International Journal of Entomology Research
www.entomologyjournals.com
ISSN: 2455-4758
Received: 02-12-2025, Accepted: 01-01-2026, Published: 16-01-2026
Volume 11, Issue 1, 2026, Page No. 93-101

Bee Venom as a potential anticancer therapeutic: Clinical significance and mechanistic insights: A detailed review

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Abstract
Toxins derived from diverse creatures have been employed for many years in unconventional and Oriental medicine, with the most research done on Apis mellifera venom. Bee venom's (BV) advantageous qualities have been the subject of numerous investigations. Apitherapy, which is mostly based on the experience using the traditional medical system in various ethnic communities, is the use of honey and other honey-based products to both prevent and treat diseases. The anticancer properties of BV, which are mostly ascribed to its basic polypeptide melittin (MEL), are the subject of numerous investigations nowadays. According to earlier research, BV and its main component, MEL, have a substantial toxic effect on a variety of cancer cells, including those of the liver, lung, my bladder, the kidneys, the prostate, breast, and leukaemia, while normal non-target cells showed a less noticeable effect. The phosphorylation of the phospholipase A2 enzyme (PLA2), MAP kinase, and matrix metalloproteinases, which are proteins that kill cancer cells is linked to their suggested mechanisms of action, which include effects on proliferation along with development inhibition, cell cycle modifications, and induction of cellular death through multiple cancer cell death mechanisms. A variety of medications were given, such as phospholipase A2, melittin, crude bee venom, and their complexes. In proportional to the dosage and duration, all medications decreased the quantity of breast cancer cells. Cytotoxicity, the death of cell targeting, and modulation of gene expression were among the mechanisms of anticancer actions. Cell lysis. In summary, human breast cancer cells are affected by the anticancer properties of bee venom as well as its constituents. It is anticipated that using different vehicles will lessen side effects, depending on how they work of anticancer actions. In the future, the venom from bees and its constituents may be used in the prevention and treatment of breast cancer.

Keywords: Natural products, apitherapy, apitoxin, Bee venom, Phospholipase A2, Breast cancer

Introduction

Pharmaceuticals derived from both animals and plants consistently contribute significantly to health in terms with the prevention as well as treatment of several diseases, despite the notable advancements in contemporary medicine Asia is the source of several medicines that are widely utilized in Western nations, and their acceptance is growing quickly. Animal venoms, particularly those from insects, have long been employed in scientific studies and are currently used to make a variety of goods and medications with possible medical uses [1]. Breast cancer can be divided into three subtypes based on the presence of molecular markers, including receptor for hormones positive/human epidermal stimulating factor receptor II gene (ERBB2) absence of the ERBB2 positive, and double-negative The median 5-year survival rate for all stages combined is 90%, which is the third highest overall survival rate among serious cancers in the United States However, just like the stage advances, the probability of survival also decreases dramatically Thirty percent of all newly recognised malignancies are breast cancer, making it as one of those most prevalent tumours among women The American Cancer Society's reports that in 2020 [2]. there were around 2.3 million new cases of breast cancer identified and 685,000 deaths from the disease, making it the seventh most common cause of cancer-related death globally [3]. With a relative survival rate for five years of nearly ninety percent for all stages combined, female breast cancer currently has the third-highest survival rate across major malignancies in the US [4].

Venom of Bees

Bees employ BV, a secretion from their venom gland, as a warning signal and to protect their nests from the attacker. A volatile portion of the venom is thought to evaporate following a bee sting and alert other bees to the presence of an adversary. BV is located in the bee's abdominal cavity, which has a short canal leading to the stinger on one side and a venom gland that secretes venom on the other. Venom is produced by the venomgla and flows into the stinging gland. Bees have the most venom in their glands a few weeks following metamorphosis. The amount of poison steadily drops as it flies and gathers nectar. A bee injects 50–140 µg of venom when it stings. The bee stinger is made up of two parallel needles that discharge venom into a channel and includes hooks for more profound penetration and adhesion. When it stings, the stinger, which is found in the abdomen, is expelled. Because of its unique structure, bees are unable to remove the stinger after a sting, and both the stinger and the venom gland stay in the vertebrate's skin. The bee perishes when the muscles supporting the framework rupture [5].

