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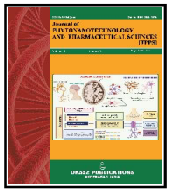

Review Article : Open Access

Bee venom and melittin: A promising therapy for breast cancer

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Abstract

Bee venom, derived from *Apis mellifera*, contains bioactive compounds such as peptides (*e.g.*, melittin), enzymes (*e.g.,* phospholipase A2), and amines (*e.g.,* histamine), demonstrating therapeutic potential across various ailments, including cancer. Melittin, predominant in bee venom, constitutes a significant portion of its dry weight and exhibits potent anticancer properties. This review explores the mechanisms underlying bee venom's efficacy in breast cancer treatment. Despite advancements in conventional therapies, rising cancer incidence necessitates the exploration of alternative treatments. Bee venom and its constituents have gained attention for inducing apoptosis, inhibiting proliferation, and modulating metastasis in cancer cells. Mechanistically, melittin induces apoptosis through mitochondrial dysfunction, reactive oxygen species (ROS) generation, and caspase activation, disrupting cancer cell membranes *via* pore formation and inducing endocytosis. Engineered peptides like RGD1-melittin use integrin binding motifs to selectively target breast cancer cells, enhancing melittin's efficacy in targeted therapies. Experimental studies demonstrate the synergistic effects of melittin with conventional chemotherapies, nanoparticle carriers, and immune modulation strategies, enhancing treatment outcomes. This review consolidates knowledge on bee venom's composition, mechanisms of action, and experimental findings in breast cancer therapy. It addresses challenges and proposes future research directions to optimize bee venom's therapeutic application.

1. Introduction

Venom, a complex substance produced by the western honeybee *Apis mellifera*, is used to treat a variety of illnesses, such as cancer, inflammation, and discomfort. Peptides like apamin and melittin, as well as enzymes like hyaluronidase and phospholipase A2, and physiologically active amines like histamine and adrenaline, are all found in bee venom (Kim *et al.,* 2016; Son *et al.,* 2007). Melittin is one of the most important of them; it makes up between 40 and 50 per cent of the dry weight of bee venom. Apamoxin (2-4%) and phospholipase A2 (10-12%) are two other noteworthy ingredients (Kim, 2021).With an emphasis on the treatment of breast cancer, this review seeks to clarify the therapeutic benefits of bee venom in the suppression of tumour cells.

Despite advancements in modern medicine, natural products derived from plants and animals continue to play a crucial role in the prevention and treatment of numerous diseases. Many treatments utilized in Western medicine have their origins in Asia, with an increasing trend towards alternative medicine. Animal venoms, especially from insects like bees, have a longstanding history in scientific research and are presently used to develop various medicinal products. Bee venom, isolated from *A. mellifera,* has shown a range of beneficial properties including radioprotective, antimutagenic, anti-inflammatory, antinociceptive, and antimicrobial effects (Baskar *et al.,* 2012).

The rising incidence of cancer, particularly among the ageing population, necessitates the development of novel drugs and treatment strategies (Ferlay *et al.,* 2015). Despite the effectiveness of conventional therapies such as surgery, radiotherapy, and chemotherapy, the mortality rate remains high, prompting a search for alternative treatments. Natural compounds, including bee venom, have emerged as potential therapeutic agents against tumours. Bee venom and its components have been extensively studied for their anticancer properties, which include influencing cell cycle changes, affecting cell survival and proliferation, and inducing apoptosis and necrosis in cancer cells (Fitzmaurice *et al.,* 2018).

Figure 1: Bee venom used in breast cancer.

Breast cancer, a leading cause of mortality among women worldwide, often originates in the lobules and ducts of the breast. Early detection is crucial for reducing mortality rates, as the severity of breast cancer

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is classified based on the stage of cancer (Rahimzadeh *et al.,* 2014) which ranges from 0 to IV. Genetic factors, including mutations in BRCA1 and BRCA2 genes, significantly contribute to the risk of developing breast cancer (Rahimzadeh *et al.,* 2014). Research into novel and combined therapeutic approaches is ongoing, with honeybee venom showing promising results in cancer treatment by inducing apoptosis, inhibiting cell proliferation, and controlling metastasis.

