VER
Vascular & Endovascular Review

Apitoxin (honey bee venom) derived compounds - a new frontier in breast cancer research: systematic review

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ABSTRACT

Background: Breast cancer remains one of the most prevalent and fatal cancers affecting women globally, despite advances in conventional treatments such as chemotherapy, radiotherapy, and immunotherapy. However, these approaches often lack specificity and cause significant side effects. Natural compounds, including those derived from bee venom (apitoxin), have recently gained attention for their selective anticancer potential with minimal toxicity.

Objective: This systematic review aims to evaluate existing evidence on the anticancer activity of honey bee venom and its major component, melittin, against breast cancer cell lines.

Methods: Relevant in vitro studies published between 2007 and 2024 were identified from PubMed, Google Scholar, ScienceDirect, and ResearchGate using keywords such as “Bee venom AND Breast cancer,” “Apitoxin AND Breast cancer,” and “Melittin AND Antitumor.” After screening 300 records, five studies meeting inclusion criteria were analysed for intervention characteristics, cytotoxic outcomes, and underlying mechanisms.

Results: All included studies demonstrated dose- and time-dependent cytotoxicity of bee venom and melittin against various human breast cancer cell lines (MCF-7, MDA-MB-231, and HER2-enriched subtypes). The primary mechanisms involved apoptosis induction via mitochondrial dysfunction, ROS generation, and inhibition of receptor phosphorylation (EGFR and HER2). Melittin exhibited selective cytotoxicity toward aggressive triple-negative breast cancer cells while sparing normal cells. Bee venom–derived nanoparticles also showed promising biocompatibility and anticancer activity. Combination therapy with chemotherapeutic agents, such as docetaxel, enhanced antitumor effects.

Conclusion: Apitoxin and its bioactive peptides, particularly melittin, exhibit potent and selective anticancer properties against breast cancer through multiple molecular mechanisms. While these findings highlight their potential as complementary or alternative therapies, further in vivo studies and clinical trials are necessary to confirm their safety, specificity, and therapeutic efficacy.

KEYWORDS: Bee venom, Apitoxin, Melittin, Breast cancer, Apoptosis, Cytotoxicity, Natural anticancer agents.

How to Cite: Abirami S, Lubna Fathima, Gibbson Derick D, Dinesh Dhamodhar, Sindhu R, Prabu D, Rajmohan M, (2025) Apitoxin (honey bee venom) derived compounds - a new frontier in breast cancer research: systematic review Vascular and Endovascular Review, Vol.8, No.16s, 314-320.

INTRODUCTION

Cancer is a major health challenge worldwide, affecting populations in both developed and developing nations. Cancer development is caused by genetic alterations that interfere with regular cellular control, changing the production, activation, or location of proteins. These alterations impact important signalling pathways, typical regulatory mechanisms are altered, allowing uncontrolled cell proliferation.[1] Despite the presence of numerous conventional and clinical treatments, most of them are not accurate enough to differentiate between neoplastic and healthy cells, which leads to numerous serious side effects and others have hindered limited treatment success.[2] Safer, more targeted therapies that spare normal cells are in great demand, regardless of the advancements in cancer treatments including chemotherapy, radiation, immunotherapy, and gene therapy. Natural compounds with minimal side effects are being explored as potential alternatives.[1] Breast cancer is the most common type of cancer worldwide. Breast cancer has the highest incidence among all cancers, being the second most common cause of death in women around the world.[3] Several elements are either directly or indirectly responsible for the development of breast cancer. A few women who had breast cancer or who have family history that makes them vulnerable to this illness.[4] Age, genetics, lifestyle, hormones, and environmental exposures are some of the factors that affect the risk of breast cancer. Death rate can be significantly decreased in the event if breast cancer is identified in the early phases, and that can only occur when the examined