BV has detrimental consequences on the entire body of mammals, particularly the neurological and cardiovascular systems.In the human body, BV causes an inflammation response that manifests as swelling, redness, alongside pain

at the place of administration site; the most hazardous instances are stings in the mouth, tongue, or eyeball; a large amount during BV can also be fatal in certain cases, and death can result from the bronchial contractility that arises in response to the immobility of the brain centre responsible for breathing. The stinging substance itself causes the degeneration of circulation cells, reduces the likelihood of blood clotting, along with improves the permeability regarding blood vessels, as evidenced by bleeding and inflammation in internal organs. This apparatus is positioned near the bee hive's entrance. An electric field causes angry bees to release their venom straight onto the slide, where it is scraped following drying. BV is a dense drink with a distinct honey-like smell and a sour, bitter flavour. When lyophilised BV is dried without the liquid phase, it turns into a volatile powder that ranges in colour from light grey to grayish-yellow Therefore, in accordance with the manufacturer's directions, BV is stored in tightly packed containers at −20 °C [6].

Bee Venom's Composition

Water, which comprises roughly 88% of the animal venom itself, is the primary component of BV. Peptide compounds such as melittin (MEL), apoptotic secapin, procamine A and B, adolapin, tertiapin, as mast cellphone degranulating (MCD) peptide are among the other dry components of BV. Phospholipase A2 (PLA2) and, to a lesser extent, phospholipase B (PLB), the hyaluronidase enzyme, acid phosphomonoesterases, or lysophospholipase, and α-glucosidase are the predominant enzymes in BV. A number of naturally occurring amines and neurotransmitter (histamine, dopamine, and noradrenalin) along with both fructose and glucose, the phospholipids, amino acids, amino acids, and larger concentrations of mineral compounds make up BV Almost every one of these elements found in BV has some impact on a variety of cell systems [7].

1. Melittin

MEL is a significant toxin and component of BV. containing, according to literature data, over 50% of the dry venom.MEL is a basic peptide with a molecular weight of 2847.5 Da that consists of the 26 known amino acid sequences (Figure 3). Gly-Ile-Gly-Ala-Val-Leu-Lys-Val-Leu-Thr-Thr-Gly-Leu-Pro-Ala-Leu-Ile-Ser Trp-Ile-Lys-Arg-Lys-Arg-Gln-Gln is the peptide amino acid Because of the particular arrangement of amino acids in a chain, MEL is an amphoteric molecule.Non-polar, hydrophobic, and neutral amino acids are found at the N-terminus while hydrophilic and basic amino acids are found at the C-terminus According to available evidence, MEL is toxic to intestinal cells and haematopoietic cells, such as lymphocytes, erythrocytes, and thymocytes [8].Additionally, MEL may affect a number of cell metabolic processes by disrupting the plasma membrane's functions and altering the enzymatic system, though its lytic action is mostly associated with the potential to integrate into the phospholipid bilayer of the cell membrane [9]. may affect a number of cell metabolic processes by disrupting the plasma membrane's functioning and altering the enzymatic system, although its lytic activities is mostly associated with the potential for integration into the cell membrane's

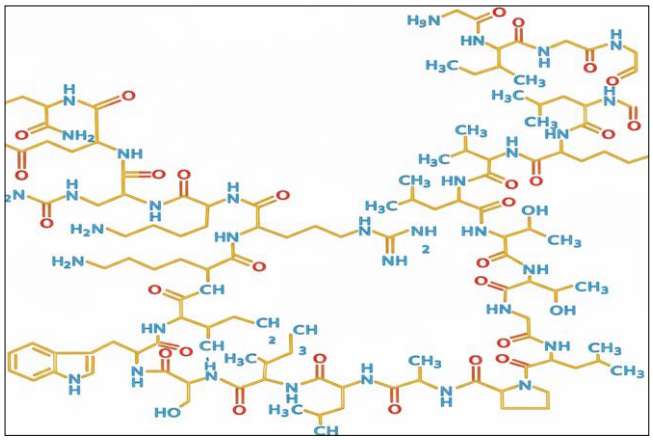

Fig 1: Chemical structure of Melittin [10]

2. Apamin

With a molecular weight of 2027.3 Da, apamin, the BV neurotoxin, is a relatively tiny basic peptide made up of 18 amino acids and two disulphide bridges, giving it a highly solid structure (Figure 4). Cys-Tyr-Cys-Lys-Ala-Pro Glu-Thr-Ala-Leu-Cys-Ala-Arg-Arg-Cys-Gln-Gln-His is the apaminamino acid sequence [89,90]. The peptide is neurotoxic. With a molecular weight of 2027.3 Da, apamin, the BV neurotoxic, is a very tiny basic peptide made up of 18 amino acids and two disulphide bridges, making the structure incredibly rigid Cys-Tyr-Cys Lys-Ala-Pro-Glu-Thr-Ala-Leu-Cys-Ala-Arg-Arg-Cys-Gln-Gln-His is the amino acid sequence of apamin [11]. Muscle spasms result from the peptide's neurotoxic effects in the spinal cord of mammals. Additionally, apamin selectively inhibits calcium-dependent potassium channels.

