation in many illnesses is unclear (Lamptey et al., 2022). BV products prove to be helpful in the management of neurological conditions (Table 8).

6.5.1 Parkinson's disease

Parkinson's disease (PD) is a degenerative movement illness that causes gradual impairment in sufferers. The illness is characterized by gradual loss of dopaminergic neurons in the substantia nigra and the appearance of Lewy bodies, which include aggregation of alpha-synuclein, extensively dispersed proteins in the cerebral tissues. Improper stimulation of microglial cells is a pathogenic marker in several neurodegenerative disorders, such as Parkinson's (Cai et al., 2021). Several preclinical experiments examined how BV affects leukocyte migration and microglial activation in animal and cellular models (Avalo et al., 2022; Gao et al., 2023). In experimental mice models of Parkinson's disease, BV acupuncture therapy (BVA) was shown to protect from rotenone-triggered oxidative damage, neurological inflammation, and cytotoxicity (Mi et al., 2024). Rotenone, a pesticide, may alter the pathophysiology of Parkinson's disease (Tanner et al., 2011). BV effectively prevented dopamine depletion following rotenone injection.

Furthermore, BV treatment in PD mouse models restored locomotor activity (Morin Jr and Boudreau, 2024). The therapy reduced DNA damage and suppressed the transcription of cell death genetic factors Bax, Bcl-2, and caspase-3 in the brains of PD mice (Eleiwa et al., 2023). BV has been shown to safeguard dopamine neuronal cells against neurodegeneration in preclinical PD studies (Hassani and Esmaeili, 2024).

6.5.2 Alzheimer's disease

Alzheimer's disease is the most prevalent neurodegenerative illness, with several pathogenic mechanisms contributing to its development (Aksoz et al., 2019). Although the cause of Alzheimer's disease is uncertain, research suggests that inflammation could have a significant role in its progression (Twarowski and Herbet, 2023). Ye et al. discovered that bvPLA2 may successfully suppress the development of Alzheimer's disease in transgenic mice (Ye et al., 2016b). BvPLA2 reduces Aβ buildup and improves cognitive performance in mouse brains. The study found that bvPLA2 can improve glucose metabolism and minimize neuroinflammatory reactions in the hippocampus, perhaps limiting AD development (Ye et al., 2016b). Recent research found that bvPLA2 therapy can change regulatory T-cell populations in a 3xTg-AD animal model. The investigators proposed pairing bvPLA2 therapy with Aβ vaccine therapy to slow the onset of Alzheimer's disease while preventing harmful inflammatory responses (Baek et al., 2018).

TABLE 8 Application of bee venom in the treatment of neurological diseases and disorders.

Active component	Disease	Model	Outcomes	Reference
Wistar rats	Spinal Cord Injury (SCI)	3–4 animals/group	BVA raised IL-10 expression at six h and decreased IL-6 production at 24 h following SCI compared to controls.	de Souza et al. (2017)
Bee venom	Intervertebral Disk Disease (IVDD)	Canines	BV injection effectively treated dogs with moderate to severe IVDD, reducing clinical rehabilitation time.	Tsai et al. (2015)
Melittin	Peripheral Neuropathy	Human	Following BVA, Patient Health Questionnaire (PHQ) scores and WHO Chemotherapy-induced peripheral neuropathy (CIPN) grades fell. VAS has also decreased.	Yoon et al. (2012)
Bee venom	Peripheral Neuropathy	Sprague–Dawley rats	BVA decreases oxaliplatin-induced acute cold allodynia by activating the serotonergic system and spinal 5-HT3 receptors.	Lee et al. (2014a)
Bee venom	Neuropathic Pain	ICR mice	BVA inhibits nociception through alpha2-adrenoceptors but not naloxone-sensitive opioid receptors.	Kwon et al. (2001)
bvPLA2	Parkinson's disease		Injecting bvPLA2 has been demonstrated to improve motor function, reduce α-sympathy, increase microglial deactivation in the spinal cord, and normalize the M1/M2 microglial phenotypic ratio.	Ye et al. (2016a)
Bee venom/apamin	Parkinson's disease	C57BL/6 mice	Apamin can somewhat mimic the neuroprotective properties of dopaminergic neurons.	Alvarez-Fischer et al. (2013)
Bee venom	Parkinson's disease	C57BL/6 mice	Avoided the breakdown of tyrosine hydroxylase and reduced phospho-Jun immunoreactivity.	Doo et al. (2010)