This review will explore the composition of bee venom and its potential anticancer properties, particularly focusing on its application in breast cancer treatment. Additionally, it will address the challenges of using bee venom as a therapeutic modality and propose potential strategies to overcome these obstacles.

1.1 Methods for using bee venom in breast cancer treatment

Bee venom (BV) and its major constituent, melittin (MEL), have demonstrated significant potential in the treatment of various cancer types, including breast cancer. This document summarizes the key methods and findings regarding the use of bee venom and melittin in breast cancer treatment, highlighting their mechanisms, effects, and potential applications.

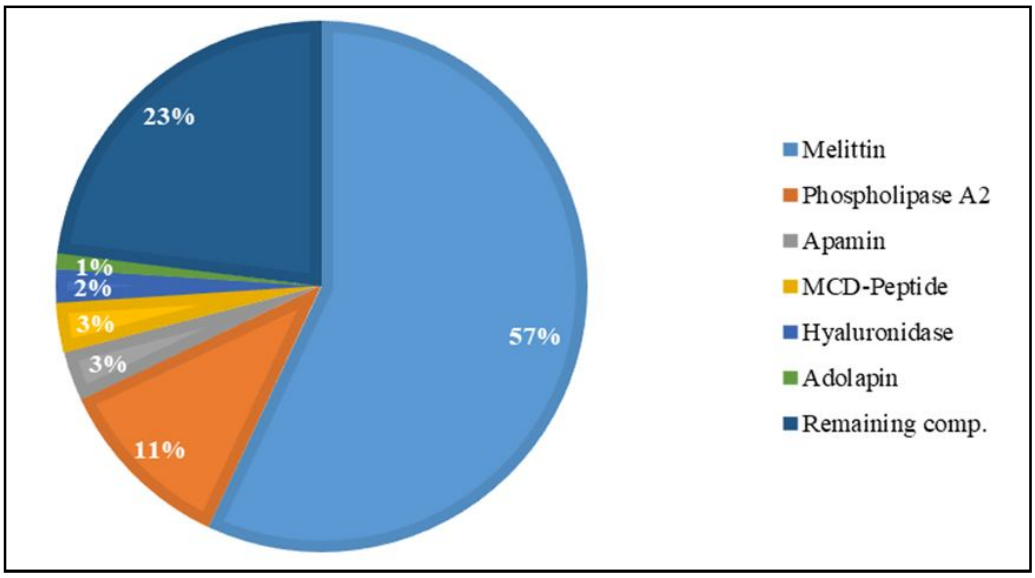

Figure 2: The composition of the venom depends on many factors, including the region of the world and the time of year when the venom is collected (Obeidat *et al.,* 2023).

2. Mechanisms of action

2.1 Apoptosis induction

Melittin induces apoptosis in cancer cells through various pathways, like activation of caspases and matrix metalloproteinases, leading to programmed cell death, (Gajski *et al.,* 2013) including breast cancer cells like MCF7, through several mechanisms involving mitochondrial pathways and reactive oxygen species (ROS) production.

(a) Mitochondrial pathway: BV triggers apoptosis by influencing mitochondrial function. This involves:

- **Mitochondrial membrane potential (ΔΨm)**: BV can disrupt the mitochondrial membrane potential, leading to mitochondrial dysfunction. This disruption is a critical step in initiating apoptosis.
- **Release of cytochrome C**: BV can induce the release of cytochrome C from mitochondria into the cytosol. Cytochrome C release activates caspase-3 and other caspases, which are key executioners of apoptosis (Earnshaw *et al.,* 1999).
- **ROS production:** BV induces the generation of reactive oxygen species (ROS) within cancer cells. ROS accumulation can lead to oxidative stress, which in turn activates signalling pathways that promote apoptosis. Excessive ROS can also cause damage to cellular components like DNA and proteins, contributing to cell death(Strasser*et al.,* 2000).
- **Caspase activation**: As mentioned earlier, caspases are crucial in the apoptotic process. BV has been shown to activate caspase-3 in various cancer cell types, including cervical cancer cells. Caspase-3 activation leads to the cleavage of cellular proteins and ultimately cell death by apoptosis(Jang *et al.,* 2003).
- **Specific effects in breast cancer (MCF7 cells)**: While specific data on MCF7 cells from the provided text is not detailed, based on general mechanisms observed in other cancer cell types, BV likely induces apoptosis in MCF7 cells through similar pathways involving mitochondrial dysfunction, ROS production, and caspase activation (Strasser *et al.,* 2000).