right away upon the appearance of obvious signs. Treatment advancements and early detection through screening techniques like mammography have greatly increased patient survival rates and quality of life. Notwithstanding these advancements, breast cancer continues to rank among the world's leading causes of cancer-related deaths, underscoring the significance of early detection, effective care access, and awareness. But the molecular factors that contribute to bee venom's anticancer effects continue to be poorly understood, especially in relation to breast cancer, the most prevalent cancer in women globally. Recognizing the bee venom's molecular basis and specificity against cancer cells leads to inexpensive, widely accessible natural product that fight against breast cancer. Three subtypes of breast cancer can be distinguished based on the existence of molecular markers: human epidermal growth factor receptor-2 or hormone receptor -2 gene, ERBB2 negative, ERBB2 positive and triple-negative.[5]. There is a list of breast cancer types and incidence. About 70–80% of cases are invasive ductal carcinoma, making it the most prevalent type. About 10–15% of cases are invasive lobular carcinoma. About 15–25% of cases of breast cancer are HER-2 positive. About 10–20% of cases are of the more aggressive kind of breast cancer known as triple-negative breast cancer. According to reports, a variety of active compounds made by plants, animals, and microorganisms have been used to create innovative cancer treatment medications. Bee venom has been utilized in apitherapy for many years. Although it contains a wide variety of proteins and peptides, melittin is the main protein. Melittin possesses antibacterial, anti-inflammatory, and anti-analgesic properties.[6] Melittin, which is extracted from bee venom and has been reported to have anticancer potential which affects the physiology of cancer cells through a variety of methods. Melittin's cytotoxicity in tumor cell lines and its impact on signaling pathways are believed to prevent cell division. Melittin, a short, linear, cationic, hemolytic peptide made up of 26 amino acid residues, is the main toxic component in the venom of the European honey bee (Apis mellifera). The peptide's structure features a hydrophobic amino-terminal region and a hydrophilic carboxy-terminal region. This is because a sequence of positively charged amino acids is present.[7] Because of this amphipathic property, the peptide can interact with phospholipid membranes. Furthermore, it has been assessed if melittin causes necrotic or apoptotic cell death in malignant cells [8] Bee Venom has antimutagenic and anti-inflammatory properties, and it can induce cell-cycle arrest and apoptosis in a variety of cancer cell types. Melittin may be used in the treatment of breast and lung cancer, hepatoma, leukemia , rheumatoid arthritis, prostate, and ovarian cancer by inducing apoptosis when exposed to melittin or BV.[9] By demonstrating the potential therapeutic role of apitoxin (honeybee venom) in inducing cytotoxic effects on breast cancer cells, this systematic review offers a thorough synthesis of the evidence, justifying additional research into its clinical applications.

MATERIAL AND METHOD

ELIGIBILITY CRITERIA

Inclusion criteria

This study includes in vitro experimental study that has been done in between 2007-2024, especially on bee venom compound properties in breast cancer.

Exclusion criteria

The review excluded articles with simplistic abstracts or those published in languages other than English and studies of bee venom without cancer related.

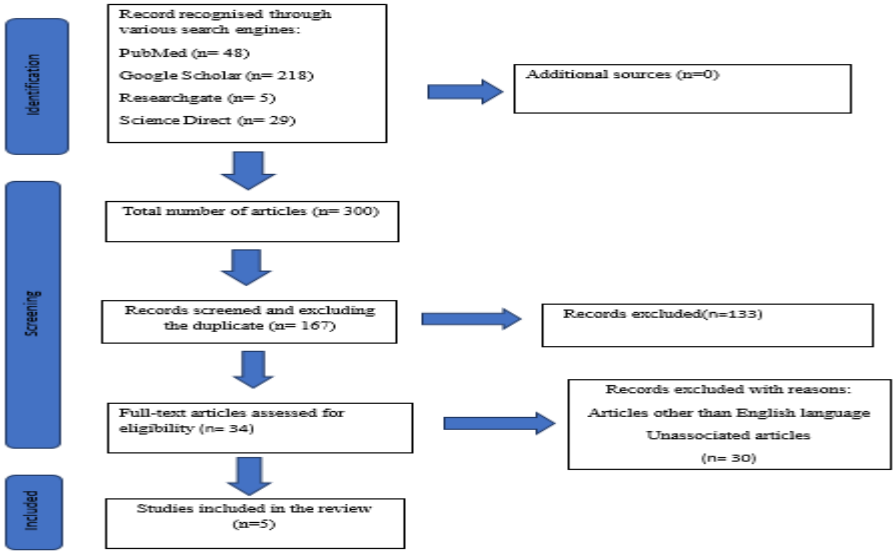
INFORMATION SOURCES

Articles were gathered from databases such as PubMed, Google Scholar and ScienceDirect.

SEARCH STRATEGY

Search labels used for identification of the studies were: “Bee venom AND Breast Cancer”, “Apitoxin AND Breast Cancer”, “Mellitin AND Antitumour”.