6.5.3 Amyotrophic lateral sclerosis (ALS)

ALS is a CNS illness that leads to the loss of nerve cells that control movement. ALS is characterized by aberrant buildup of mutant superoxide dismutase (SOD) 1 protein complexes (Quatorze et al.). Soares et al. characterized a mouse model of ALS with a mutant mtSOD1 gene with a Glycine to Alanine substitution (SOD1G93A) to clarify the etiology of the disease (Soares et al., 2023). Previous investigations on mutant SOD1 transgenic mice revealed pathogenic processes in motor neurons, including protein misfolding, mitochondrial malfunction, and neurofilament buildup (Zhou et al., 2023). Additionally, BV showed some potential for treating this illness. Unlike age-matched control mice, BV treatment at a particular stage of ALS development increases motor function and longevity in SOD1G93A mutant mice. This might be due to blocking active microglia, as shown in mouse models of ALS (Barreto-Núñez et al., 2024). The research found that BVA at ST36 reduces inflammation in neurons in the spinal cord of ALS animals, including TLR4, CD14, and TNF-α (Cai et al., 2015).

6.5.4 Neuropathic pain

BV also helps to alleviate neuropsychiatric problems. Cold allodynia is a crucial indicator of neuropathic pain. Research suggests that BV injections may alleviate cold allodynia in mice with sciatic nerve CCIs (Er-Rouassi et al., 2023). BV, combined with peripheral β-adrenoceptor limitation, may help reduce inflammation-related pain. BVA may impact other receptors, including α4β2 nicotinic acetylcholine receptors, and relieve cold allodynia in oxaliplatin-injected mice (Yoon HeeRa et al., 2015). Numerous studies show that BV boosts Fos transcription and decreases nociceptive behavior. Coupled with BV, intrathecal clonidine-induced painkilling was much more effective (Ullah et al., 2023).

6.5.5 Peripheral neuropathy

Chemotherapeutic drugs can produce peripheral neuropathy by damaging sensory and motor nerves in the peripheral nervous system. Oxaliplatin, an anticancer medication, causes neuropathic cold allodynia. A few studies have explored whether BVA can reduce mechanical allodynia (Liu F. et al., 2023; Peralta et al., 2023). Yoon et al. found that injecting DBV (0.1 mg/kg) at ST36 of the right hind leg for 2 weeks and then administering oxaliplatin (10 mg/kg) resulted in significantly decreased ipsilateral mechanical allodynia (Yoon et al., 2013). Another research study found that methysergide can inhibit BVA's antiallodynic action linked to the serotonin system. BV has been shown to boost serotonin levels in the spinal cord and relieve cold allodynia in rats treated with oxaliplatin via activating spinal 5-HT3 receptors (Kim WooJin et al., 2016). Paclitaxel, a chemotherapy medication used to treat tumors, also caused agonizing peripheral neuropathy. In this research, BV reduced the negative consequences of paclitaxel. Additionally, BVA therapy had a strong antihyperalgesic impact at acupoint ST36 (Choi et al., 2017). Yoon et al. found that BV pharmacopuncture can lower the recommended toxicity guidelines for peripheral neuropathy (Yoon et al., 2012).

6.6 Male reproductive impairment

Recent research suggests that bee products may have preventative and therapeutic benefits for health, particularly infertility in men (Table 9). According to World Health Organization recommendations, 15%–25% of couples struggle to conceive. Infertility in men is triggered by changes in sperm quantity, movement, and/or shape that are found in collected samples. Recent research suggests that bee products may have preventative and therapeutic benefits for health, particularly infertility in men (Regeai et al., 2021; Suleiman et al., 2021).

TABLE 9 Application of bee venom in controlling the male reproductive impairment.