(b) Other apoptotic features: BV induces typical apoptotic features in cancer cells, such as: Cellular morphological changes (cell shrinkage, membrane blebbing).

- Chromatin condensation and DNA fragmentation (oligonucleosomal DNA cleavage).
- Externalization of phosphatidylserine on the plasma membrane, marking cells for phagocytosis.

2.2 Cell cycle alteration

Bee venom (BV), specifically its main component melittin, exerts significant effects on cell cycle regulation in breast cancer cells, contributing to its anticancer properties (Gajski *et al.,* 2013).

a. **Induction of cell cycle arrest:** Bee venom components, such as melittin, have been shown to induce cell cycle arrest at various phases, depending on the specific cancer cell type and conditions:

- In studies on MCF-7 breast cancer cells, melittin has been reported to cause cell cycle arrest predominantly at the G0/G1 phase. This arrest prevents cells from progressing into the S phase where DNA replication occurs. Without completing the G1 phase, cells cannot initiate DNA synthesis, effectively halting their proliferation.
- The mechanism of G_0/G_1 phase arrest involves the inhibition of cyclin-dependent kinases (CDKs) and cyclins, which are crucial regulators of cell cycle progression. By blocking these proteins, melittin prevents the phosphorylation events necessary for the cell to progress through the G1 checkpoint.

b. **Inhibition of cyclin/CDK complexes:** Melittin interferes with the formation and function of cyclin/CDK complexes that drive the cell cycle forward Specifically:

- Melittin downregulates cyclin D1 and cyclin E, which are required for progression from G1 to S phase.
- It also inhibits CDK4 and CDK2 activities, which are necessary for phosphorylating the retinoblastoma protein (pRb), a key step in allowing cells to enter the S phase.

c. **Activation of cell cycle checkpoints**: Melittin activates cellular checkpoints that monitor DNA integrity and cell cycle progression:

- It enhances the expression and activity of tumour suppressor proteins like p53. Activated p53 can induce cell cycle arrest to allow time for DNA repair or initiate apoptosis if the damage is irreparable.
- Melittin-induced oxidative stress and DNA damage trigger signalling pathways that lead to p53 stabilization and activation, reinforcing cell cycle arrest mechanisms.

2.3 Membrane disruption

Bee venom, which contains melittin as its main active component, disrupts cell membranes through several mechanisms, particularly in the context of breast cancer cells (Khamis *et al.,* 2018).