Figure 1: Flow chart showing the number of studies identified, screened, assessed for eligibility, excluded and included in the systematic review



RESULTS

Table 1: Characteristics of interventions in the study

sno	Author	Study design	Sample	Intervention	Results
1.	Sima Khalilifard Borojeni et al 2020 Nov	In vitro experimental study	Crude venom from Apis mellifera (AmV) is the intervention material. Human breast cancer cell line MDA-MB-231 is used as test sample.	Treatment: For predetermined amounts of time, cancer cells were exposed to different AmV concentrations. Dose-Response Analysis: MTT assays were used to obtain the IC_{50} values. Although LD_{50} (in mice) has also been documented, the main emphasis is on effects at the cell level.	Half maximal inhibitory concentration IC_{50} (24h and 48h): MDA-MB-231: 6.25 µg/mL (24 h); 3.125 µg/mL (48 h)
2.	Gyeong Bok Jung et al 2018 Nov	In vitro experimental study	MDA-MB-231 human breast cancer cells are used as a model for aggressive, triple-negative breast cancer. Although the main focus is on cancer cells, peripheral blood mononuclear lymphocytes (PBMLs) may also be considered in the viability context.	Bee venom (BV), a complex mixture of bioactive peptides such melittin, is the treatment agent. The following dosages were tested: around 0.7 µg/mL, 1.5 µg/mL, and 3.0 µg/mL (and perhaps higher up to 6.0 and 12.5 µg/mL for viability experiments). Exposure times were diverse; time-dependent evaluation is made possible by data collected at 12, 24, and 48 hours.	• Diminished Raman signals due to damage to proteins or DNA Reduced levels of caspase-3, -8, -9, and PARP; PARP cleavage; increased apoptosis (TUNEL, Annexin V/PI); decreased viability (dose/time dependent); and morphological alterations via AFM
3.	Vikram Jadhav et al 2024 Oct	In vitro experimental study	Bee venom–derived nanoparticles (BVNPs) made from the venom of Apis mellifera are the intervention material. The human breast cancer MCF-7 cell line serves as the biological model.	MCF-7 cells were exposed to a variety of BVNP doses (0–500 µg/mL) for a whole day. MTT assays were then used to evaluate the cells.	With melittin and apamin, the nanoparticles are stable (Zeta Potential −45 mV) and have an IC_{50} of about 369 µg/mL (compared to 56 µg/mL for methotrexate). The morphology of apoptosis and dose-dependent cytotoxicity is biocompatible at less than 100 µg/mL
4.	Ciara Duffy et al 2020 Sept	In vitro experimental study	Melittin and honeybee venom (collected from multiple regions) were used to measure the selective cytotoxicity of a panel of human breast cancer cell lines, including aggressive subtypes such as triple-negative (e.g., SUM159, SUM149) and HER2-enriched cells (e.g., SKBR3, MDA-MB-453) as well as	To calculate IC_{50} values, cells were treated with different concentrations of melittin and HBV. Assessments conducted over a period of time (minutes to hours) after treatment to monitor the kinetics of cell death and signaling. Anti-melittin antibodies were used to disrupt function. Melittin with RGD	Rapid apoptosis, receptor signaling inhibition, membrane breakdown, improved targeting, selective cytotoxicity toward aggressive cancers, and synergy with chemotherapy.

			nontransformed human cells (dermal fibroblasts HDFa and mammary epithelial MCF-10A/MCF-12A).	engineering for improved specificity. Combination treatment: In animal tumor models, melittin and docetaxel are combined to assess possible therapeutic synergy.	
5.	Siu-Wan Ip et al 2007 Dec	In vitro experimental study	Crude bee venom is the test substance (BV). The human breast cancer cell line MCF-7 serves as the biological model.	Cells were treated with various concentrations of BV for different time periods, enabling dose- and time-dependent analysis. The study systematically measured changes in cell morphology, survival, and molecular indicators of apoptosis across these conditions.	• Dose- and time-dependent cytotoxicity• ROS modulation & Δψm loss• Cytochrome c, caspase-9, PARP activation• S-phase cell cycle arrest via p53, p21, p27, Cdk2• DNA damage and nuclear apoptosis (Comet, DAPI)• AIF & EndoG release: caspase-independent apoptosis• Shift in Bcl-2/Bax balance• Effects on antioxidant enzyme levels