Active component	Model	Outcomes	Reference
Bee venom	Rabbit	Lower progesterone levels, with concomitant increase in had a boost in conception (17%) and fertility (10%).	Elkomy et al. (2021)
Bee venom	Mouse	- Restoration of normal levels of reproductive hormones and increased sperm quantity and quality.	Al-Shaeli et al. (2022)
Mellitin	Rat	Mellitin binds with proteins in tight connections between Sertoli cells.	El-Hanoun et al. (2020)
Bee venom	Rabbit	BV demonstrated a considerable favorable effect on several semen quality features, sexual behavior, antioxidant activity, lipid peroxidation indicators, and immunological response	(Al-Sayigh et al.)

TABLE 10 Application of bee venom in skin diseases.

Skin diseases	Model	Mechanism	References
hyperpigmentation	Hartley guinea pigs	Photoprotective, anti-melanogenic	Han et al. (2017)
Atopic dermatitis (AD)	BALB/c mouse	This medicine inhibits T cell proliferation and access and the production of Th1 and Th2 cytokines, IL-4, and IgE, which are common allergic Th2 responses in the bloodstream.	Sur et al. (2015)
Acne Vulgaris	HaCaT and THP-1 cells	Includes anti-inflammatory effects for Propionibacterium acnes. P. acnes secreted less IFN-γ, IL-1β, IL-8, and TNF-α after TLR2 expression was blocked.	Kim et al. (2015b)
Alopecia	C57BL/6 mouse	Increase the concentrations of the growth factors FGF-2, IGF-1R, and VEG.	Park et al. (2016)
Tissue regeneration	Mouse	Preventing inflammatory reactions may promote collagen synthesis and wound healing.	Sarhan and Azzazy (2017)
Aging marks	Human trial	Clinical investigations revealed decreases in total wrinkle area, count, and average depth, although the exact mechanism is uncertain.	Han et al. (2015)
Vitiligo	Normal human epidermal melanocyte	Triggers melanocytes to generate cAMP. The number of melanocytes increased.	Jeon et al. (2007)
Psoriasis	Twenty-five patients	TNF-α concentrations were significantly reduced than in the control group.	Eltaher et al. (2015)

According to WHO recommendations, 15%–25% of couples have difficulty conceiving. Infertility in men is triggered by changes in sperm quantity, movement, and/or shape that are found in collected samples. Infertility can be caused by various mechanisms, including steroidogenic pathway defects, pro and antioxidant activity imbalances, apoptotic pathway irregularities, pro and anti-inflammatory markers, and reactive oxygen species production (El-Hanoun et al., 2020). A study found that Iraqi bee stings protect and maintain sexual performance in mice by inhibiting Sertoli cell discharge of activin-B, which promotes spermatogonia and induces replication to create spermatocytes (Al-Sayigh et al.).

6.7 Skin care

BV has been utilized in medicine for therapy and as a beauty component. It has antimicrobial and anti-inflammatory properties, making it suitable for use in dermatology (Table 10). BV has a suppressive impact on *Cutibacterium acnes*. *C. acnes* is the primary cause of inflammation in acne.

An et al. found that applying BV to mice's skin after injecting *C. acnes* into their ears decreased inflammation and levels of TNF-α and IL-1β. BV decreased the levels of TLR2 and CD14 in *C. acnes*-injected tissue (An et al., 2014). The results imply that BV can successfully cure acne. Research suggests that BV-based cosmetics can effectively treat acne vulgaris. At a dosage of 0.5 mg, concentrated BV effectively decreased C. acnes numbers (Han et al., 2013). Melittin in BV has antibacterial properties (Elieh Ali Komi et al., 2018). It effectively eliminates *S. aureus*, *Staphylococcus* epidermidis, and *Staphylococcus* pyrogens (Kim H. et al., 2019). Melittin is a poisonous peptide that destroys the bacterial cell wall (Abd El-Wahed et al., 2019). BV can treat fungal and viral skin problems. BV has been proven to have antifungal properties (Kim H. et al., 2019). The antiviral impact of BV on herpes simplex virus has been investigated. BV reduced the growth of this virus (Uddin et al., 2016). BV can block five α-reductase, which converts testosterone to dihydrotestosterone and promotes hair development, as demonstrated by studies on alopecia. Various percentages of BV (0.001%, 0.005%, and 0.01%) were compared to 2% minoxidil. BV enhanced hair development and prevented shifting from the anagen to the catagen phase. BV suppressed the levels of SRD5A2, a 5-α-reductase (Park et al., 2016).