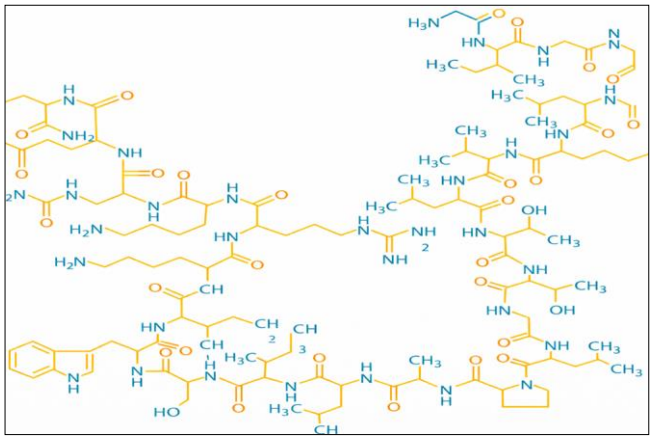

Fig 2: Chemical structure of Apamin [12]

3. Mast Cell Decaying Peptide (MCD)

The MCDpeptide has a molecular amount of 2587.2 Da and is a basic neuropeptide made up of 22 amino acids, each with two disulphide bridges (Figure 5). The amino acid sequence of the MCD peptide [95]. At low concentrations, the MCD peptide inhibits potassium channels by causing degranulation of mast cell and histamine release. Additionally, this peptide causes both the allergic reaction and the bruising and pain following a sting [13].

4. A2 phospholipase

The most significant enzyme in BV, PLA2, makes up almost 10% of the dry venom. This enzyme produces a variety of biological effects by catalysing the hydrolysis of

the sn-2 greasy acyl-ester link of membrane glycero-3-phospholipids. These substances are hydrolysed to produce lysophospholipids. Biological membranes are similarly impacted by PLA2 and its hydrolysis products. The cell membrane is lysed when this enzyme and MEL are combined. The byproducts of this enzyme's hydrolysis, unsaturated fatty acids, serve as building blocks for the production of inflammatory mediators such prostaglandins and leukotrienes [14].

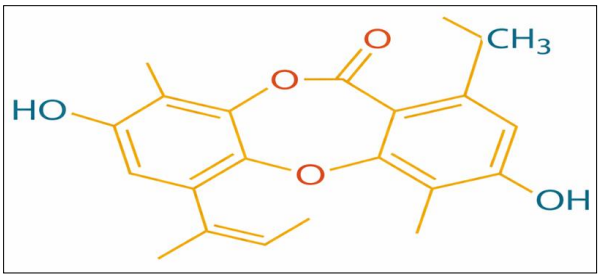

Fig 3: Chemical structure ofA2 phospholipase [15]

The Therapeutic Properties of Bee Venom

Apitherapy has its roots in ancient Egyptian medicine, which dates back 6000 years. Additionally, a number of bee products were employed for therapeutic purposes by the ancient Greeks and Romans. Hippocrates, the works of Aristotle, Pliny, and Galen's ancient literature contain the earliest documented accounts of the use of BV as a medicinal agent. Russian and Austrian medical periodicals from the 19th century described rheumatism, neuralgia, and aching joints. Bee stings have been used to treat aching joints, rheumatism, neuralgia, and pain in the heart [16]. BV is used in traditional medicine, particularly in Oriental medicine, to treat rheumatism, relieve pain, and decrease blood pressure and cholesterol. Additionally, BV has been employed for overall immunological resilience as well as to treat specific inflammations and infectious illnesses. A direct honeybee sting in the targeted body location was the earliest and only viable treatment for BV in traditional medicine. In addition to a direct beehive sting, BV-based acupuncture, also known as apipuncturewasVenom was injected subcutaneously into the afflicted area along with acupuncture sites when methods for isolating BV were developed [17].