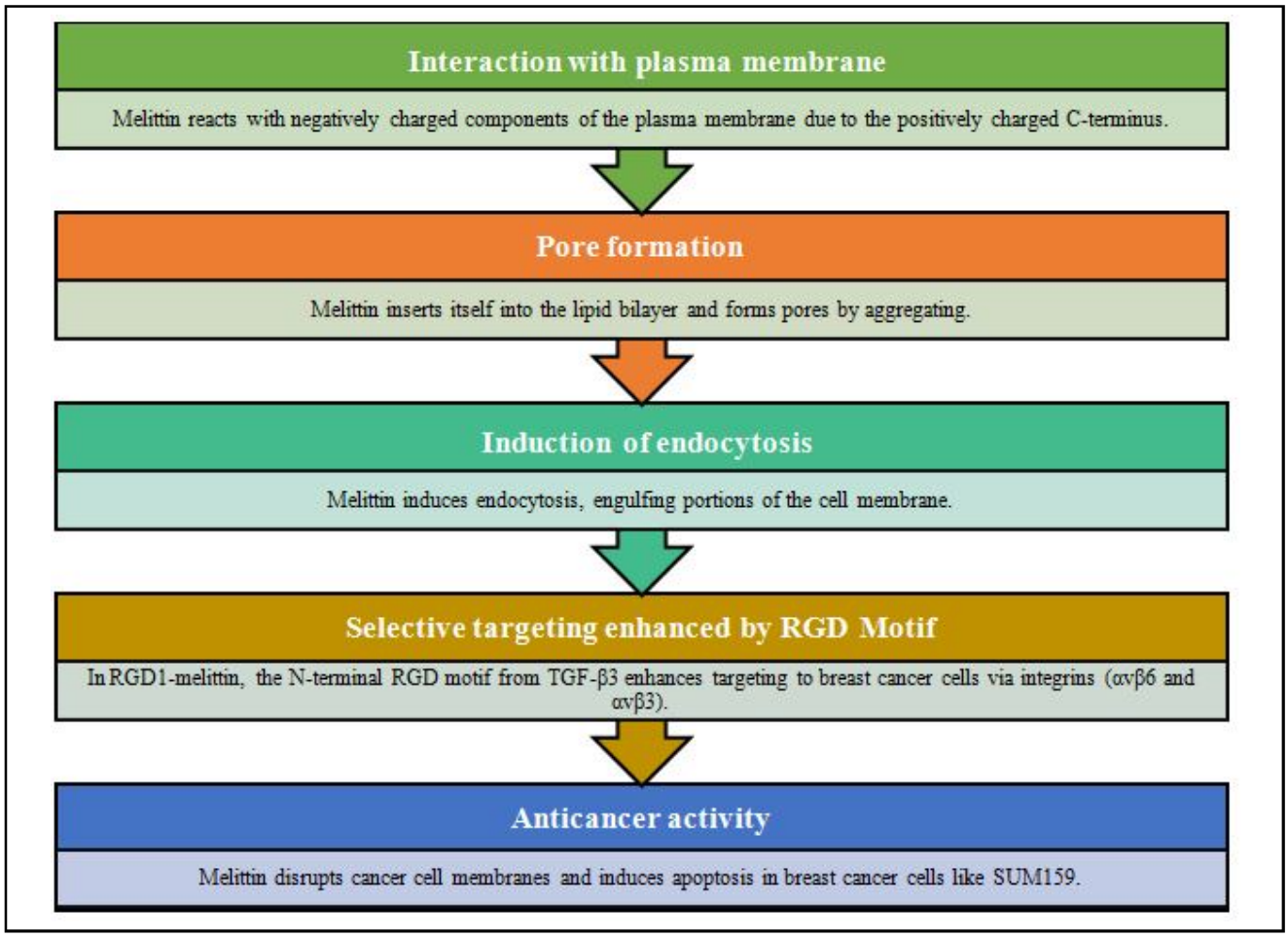

Figure 3: Membrane disruption by bee venom.

a. **Interaction with plasma membrane:** Melittin, a peptide derived from bee venom, interacts with the negatively charged components of the plasma membrane due to its positively charged C-terminus. This interaction is crucial for its initial binding to the cell membrane (Hall *et al.,* 2011; Rai *et al.,* 2016; Krauson *et al.,* 2015).

b. **Pore formation:** Upon binding, melittin can insert itself into the lipid bilayer of the plasma membrane. Its amphipathic nature allows it to form pores by aggregating and disrupting the lipid bilayer structure. These pores are large enough to allow ions and small molecules to pass through, leading to cell lysis and death (Hall *et al.,* 2011; Sharma, 1992).

c. **Induction of endocytosis:** Melittin has also been shown to induce endocytosis, where the cell engulfs portions of its membrane, potentially contributing to intracellular trafficking and membrane disruption.

d. **Selective targeting enhanced by RGD motif:** In the engineered peptide RGD1-melittin, an N-terminal RGD motif derived from TGF-β3 enhances the targeting of breast cancer cells by binding specifically to integrins (αvβ6 and αvβ3) that are overexpressed on their surfaces. This selective binding enhances the localization of melittin to cancer cell membranes, potentially increasing its effectiveness in disrupting these membranes compared to normal cells (Dong *et al.,* 2016; Li *et al.,* 2016; Sorolla *et al.,* 2019).

e. **Anticancer activity**: Melittin's ability to disrupt membranes is crucial for its anticancer activity. It induces apoptosis in breast cancer cells like SUM159, as observed in the study, and this effect is partly mediated by its membrane-disrupting capabilities (Kohno *et al.,* 2014; Kokot *et al.,* 2012).