BV may serve as a novel therapeutic for localized plaque psoriasis. Localized plaque psoriasis can be effectively treated with intradermal BV alone or oral propolis. BV includes melittin, which inhibits the production of inflammatory genes. BV suppresses COX-2 transcription, reducing the generation of inflammatory prostaglandins (Hegazi et al., 2013). BV components can have varying and sometimes contradictory immunological responses. Polypeptide adolapin suppresses prostaglandin production and inhibits the action of PLA2 and human lipoxygenase (Tusiimire

et al., 2016). BV's anti-inflammatory properties make it effective for treating atopic dermatitis. Emollients containing BV resulted in decreased eczema areas, severity indexes, and visual analog scale values compared to those without (You et al., 2016). BV's biological activity has been utilized to cure wounds. Wound healing involves the production of TGF-β1, fibronectin, VEGF, and collagen-I.

The study on mice found that lowering wound size led to increased epithelial division. Local application of BV reduces wound size in animal models (Zhao et al., 2024). BV is used in wound dressing alongside polyvinyl alcohol and chitosan. Using 4% BV as a wound treatment in diabetic rats led to faster healing and less inflammation (Ivanov et al., 2023). Research found that combining 6% BV with chitosan improved wound healing (ÖZgenÇ and Sevin, 2023). BV was shown to enhance the growth and movement of human epidermal keratinocytes. Combining BV with hydrogel led to enhanced collagen synthesis. BV promotes wound healing through anti-inflammatory, antimicrobial, and antioxidant properties. BV is extremely successful in treating human melanoma A2058 cells. It was found that BV causes cell death by generating hydroxyl radicals (Gajski et al., 2024). In recent years, BV has been employed as an antiwrinkle treatment. Twenty-two women from South Korea used 0.006% BV serum as a cosmetic component, using 4 mL twice a day for 12 weeks. It reduced overall wrinkle area, measurement, and thickness. BV inhibits tyrosinase-related proteins, resulting in antimelanogenic action (Han et al., 2015). Han et al. found that BV reduces matrix metalloproteinase protein levels, indicating photoprotective action.

BV efficiently suppresses photoaging mechanisms and can treat photodamaged skin (Han et al., 2017). A gel with 0.06% BV did not cause photosensitive dermatitis, as proven in animals (Han et al., 2017). Melittin treats skin inflammation and protects against P. acnes-induced inflammatory reactions *in vitro* and *in vivo*. They studied the anti-inflammatory effects of melittin therapy in heat-killed P. acnes-treated HaCaT cells, which inhibited NF-B and p38 MAPK signaling. Furthermore, the anti-inflammatory efficacy of melittin was studied in a live P. acnes-induced inflammatory skin disease animal model. In the animal model, melittin-treated ears showed considerably lower swelling and granulomatous responses to P. acnes injection. Another study found that melittin reduced heat-killed P. acnes-induced apoptosis and inflammation in human THP-1 monocytic cells (Zhang et al., 2024).

6.8 Prevention and treatment of common cardiovascular diseases

BV can enter the body via direct stings or manual injection (Ali, 2012; Moreno and Giralt, 2015). Wehbe et al. thoroughly examine BV's chemical makeup, biological characteristics, and mechanisms of action (Wehbe et al., 2019). Yook et al. discovered that sweet BV may impact fluctuations in heart rate, although nothing is known about its effect on CVDs (Yook et al., 2008). Wang et al. discovered that melittin, a polypeptide present in BV, can attenuate CVB3-induced myocarditis. Melittin treatment (0.1 mg/kg) lowered myocardial cell death, lowered Bax and caspase-3 expression, and increased Bcl-2. It also improved cardiac activity, as seen by echocardiography (Wang et al., 2016).

6.9 Management of asthma

Asthma is a potentially fatal inflammatory lung disorder with elevated CD4+ T cell counts. Research discovered that injecting BV (0.1 and 1 micro g/mL) increased regulatory T cells, inhibited cytokine production, and reduced peribronchial and perivascular inflammatory cell infiltrates in Balb/c mice with an ovalbumin-induced allergic asthma model (Reuter et al., 2024). Natural regulatory cells expressed more CD4+, $CD25^{+}$, and FOXP3, whereas IgE levels in test animals' blood dropped considerably (Haque et al., 2024).