Anticancer Effects of Bee Venom and Its Components

1. Anticancer Effects of Bee Venom

Numerous researches are currently being carried out to investigate the antitumor effect of BV against various cancer types and its mechanism of action. MEL, a basic polypeptide that accounts for around half of the dry BV, is primarily responsible for the anticancer action. One of the earliest researchers to document the effect that BV on malignant cells was Havas [18]. The ability of MEL to flow through a phospholipid bilayer was later observed by Mufson and associates the relationship between MEL and cell membranes resulted in increased production of prostaglandins through arachidonic acid released from phospholipids, impairment of the phospholipid's acyl groups, and increased sensitivity to phospholipid hydrolysis by phospholipase. Additionally, while life expectancy from different illnesses was comparable to that of the general population, beekeepers who were substantially exposed to BV during their working lives had a somewhat reduced incidence of cancer deaths and a much lower rate of death from lung cancer. The results were probably the first to indicate that BV might have anticancer properties. Subsequent research revealed that BV and its main component has anticancer effects.

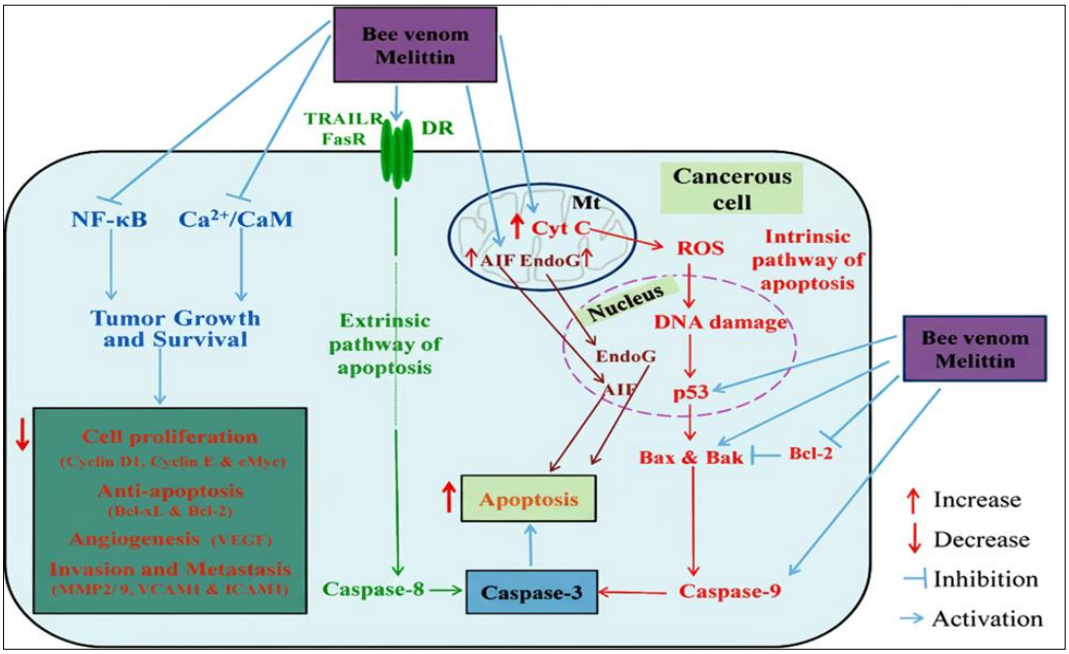

Fig 4: Schemetic diagram of Anticancer Effects of Bee Venom [19]

2. Melittin's Anticancer Effect

MEL's inhibitory potential was initially shown *in vitro* demonstrated how MEL, as a calmodulin inhibitor, prevents human leukaemia cells from proliferating and becoming clonogenic. Additionally, Lee and Hait for example, have observed that MELonastrocytomacell development is inhibited. According to Lazoetal. [MEL inhibits calmodulin in leukaemia cells through a similar mode of action.

Additionally, they observed that MEL increases bleomycin toxicity in colonies of erythroid stem cells and human granulocyte macrophages. Furthermore, Killion and Dunn and colleagues [20]. demonstrated that leukaemia cells are more dependent on MELaction than conventional mouse lymphoid cells and cells from the bone marrow. This was explained by the fact that bone marrow cells have multiple carbohydrate attachment points on the membrane, which vanish in adult spleen cells and are nearly absent following neoplastic alterations that may increase cancer cells' sensitivity to the peptide. MEL does not stop normal cell growth at a dose that stops cancer cells, including lung cancer cells, from proliferating.A. MEL has shown exceptional efficacy in cultivated cells with elevated ras oncogene expression Additionally, MEL increases PLA2 activation in ras oncogene-transformed cells, which leads to its targeted death. The findings imply that MEL's cytotoxicity against cancer cells may target the increased activation of the PLA2 by MEL [21].