2.4 Immune modulation

Melittin, the main component of bee venom, exhibits intriguing immune-modulating properties that contribute to its potential in cancer therapy:

a. **Reduction of immune suppression**: Melittin has been shown to reduce the immune-suppressive effects within the tumour microenvironment. This includes decreasing the activity of regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), which are known to inhibit the antitumoral immune response. By mitigating these suppressive mechanisms, melittin can help promote a more robust immune response against cancer cells.

b. **Enhancement of antitumoral immunity**: Melittin can stimulate various immune cells involved in antitumoral responses, such as dendritic cells (DCs) and cytotoxic T lymphocytes (CTLs) (Kepp *et al.,* 2014; Galon *et al.,* 2019).This activation leads to enhanced antigen presentation and cytotoxic activity against tumour cells, further bolstering the immune system's ability to recognize and eliminate cancerous cells.

c. **Attenuation of immune checkpoint proteins**: Immune checkpoint proteins, such as PD-1/PD-L1 and CTLA-4, play crucial roles in regulating immune responses and can be exploited by tumours to evade immune surveillance. Melittin has been reported to attenuate the expression of these checkpoint proteins, potentially reversing immune suppression and restoring effective immune surveillance against cancer cells (Duffy *et al.,*2020).

d. **Synergistic effects with immunotherapy**: Melittin's immune-modulating properties complement current immunotherapy approaches. Combining melittin with immune checkpoint inhibitors or other immunomodulatory agents may synergistically enhance therapeutic outcomes by overcoming immune evasion mechanisms employed bytumours (Obeidat *et al.,*2023).

3. Experimental studies and findings

3.1 Cell selectivity and potency

Melittin selectively induces cell death in TNBC and HER2-enriched breast carcinoma with minimal effects on normal cells. It reduces cell viability and migration in MDA-MB-231 cells by decreasing EGFR and MAPK phosphorylation (Obeidat *et al.*, 2023).

3.2 Combination therapies

a. **Melittin and docetaxel:** Combined treatment shows superior tumour control in TNBC compared to either agent alone. This combination enhances efficacy and reduces the required dosage, potentially minimizing adverse effects (Obeidat *et al.,* 2023).

b. **Melittin and doxurubicin**: Demonstrated a synergistic effect between doxorubicin (DOX) and melittin, significantly enhancing antitumor activity in breast cancer cell lines at acidic pH levels (Hematyar *et al.,* 2018).

c. **Combination of hesperidin, piperine, and bee venom with tamoxifen:** Enhances the latter's efficacy while reducing the necessary dosage and side effects. This combination induces apoptosis, halts the cell cycle, and lowers ERα and EGFR expression (Khamis *et al.,* 2018).

3.3 Nanoparticle carriers

a. **Carbon nanoparticles:** Conjugation of melittin with carbon nanoparticles (graphene, graphene oxide, pristine graphene, diamond) enhances its selective cytotoxic effect on cancer cells. The nanoparticles facilitate targeted delivery, reducing systemic toxicity (Thornberry *et al.,*1998).

b. **PIC micelles:** Melittin encapsulated in PIC micelles shows improved stability and cytotoxicity in 3D cytotoxicity studies compared to free melittin. These micelles help neutralize melittin's toxicity and enhance its delivery to cancer cells (ElBakary *et al.,* 2020).

c. **AMD3100-conjugated nanoparticles**: Promelittin loaded in AMD3100 conjugated nanoparticles effectively inhibits breast cancer brain metastasis (BCBM) (Raveendran *et al.,* 2020).