6.10 Anti-hyperglycemic activity

Diabetes mellitus (DM) is a life-changing metabolic condition caused by abnormal insulin production, receptor activation, or both (Kharroubi and Darwish, 2015). Hyperglycemia causes excessive glycation of sugars and unbound amino groups in proteins, which alters their physical and chemical characteristics (Feng et al., 2023). BV doses (10, 20, and 40 μg/mL) were investigated *in vitro* for their effect on hemoglobin glycation when incubated with glucose. The amount of heme was evaluated by separating free amino groups with fluorescamine. The researchers discovered that BV prevents glycation-driven heme breakdown in hemoglobin. Because it has a solid antiglycation activity. It has been proposed as a natural therapy for glycation difficulties in DM (Jafari et al., 2024).

6.11 Protective impact against renal damage

Sepsis-induced acute kidney injury is a major worldwide health problem. Sepsis-induced acute kidney injury is a worldwide health problem. During septicemia, the endotoxin Lipopolysaccharide (LPS) causes systemic inflammation. BV, MEL, and apamin alleviated LPS-triggered severe renal damage in mice by lowering cellular oxidation damage, inflammatory processes, and cell death. MEL lowered TNF-α and IL-6 levels, decreased immune cell aggregation in the kidney, and blocked the NF-κB system. MEL decreased MDA levels, inhibited NOX4 expression, boosted Nrf2-mediated antioxidant defenses, and blocked apoptotic and necrotic processes following LPS administration. Furthermore, MEL treatment significantly prolonged the survival of mice treated with LPS (Son et al., 2007). MEL may help prevent and treat sepsis-related renal issues (Tiwari et al., 2022). In addition, MEL decreased cisplatin-induced acute kidney injury in mice by regulating M2 macrophage expression (Kim J-Y. et al., 2020).

Chronic accumulation of developing renal fibrosis produces irreversible harm to the kidneys, resulting in end-stage conditions such as renal failure. Apamin decreased renal fibrosis from unilateral ureteral obstruction *in vivo* and inhibited TGF-β1-induced activation of renal fibroblasts *in vitro*. This peptide inhibited TGF-β1/Smad2/3 and STAT3 pathways, leading to decreased inflammation, tubular atrophy, myofibroblast activation, and fibrotic gene expression (Gwon et al., 2021).

Dietary BV improved breast meat's efficiency, yield, and nutritional value in grilled chickens. It also lowered the height of internal organs, caecal short-chain fatty acid, and ileal villus. This

shows that BV might be an organic alternative to antibiotics in feed for improving animal health (Kim et al., 2018).

7 Clinical studies on the effect and safety of bee venom

BV has shown promising clinical effectiveness in treating a range of conditions, including asthma, allergic rhinitis, insomnia, headache, pain relief, and inflammation (Jang and Kim, 2020; Lin and Hsieh, 2020). However, its use is not without risk, as it can cause life-threatening adverse reactions (Jang and Kim, 2020). Despite this, BV is effective in treating skin varicosities veins, with potential benefits in dermatology. Further research is needed to fully understand the clinical applications and safety of BV therapy.

The safety of BV has been extensively studied, with mixed results (Bae et al., 2015; Cherniack and Govorushko, 2018; Sung et al., 2022). Cha, et al. found no significant adverse effects in mice, suggesting its potential as a safe natural antibiotic (Cha et al., 2012). However, Jang, et al. and Park, et al. both highlighted the need for caution, as BV therapy can lead to adverse events, including skin reactions and anaphylaxis (Park et al., 2019; Jang and Kim, 2020). Lee also emphasized the importance of practitioner education and qualifications in ensuring the safety of BV therapy (Lee CH. et al., 2019). Therefore, while BV may have potential as a therapeutic compound, its safety in clinical trials is still a matter of concern.