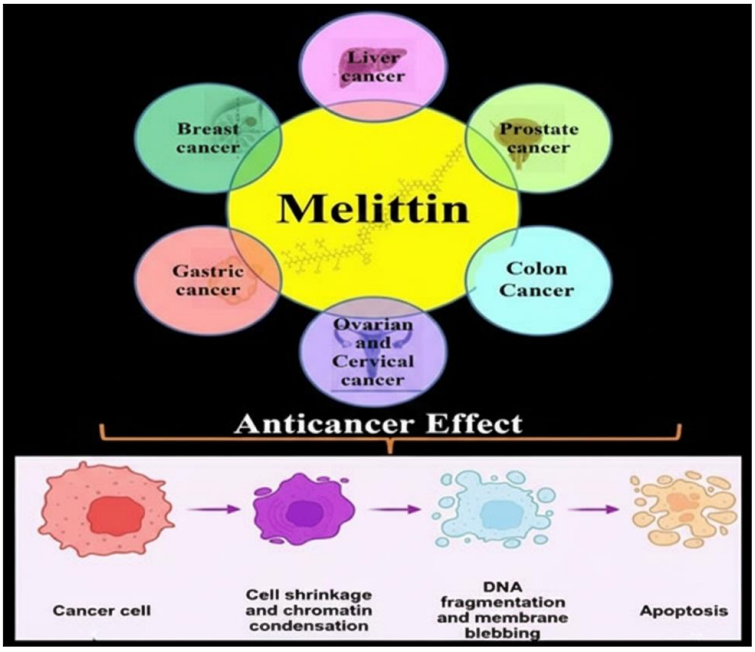

Fig 5: Anticancer potential of melittin in various preclinical cancer models [22]

3. Anticancer Effects of Phospholipase A2

AMEL's Anticancer Effects Increased stimulation of PLA2 activity and calcium intake in Ras-transformed cells may be the reason of this compound's anticancer activity [23] Following these discoveries, other investigations linked PLA2 activity to MEL's cytotoxic action on a range of tumour cells [24]. Through a variety of cell alterations, including a synergistic action of PLA2 and a substance called (3,4)-bisphosphate in initiating the process of cell death, activation of PLA2 may contribute to the cytotoxicity of tumour cells [25]. Additionally, it was discovered that their combined action produces a tumour lysate that promotes the development of immunostimulatory dendritic cells produced from human monocytes. All the components required for a potential tumour vaccination are present in such a tumour lysate, which is a complicated mixture of tumour antigens with potential action.

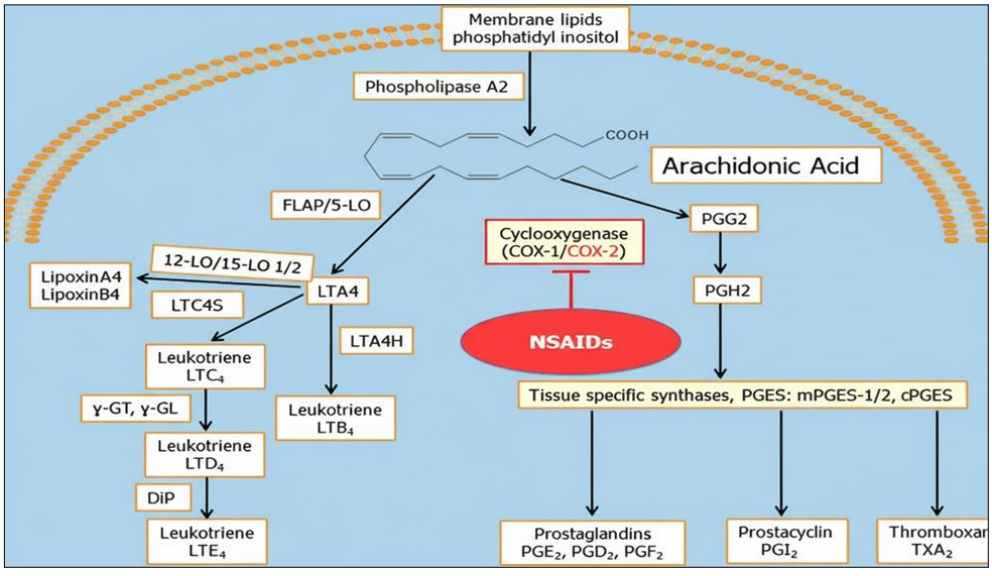

Fig 6: Schematic for arachidonic acid pathway [26]