Table 2: CHARACTERISTICS OF THE PRIMARY OUTCOME AND RESULTS OF THE STUDIES INCLUDED IN THE SYSTEMATIC REVIEW

sno	Author	Outcome
1.	Sima Khalilifard Borojeni et al 2020 Nov	Bee venom exhibited significant cytotoxicity against human breast cancer cell line—MDA-MB-231. The potential of bee venom as an anticancer drug was highlighted by its dose and time-dependent cytotoxicity against breast cancer cell line, which caused apoptosis at low microgram-per-milliliter concentrations.
2.	Gyeong Bok Jung et al 2018 Nov	Bee venom (BV) induces apoptotic cell death in MDA-MB-231 breast cancer cells—demonstrated by degradation of DNA and proteins, as detected via Raman spectroscopy—supported by conventional assays like viability, TUNEL, and Western blotting. Additionally, Raman spectroscopy coupled with principal component analysis (PCA) proved to be a noninvasive, label-free method to monitor these anticancer effects
3.	Vikram Jadhav et al 2024 Oct	Biosynthesized bee-venom nanoparticles (BVNPs), produced via a hydrothermal method, showed dose-dependent cytotoxicity against MCF-7 breast cancer cells, yielding an IC_{50} of 369.2 µg/mL, along with morphological signs of apoptosis highlighting their potential as novel anticancer nanotherapeutics.
4.	Ciara Duffy et al 2020 Sept	Melittin, which is derived from honeybee venom, selectively destroys aggressive triple-negative and HER2-enriched breast cancer cells by inhibiting receptor phosphorylation (EGFR and HER2), improving therapeutic selectivity, and working in combination with chemotherapy (docetaxel) to inhibit tumor growth.
5.	Siu-Wan Ip et al 2007 Dec	Bee venom induces apoptosis in MCF7 breast cancer cells through a mitochondria-dependent pathway that includes ROS production, mitochondrial dysfunction, cytochrome c release, caspase activation, and elevated Bax/AIF/EndoG expression, bee venom causes apoptosis in MCF7 breast cancer cells.

Table 3: Risk of Bias Assessment (Adapted RoB 2 for In Vitro Studies)

S. No.	Author (Year)	Sample Preparation Bias	Measurement Bias	Protocol Deviation Bias	Reporting Bias	Overall Risk of Bias
1	Sima Khalilifard Borojeni et al., 2020					
2	Gyeong Bok Jung et al., 2018					
3	Vikram Jadhav et al., 2024					
4	Ciara Duffy et al., 2020					
5	Siu-Wan Ip et al., 2007					

Table:3 Shows the bias analysis of all the included studies. It is categorized as Low risk; some concern; high risk. Green colour indicates low risk for adequate methods and transparency bias unlikely to affect results; yellow colour indicates some concerns for uncertainty about risk of bias due to incomplete reporting or unclear procedures; red colour indicates high risk for clear flaws in design or reporting that may significantly affect results. Categorization was done according to all the RoB 2 second version of Cochrane's risk of bias.

DISCUSSION

This systematic review includes the most recent data showing that honey bee venom (apitoxin) and its primary bioactive peptide, melittin, have anticancer properties against a range of breast cancer subtypes. In all five of the analysed in vitro trials, melittin and bee venom continuously shown notable dose- and time-dependent cytotoxicity towards aggressive triple-negative and HER2-enriched breast cancer cell lines, while preserving normal cells. The main mechanisms underlying these effects were oxidative stress, intrinsic apoptotic cascade activation, inhibition of receptor signaling pathways, and mitochondrial dysfunction. All of these findings highlight the possible use of molecules based on apitoxin as natural, selective anticancer therapies.

Sima Khalilifard Borojeni et al (2020) [15] reported a in vitro experimental study that evaluated the cytotoxic effects of Apis mellifera venom (AmV) on the human cancer cell lines A549, HeLa, and MDA-MB-231 that were assessed in this investigation. Prior to evaluating the venom's effect on cell survival and morphology, its protein content, molecular weight, and lethal dose were determined. Using just in vitro cancer cell lines (A549, HeLa, and MDA-MB-231) and not testing on normal cells or using in vivo models limits the study's findings' translational usage . In order to support the therapeutic development of bee venom, future studies should investigate its anticancer action mechanisms, safety, and in vivo efficacy. Although delivery issues like hemolytic activity necessitate more research, the results indicate that bee venom, especially its essential peptide melittin, has potential as a natural anticancer drug.

Gyeong Bok Jung et al (2018) [16] conducted a in vitro experimental study demonstrates that bee venom (BV) induces apoptosis in human MDA-MB-231 breast cancer cells, a triple-negative cell line using Raman spectroscopy combined with principal component analysis (PCA), Raman signals for proteins and DNA were significantly reduced after BV treatment indicating biochemical alterations such as DNA fragmentation and protein denaturation. These spectrum findings were verified by atomic force microscopy (AFM) and standard assays including cell viability tests, TUNEL staining, and Western blots revealing apoptotic markers. The work emphasizes Raman spectroscopy with PCA as a label-free, noninvasive method for tracking cellular alterations brought on by BV in cancer treatment. The study's in vitro focus on a single breast cancer cell line and lack of in vivo validation, technical limitations and safety concerns with bee venom limits the study's conclusions. Additional research should evaluate the safety and selectivity of bee venom, confirm its anticancer properties in vivo, and investigate Raman spectroscopy for current therapy monitoring.