8 Contraindications and provisions

Many situations limit the use of BV in human therapeutics, including children under five, pregnancy, nursing, infections, post-vaccination, and medically compromised patients (Khalil et al., 2021). Systemic responses to bee stings have been seen in up to 3.4% of children and 7.5% of adults. Hence, allergy testing should be undertaken before employing BV treatment. These allergic responses can be modest, affecting only the cutaneous tissues, resulting in life-threatening anaphylaxis. Regarding venom-related allergies, venom immunotherapy is the sole medicine to prevent additional systemic sting responses (Sturm et al., 2018). To test for allergies, 0.05 mL (1.0 mg of unprocessed dried venom dissolved in 1.0 mL of normal saline is administered into the patient's forearm flexor surface. It is infected slowly, resulting in a tiny hemispherical bleb. The absence of systemic manifestations 15–30 min after a subcutaneous administration of BV means the individual is judged not allergic to the examination. In the case of an allergic reaction, the patient should receive rapid medical assistance, which may involve the injection of adrenaline and/or dexamethasone. Since BV tolerance differs across individuals, there is no universal technique for everyone getting BV treatments. To get the finest benefits from BV treatments. All BV treatment courses should incorporate the following recommendations: (a) 2–3 mg of vitamin C daily; (b) 650 mg of acetaminophen can be administered in the event of fever and chills; (c) alcohol intake is forbidden during BV therapies; (d) an ice pack is helpful at the injection site if local reactions occur like edema; and (e) in anaphylactic shock, the patient should receive epinephrine (adrenaline) instantly and then be moved to the hospital (Bilò et al., 2019).

Advancements in controlled drug release systems and nanotechnology-based delivery methods can improve the targeted delivery of BV, increase bioavailability, and reduce side effects associated with traditional administration routes. These modern approaches allow for precise delivery of BV's active ingredients, ensuring the right amount reaches the intended site of action. Nanotechnology-based delivery systems offer high sensitivity and specificity, allowing for rapid diagnosis and treatment of conditions like bacterial vaginosis while minimizing side effects. By optimizing therapeutic outcomes through more efficient drug delivery, these advancements have the potential to enhance the efficacy and appeal of BV therapy.

9 Toxicity of bee venom

Toxicology reports on BV have highlighted both its benefits and potential risks. Studies have documented adverse effects related to BV therapy, including hyperventilation, fatigue, appetite loss, extreme pain, increased bleeding risk, and vomiting (Jang and Kim, 2020; Lee et al., 2021). Furthermore, research has focused on the cellular toxicity assessment of BV microspheres in prostate cancer treatment, emphasizing the need for a thorough understanding of its impact on cellular health (El-Didamony et al., 2022a). Toxicological studies have delved into the hemolytic activity of BV in various species, such as horses, humans, sheep, and rabbits, shedding light on its cytotoxic effects. Additionally, investigations have explored the accidental ingestion of honeybee venom, emphasizing the importance of understanding the potential risks associated with exposure to BV components (de Roodt et al., 2020; Lee et al., 2021; Tanuwidjaja et al., 2021). The presence of compounds like melittin, phospholipase A2, and biogenic amines in BV has been a subject of interest, with melittin, in particular, being a major toxin known for its cytotoxic effects (Shi et al., 2022). While, BV therapy has shown promise in treating various health conditions, including inflammation and chronic illnesses, caution is warranted due to the potential for serious side effects. The use of BV products or undergoing BV therapy should be supervised by trained medical professionals to mitigate risks. Research has highlighted the dual nature of BV, with compounds like melittin, and apamin exhibiting anti-inflammatory and pain-relieving properties, but also carrying the risk of irritation and allergic reactions in sensitized individuals (Jang and Kim, 2020; Ullah et al., 2023).

10 Scaffolds based delivery for bee venom delivery

Biological preparations comprise substances from vegetation and animals; some of these products possess an extensive record of use, while others have been found in recent years (Giannenas et al., 2020). For instance, the therapeutic efficacy of natural