4. The Mechanisms of Bee Venom and Melittin Anticancer Activity

Drug consumption should therefore be appropriate and targeted. The amphipathic nature of several insect lithic protein molecules, including those extracted from BV, allows them to attach and integrate into negatively charged cell membranes. The membrane potential of cancer cells is higher than that of normal cells [27]. As a result, certain lytic peptides specifically damage the structural makeup of the membrane of cancerous tumour cells. compared to the typical cell membrane. Therefore, MEL should have a suitable function in anticancer therapy Thus, the substance is toxic to ovarian cancer cells, and the toxicity is dose-dependent, according to Apoptosis caused by bee venom has been seen *in vivo* and *in vitro*. BV prevents melanoma cancer cells from proliferating *in vitro* and *in vivo*. One of the potentials ways by which BV reduces proliferation and causes differentiation of those same cells throughout *vitro* was thought to be the apoptosis seen in those cells. Additionally, cyclooxygenase 2 (COX-2) suppression in lung cancer cells [28]. and elevated Fas expression in osteosarcoma cells were found to cause apoptosis. These findings suggest that BV and MEL's anticancer action may be influenced by the induction of apoptosis, while the exact mechanisms back this induction remain unclear. Furthermore, it has been demonstrated that MEL gene therapy induces apoptosis in cancer cell also discovered revealed these peptides could effectively kill liver carcinoma cells inside of *vitro* and *in vivo*, which is in line with the growing interest in the potential use of BV peptides in anticancer therapy. Once more, apoptosis-induced cell death is a key method by which these peptides limit the growth of cancer. Oršoli'c and associates

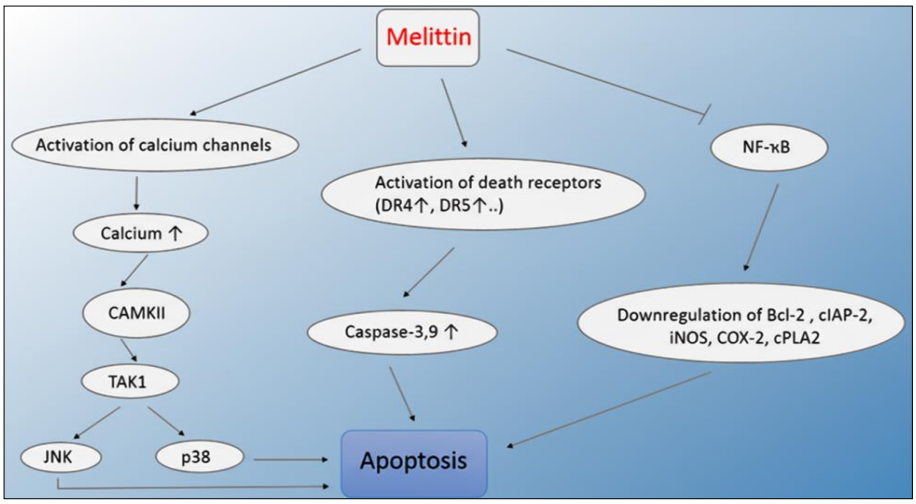

Fig 7: Schematic drawing of main mechanisms of action of melittin as an anti-cancer agent [29]