Vikram Jadhav et al (2024) [17] This study reports the green, hydrothermal synthesis of Apis mellifera bee venom nanoparticles (BVNPs), In order to conserve the bioactive components of venom, such as melittin and apamin, while maintaining good colloidal stability (zeta potential ≈ –45 mV) Significant anticancer potential was demonstrated by the evident dose-dependent cytotoxic effect observed in in vitro experiments against MCF-7 breast cancer cells. In vitro cytotoxicity against a single breast cancer cell line (MCF-7) is its only use; in vivo efficacy, and safety in more complicated models are not explored. More effort is required to increase efficacy because BVNPs' IC_{50} is significantly higher than methotrexate's, indicating less potency. It is also necessary to

look into pharmacokinetics, long-term stability, and possible off-target effects. In order to maximize the therapeutic potential of BVNPs, future research will concentrate on improving their biocompatibility by surface modification. All things considered, these results confirm that hydrothermal synthesis is a practical technique for creating structurally stable, physiologically active BVNPs, which makes them excellent options for further anticancer studies.

Ciara Duffy et al (2020) [18] Melittin, the primary component in honeybee venom, has strong and specific cytotoxicity against aggressive breast cancer subtypes, particularly triple-negative and HER2-enriched cells, while leaving healthy cells unaffected. This selectivity results from melittin's disruption of growth signaling through the PI3K/Akt and MAPK pathways, which interferes with the phosphorylation of EGFR and HER2 receptors. Melittin's membrane targeting is mediated by its positively charged C-terminal domain, and its cancer-cell selectivity is further improved by the addition of an RGD motif. Additionally, melittin increases docetaxel's effectiveness in mouse allograft models, highlighting its promise as a combinatorial treatment approach. The study's findings are based only on mouse and lab models; there is no evidence of human safety or effectiveness to warrant clinical translation. For clinical translation, more research should concentrate on improving melittin delivery techniques and evaluating its safety and dosage.

Siu-Wan Ip et al (2007) [19] According to the article "The Role of Mitochondria in Bee Venom-induced Apoptosis in Human Breast Cancer MCF7 Cells," the mitochondrial (intrinsic) route is the main mechanism by which bee venom (BV) causes apoptosis. BV treatment caused cytochrome c release, ROS production, and a decrease in mitochondrial membrane potential ($\Delta\psi m$), which in turn caused caspase-9 activation and PARP breakage. Additionally, it changed the expression of Bcl-2/Bax, which encouraged mitochondrial instability. Furthermore, BV elevated EndoG and AIF, suggesting a caspase-independent mechanism. Its pro-apoptotic effects were further supported by nuclear condensation, DNA damage, and S-phase cell cycle arrest. Limitations: There was no in vivo or clinical validation, and the study was limited to MCF7 cells cultured in vitro. Safe dosage levels and selectivity for cancer versus healthy cells were not evaluated. Cancer is a complex condition marked by unchecked cell division and growth, which results in the formation of tumors and their spread to other parts of the body. Conventional approaches like chemotherapy and radiation often cause considerable adverse effects, prompting the pursuit of more precise and less harmful treatment options Noor et al [20] and both aloe vera and apitoxin suppress cancer cell proliferation in similar mechanism [21]. Other pathways remained unexplored as mechanistic discoveries were primarily restricted to mitochondrial apoptosis. Further investigations should include in vivo animal models, testing on normal cells, and extensive toxicity profiling. More thorough mechanistic study, combination therapy inquiry, and the development of tailored delivery systems are needed to support clinical translation.

CONCLUSION

This systematic review shows that melittin, the main component of honey bee venom (apitoxin), has significant anticancer potential against numerous breast cancer subtypes, especially triple-negative and HER2-enriched cells. In all of the examined investigations, melittin and bee venom demonstrated dose- and time-dependent cytotoxicity, including cell cycle arrest, ROS production, mitochondrial dysfunction, and apoptosis. Interestingly, these effects were relatively less harmful to normal cells, but they were particularly noticeable in aggressive breast cancer phenotypes, such as triple-negative and HER2-enriched cell lines. Apitoxin's adaptability is further highlighted by new formulations such bee venom-derived nanoparticles, which improve stability and biocompatibility. Combination treatments, especially melittin with chemotherapeutic drugs like docetaxel, show improved therapeutic synergy. However, the available data is still restricted to in vitro results, despite encouraging preclinical results. There are still significant gaps in the areas of targeted delivery, pharmacokinetics, in vivo efficacy, and possible systemic toxicity.

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