extracts and components has been hampered by a variety of issues, notably an absence of targeting capability and low bioavailability. Scientists recommended employing scaffolds infused with BV to address its disadvantages and boost its physiological and medicinal benefits (Atia GA. et al., 2023; Liu H. et al., 2023; Atia et al., 2024; El-Nablaway et al., 2024). Despite advances in cancer treatment, the illness remains the leading cause of death globally. BV has a variety of biological characteristics and has been shown *in vitro* to be cytotoxic against many cancer cell lines. However, its use in humans remains challenging because to allergic responses, discomfort at administration sites, and other serious toxic events including hemolysis, nonspecific cytotoxic effects, itching feeling, and hypersensitivity during therapeutic therapy. BV-loaded nanoliposomes (BV-NLs) were synthesized and characterized, and their anticancer efficacy was tested *in vitro* against the HepG-2, MCF-7, and HCT-116 cell lines. They outperformed raw BV in terms of anticancer efficacy against the 3 cell lines evaluated. It demonstrated preferential cytotoxicity and was more potent against the HCT-116 cell line, with an IC50 of 4.16 μg/mL. BV-NLs also regulate the mRNA transcription of apoptosis genes (Abd El-Gawad et al., 2023). Another study used the freeze-thawing process to create various formulations of polyvinyl alcohol (PVA) and chitosan (Ch) hydrogel wound dressings incorporating BV. It was more swollen, flexible, and elastic than the other formulations. Furthermore, it demonstrated anti-inflammatory properties equivalent to diclofenac gel, commonly used anti-inflammation medicine. Meanwhile, wound tissues coated with this mixture demonstrated greater hydroxyproline and glutathione amounts and decreased IL-6 levels relative to the control (Amin and Abdel-Raheem, 2014). The BV or its contents (e.g., melittin) were intensively explored as prospective therapy and antagonists of tumor types; they shown numerous prospective biological anticancer processes (Borojeni et al., 2020; Lebel et al., 2021; Zein et al., 2024). Nanotechnology has become widely used in most medical disciplines, with nanomaterials being used as antimicrobial, cancer-fighting, or loaded with biologically active drugs/compounds that improve their solubility, stability, performance, and transport to the human body (Alkhursani et al., 2022; El-Nablaway et al., 2024). In this line, nano chitosan produced from Fusarium oxysporum-grown mycelia had been utilized to transport BV. The *in vitro* antitumor capacity evaluation against HeLa cervical carcinoma indicated that they all displayed significant dose-related cancer-fighting properties, with BV/NFC nanoconjugates being the most efficient. The fluorescent labeling of these cells demonstrated the presence of initial apoptosis, subsequent apoptosis, and additional necrosis indicators, and their increase with contact extension (Alalawy et al., 2020). Due to the increasing prevalence of adaptive human microorganisms across the world, antimicrobial resistance has become one of the most pressing medical concerns. Chitosan synthesized from dead bee exoskeletons laden with BV has previously been developed and evaluated against eight prevalent human infections (two fungal and six bacterial strains) as well as two cancer cell lines. It has increased antibacterial action against six prevalent human diseases, including Gram-positive and Gram-negative bacterial and fungal strains. Although hazardous at high doses, the nanoparticles demonstrated exceptional activity against the human colon cancer cell line (Caco2 ATCC ATP-37) and human liver cancer cell line (HepG2 ATCC HB-8065), eliminating around 72% of cancer cells (Sharaf et al., 2024b). In another work, BV-loaded chitosan nanoparticles (ChNPs) had weak anti-MERS-COV activity (SI = 4.6), whereas ChNPs had considerable anti-MERS-COV activity (SI = 8.6). Meanwhile. It showed significant anti-MERS-COV activity (SI = 12.1). Furthermore, the synthesized platform demonstrated better antibacterial action against both Gram-positive and Gram-negative bacteria when contrasted with ChNPs, BV, or the used experimental medication (Elnosary et al., 2023).

11 Conclusion

BV is a complex combination of compounds widely researched because of their biological effects. Proteins and peptides comprise most of its content, with additional molecules present in small amounts. Between its constituents, melittin is the most prevalent and researched constituent of BV, after which comes PLA2, an enzyme that is regarded (along with histamine) as the primary allergen of BV. Furthermore, additional investigation is needed, particularly on BV's less significant elements. Numerous physiological characteristics have been documented. However, a study has focused chiefly on anti-inflammation and immune-modulating benefits. However, further *in vitro* and *in vivo* research is required to understand the BV action mechanisms better. Due to its beneficial effects on certain conditions, including musculoskeletal and neurological ailments, BV's primary applications are therapeutic. Nowadays, attempts are being made to develop safer dosages and methods and new trends like novel delivery technologies to reduce undesirable effects. In addition, the study advances the comprehension of the pathways of BV ingredients and evaluates their medicinal applicability.