4. Inhibition of metastasis and invasion

4.1 Matrix metalloproteinase inhibition

Increased doses of melittin (0.5 to 2.5 μg) inhibit MMP2 and CD147 expression, significantly reducing the invasion potential of MCF-7 breast carcinoma cells (Raveendran *et al.,* 2020). In addition to its effects on matrix metalloproteinase (MMP) inhibition and CD147 expression, melittin has been observed to exert further impacts on metastasis and invasion in breast carcinoma cells

a. **Suppression of cell migration:** Melittin treatment has been shown to significantly inhibit the migratory ability of breast carcinoma cells. This effect is crucial in impeding the initial steps of metastasis, where cancer cells migrate away from the primary tumour site and invade surrounding tissues.

b. **Disruption of focal adhesion kinase (FAK) signaling:** Melittin interferes with FAK signalling pathways, which are essential for cancer cell migration and invasion. By disrupting FAK activation, melittin can attenuate the ability of cancer cells to adhere to and migrate through the extracellular matrix, thereby hindering their invasive potential (Jeong *et al.,* 2019).

c. **Downregulation of pro-metastatic factors:** Beyond MMP2 and CD147, melittin treatment has been associated with the downregulation of various other pro-metastatic factors in breast carcinoma cells. These include vascular endothelial growth factor (VEGF), which promotes angiogenesis and facilitates metastatic spread, and interleukin-6 (IL-6), which is implicated in promoting cancer cell survival and migration (Lee *et al.,* 2017).

d. **Induction of apoptosis in metastatic cells:** Melittin induces apoptotic cell death specifically in metastatic cells, thereby selectively targeting cells with enhanced invasive potential. This selective cytotoxicity is advantageous in targeting metastatic lesions while sparing normal tissues.

e. **Synergistic effects with chemotherapy:** Melittin has shown synergistic effects with conventional chemotherapeutic agents used in breast cancer treatment. This combination therapy not only enhances cytotoxicity against primary tumours.

5. Discussion

The introduction and background provide a detailed overview of bee venom's composition and its potential therapeutic applications, specifically in treating breast cancer. The composition of bee venom, including key components like melittin, apamin, and enzymes such as phospholipase A2, underscores its complex biochemical profile with diverse biological activities. These components have been extensively studied for their roles in anticancer properties, including apoptosis induction, cell cycle regulation, and immune modulation.

Bee venom's anticancer mechanisms, particularly through melittin, involve several pathways crucial for inhibiting cancer cell growth. These mechanisms include disrupting mitochondrial function, generating reactive oxygen species (ROS), activating caspases, and inducing programmed cell death (apoptosis). Such targeted actions highlight bee venom's potential as a selective therapy against breast cancer, capable of distinguishing between cancerous and normal cells to minimize collateral damage.

The selective toxicity of bee venom, notably effective against triple-negative breast cancer (TNBC) and HER2-enriched types, presents a significant advantage over conventional chemotherapies that often affect healthy tissues. Studies demonstrating synergistic effects with existing chemotherapeutic agents like docetaxel and doxorubicin underscore its potential to enhance treatment efficacy while reducing overall drug dosages and associated side effects.

Despite promising findings, several challenges in utilizing bee venom as a therapeutic agent persist. These include standardizing venom extraction methods, optimizing dosage regimens, and managing potential allergic reactions in patients. Strategies such as employing nanoparticle delivery systems and exploring combinations with other therapeutic modalities aim to address these challenges, enhancing treatment precision and patient safety.

6. Conclusion

In conclusion, bee venom, particularly melittin, represents a promising frontier in developing innovative therapies for breast cancer. Its multifaceted mechanisms of action, including selective cytotoxicity, apoptosis induction, and immune modulation, position it as a potentially effective and targeted treatment option. Moving forward, continued research efforts, including rigorous clinical trials, are essential to fully elucidate bee venom's therapeutic potential, validate its safety and efficacy profiles, and integrate it into mainstream oncological practice. By overcoming current challenges and leveraging its unique biochemical properties, bee venom could emerge as a valuable addition to the therapeutic arsenal against breast cancer, offering renewed hope for improved patient outcomes and quality of life.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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