Discussion

1. Cytotoxic Activity

Melittin and chemotherapeutic drugs may work well together as a synergistic treatment since cancer cells are more unlikely to become resistant to a cell membrane pore forming [30]. All drug formulations, including melittin, doxorubicin, and doxorubicin/ melittin-loaded the citric acid-activated Fe3O4 magnetic nanoparticles (doxorubicin/melittin-loaded CA-MNPs), reduced cell growth in a dose-dependent manner, and doxorubicin and melittin administered together showed a synergistic effect on MCF-7 breast cancer cell proliferation, [31]. Doxorubicin/melittin loaded CA-MNPs demonstrated superior cytotoxic action compared to free doxorubicin/melittin because anticancer medications were more efficiently transported into cells via internalised nanotechnology at the same dose. It is crucial to lower the dosage of melittin, a peptide present in bee venom, for the treatment of cancer because known to produce haemolysis and nonspecific cytotoxicity. By mixing melittin with plasma-treated phosphate-buffered ordinary saline (PT-PBS), which can cause cancer cell death via oxidative stress-mediated pathways, tried to reduce the dosage of melittin. Melittin by itself caused apoptosis, lipid peroxidation, and a dose-dependent cytotoxic impact in MCF-7 cells. On the other hand, a synergistic impact was noted when synthesised with PT-PBS. This action is believed to be due to melittin's enhanced potential through the membrane of a cell during plasma-induced oxidative of phospholipids, since melittin is not oxidised by plasma. confirmed the cytotoxic and necrotic effects of the venom from bees by giving MCF-7 cells bee venom with respect to the dose. In a three-dimensional culture, the findings about the decrease in the longevity of cells and the suppression of cellular development were validated. As in previous research, a 3D culture showed a stronger response to the cytotoxic action of bee venom than a 2D culture.

2. Apoptosis Activity

Apoptosis is a sophisticated human defence mechanism that is genetically regulated by viral infection, DNA damage, and particular stages of occurrence [32]. It can be the primary reason for a divergence from the regular cell cycle and is crucial in eliminating damaged cells at the individual conservation level [33]. investigated the apoptotic consequences of stings from bees in the cell line MCF-7 by calculating the coefficient of cells that were alive, morphological alterations, biochemical alterations, and changes in gene expression. When combined, their findings showed a connection between the development of apoptosis and the inhibition of human breast carcinoma cell proliferation brought on by bee venom. In a similar vein, melittin is parasitic and can cause defects, disruption, including pore formation in the tumour cell membrane

bilayer. Melittin has an exceptional anticancer impact, but it is known to be harmful to healthy cells, so a suitable vehicle is needed to provide the therapeutic effect. However, it has been *et al*. [34] shown that melittin may be hazardous to cells with tumours and that the amount being administered was effective just prior to its effects on normal cells. Additionally, as supported by other research,

3. Cell Targeting

In comparison to normal cells, fibroblast activation protein-α (FAP) gene expression was found to be considerably higher in a prior study FAP, a tumour stromal antigen generated by cancer-associated fibroblasts, was assessed] as a tumor-specific target [35]. Their research showed that FAP's enzyme activity might be utilised to selectively stimulate high-intensity cytotoxins in peritumoral injection, notwithstanding FAP's role in tumours. Tumour cells may die as a result of this activation, creating a synergistic impact that kills tumours both inside and outside the stromal compartment. Although cell targeting presents been shown to be effective, it has a drawback in that it must be done intratumorally and inside the organ.

4. Regulating Gene Expression

A class of enzymes known as matrix metalloproteinases (MMPs) is necessary for the breakdown of extracellular matrix in order for cancer cells to proliferate at metastatic sites [36]. Human cancer cells invade and spread thanks in large part to MMP-9 [37]. bee venom directly prevented MCF-7 cells from invading and migrating by decreasing the expression of MMP-9, but it did not eliminate the expression of tissue antagonists of metalloproteinases-1 and -2. Melittin was one of the ingredients of the honeybee's venom that inhibited p39, the transcription factor JNK, and NF-Kb production, which in turn inhibited MMP-9 enzyme activity. demonstrated how melittin and bee venom dynamically modulated the downstream signalling system of carcinoma of the breast cells by preventing the phosphorylation of HER2 and EGFR ligands. Additionally, melitin was more lethal than bee venom and reacted more selectively to breast cancer cells that overexpressed HER2 and EGFR [38].

5. Cell Lysis

When re-injected into patients, monocyte-produced dendritic cell populations (moDCs), which are generated in peripheral blood precursor cells loaded with tumour lysates or antigen, trigger anticancer immune responses [39]. The maturation of moDCs is caused by phospholipase A2 through its activation of enzymes and NF-kB, activating protein-1, a nuclear component that activated T-cells, according to a prior study in an effort to prevent the synergistic impact between phospholipase A2 (bv-sPLA2) and phosphatidylinositol (3,4)-bisphosphate (PtdIns (3,4) P2) that occurs during the formation of immunostimulatory moDCs driving tumour cell lysis,