Author contributions

KS: Conceptualization, Software, Visualization, Writing–original draft, Writing–review and editing. NS: Conceptualization, Software, Visualization, Writing–original draft, Writing–review and editing. ET: Writing–original draft, Writing–review and editing. FR: Writing–original draft, Writing–review and editing. MS: Conceptualization, Software, Visualization, Writing–original draft, Writing–review and editing. GA: Software, Visualization, Writing–original draft, Writing–review and editing. NT: Writing–original draft, Writing–review and editing, Software, Visualization. ME-N: Writing–original draft, Writing–review and editing. AI: Writing–original draft, Writing–review and editing. MR: Writing–original draft, Writing–review and editing. AfA: Writing–original draft, Writing–review and editing. MA: Writing–original draft, Writing–review and editing. II: Writing–original draft, Writing–review and editing, Software. EP: Writing–original draft, Writing–review and editing. LA: Data

curation, Visualization, Software, Writing–review and editing. AhA: Conceptualization, Writing–original draft, Writing–review and editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Glossary

ACHE	Acetylcholinesterase
AD	Alzheimer's disease
ALF	Acute liver failure
ALS	Amyotrophic lateral sclerosis
ALS	Amyotrophic lateral sclerosis
ALT	Alanine aminotransferase
Amps	Antimicrobial peptides
AOA	Antioxidant activity
AST	Aspartate transaminase
ATF3	Activating transcription factor 3
BV	Bee venom
BV-nls	BV-loaded nanoliposomes
Bvpla2	Bee venom phosphao lipase A2
Camp	Cyclic adenosine monophosphate
C-AMP	Cyclic adenosine monophosphate
CDK	Cyclin-dependent kinase
C-GMP	Cyclic guanosine monophosphate
Ch	Chitosan
ChNPs	Chitosan nanoparticles
CIA	Collagen-induced arthritis
CK-MB	Creatine Kinase MB
CLD	Chronic liver disease
COX-2	Cyclooxygenase-2
CTNI	Cardiac Troponin I
DM	Diabetes mellitus
DPIV	Dipeptidyl peptidase IV
DSNS	Dual-secured nano-sting
EAE	Experimental autoimmune encephalomyelitis
ECM	Extracellular matrix
Foxp3	Forkhead box P3
GSH	Glutathione
GST	Glutathione S-transferase
HCC	Hepatocellular carcinoma cells
HCV	Hepatitis C virus
HFD	High-fat diet
HIF-1α	Hypoxia-inducible factor 1-alpha
HIV	Human immunodeficiency virus
HPV	Papillomaviruse
Hscs	Hepatic stellate cells
HSV	Herpes simplex virus
IFN-γ	Interferon-gamma
IL-8	Interleukin-8
iNOS	Inducible nitric oxide synthase
LDH	Lactate Dehydrogenase
LPS	Lipopolysaccharides
MAPK	Mitogen-activated protein kinase
MCD	Mast cell degranulating
MDA	Malondialdehyde
MEL	Melittin
MIC	Minimum inhibitory concentration
MMPS	Matrix metalloproteinases
NAD^+	Nicotinamide adenine dinucleotide
NAFL	Nonalcoholic fatty liver
NF-κB	Nuclear factor kappa B
NO	Nitric oxide
PDGF-BB	Platelet derived growth factor-BB
PI3Ks	Phosphoinositide 3-kinases
PLA2	Phospholipase A2
PVA	Polyvinyl alcohol
RA	Rheumatoid arthritis
RANKL	Receptor activator of nuclear factor kappa-B ligand
RLPP	Recalcitrant localized plaque psoriasis
RNA	Ribonucleic acid
SK	Small-conductance calcium-activated potassium
SOD	Superoxide dismutase
STAT3	Signal transducer and activator of transcription 3
TAC	Total antioxidant capacity
TBARS	Thiobarbituric acid–reactive substances
TGF-β	Transforming growth factor beta
Th cells	T helper cells
TLR4	Toll-like receptor 4
TMDs	Tempormandibular disorders
TMZ	Temozolomide
TNF-α	Tumor necrosis factor-α
Tregs	Regulatory T-cells
UCF	Unicellular fungal
VEGF	Vascular endothelial growth factor