Clinical Data

Study / Trial	Type of Study	Cancer Model / Context	Key Findings	Reference
– General human clinical trials	Clinical trials (human)	Any type of cancer	No registered results showing effectiveness of bee venom for cancer in humans. According to systematic reviews and evidence summaries, there are no human cancer clinical trials proving efficacy; bee venom apitherapy is listed as unproven for cancer treatment.	[40]
In vitro: Tongue squamous cell carcinoma (TSCC)	Laboratory cell culture	Human TSCC cell line (HNO-97)	Bee venom showed dose-dependent cytotoxicity, induced apoptosis, caused cell cycle arrest, and reduced migration at IC_{50} ~12.96 µg/mL.	[41]
In vitro: Combination with thymoquinone (TQ)	Laboratory cell culture	HeLa (cervical), MCF-7 (breast), HCT (colon) cancer cell lines	The BV + TQ combination showed synergistic reduction in cell viability, increased apoptosis, and cell cycle arrest	[42]
In vitro + *in vivo*: Colon cancer cells & tumor growth	Lab + animal experiments	HCT116 & SW480 colon cancer cells; mice tumor models	BV induced apoptosis, increased death receptor expression, inhibited NF-κB, and suppressed tumor growth *in vivo*.	[43]
In vitro: Pancreatic cancer cells	Cell culture	AsPC-1 & PANC-1 pancreatic cancer cells	BV suppressed proliferation, caused cell cycle arrest, and induced apoptosis in a dose-dependent manner.	[44]
Review: Breast cancer cell studies	Literature review	Various breast cancer cell lines	BV and components (melittin, PLA_2, etc.) reduced breast cancer cell viability *in vitro* with multiple anticancer mechanisms reported.	[45]
In vitro: Leukemia (K562)	Laboratory cell culture	K562 human leukemia cells	Crude BV and melittin exhibited cytotoxic effects with IC_{50} ~3.7 µg/mL (JCBV) and ~1.84 µg/mL (melittin).	[46]
Clinical trial registry: Bee venom phonophoresis (non-cancer)	Registered trial	Not cancer	A clinical trial exists for bee venom phonophoresis (e.g., ulcers) but not for cancer therapy; no data shows BV efficacy for cancer patients.	[47]
Clinical trials of bee venom preparations (historical)	Clinical research	Not specific to cancer therapy	Some older studies looked at safety/effects of bee venom for non-cancer conditions; none supports cancer treatment.	[48]

Future Prospects

Numerous natural substances, vegetables, and spices have been utilised to cure a wide range of illnesses, including cancer, since ancient times Chemoprevention, a phrase coined in the late 1970s, refers to the use of chemicals, typically derived from plants, to prevent and treat tumours. These substances are being investigated in the field of chemoprevention research to determine their possible efficacy in recent years, there has been a significant growth in the use of natural products as chemotherapy-preventing agents, and many of these chemicals are being studied on various models. Many of the chemicals and compounds that

showed promise in experimental settings are currently undergoing pre-clinical research, and scientists are still trying to figure out the precise mechanism of action for many of them. Folk medicine has long used insects or their products to treat a wide range of illnesses. Several studies suggest that using those products in addition to traditional therapies could be very beneficial in the fight against a number of challenging but avoidable diseases. Experimental testing has previously been done on a few potential treatments Bee products, such as honey, have been used to heal burns and chronic and post-surgical wounds, and they have frequently shown themselves to be just as successful as conventional pharmaceutical preparations. Additionally, a number of dermatological conditions, such as psoriasis, dermatitis, and various fungal skin illnesses, can be effectively treated with beeswax [49].

Conclusion

In addition to the conventional uses of BV, contemporary science has started investigating the potential anticancer properties of both BV and its constituent parts. MEL the PLA2, both of whose activity is enhanced by MEL, as well as a number of other short peptides such apamin and MCD peptide, are necessary for BV toxicity Both Oriental and Western medicine frequently do research on the therapeutic uses of natural substances originating from plants and animals. Many of these research focus on how different cancer cells are affected by venoms, particularly BV. Numerous studies that are now available indicate that this toxin may be used to treat different types of cancer. However, it is still unclear exactly how this anticancer effect works. Activation of PLA2, the formation of matrix and proteins called caspases that can kill cancer cells are some of the causes of BV and MEL The improvement of cancer treatment may involve the association of MEL with hormones receptor and the application of MEL in gene therapy observed that the recombinant virus containing the MEL gene had an inhibitory effect on carcinoma both *in vitro* and *in vivo*, and may be another strategy for fighting cancer.Thus far, studies have demonstrated that both pure bee venom and MEL have a strong anticancer potential through apoptosis induction and cell cycle inhibition without appreciably harming physiological cells. Furthermore, a growing body of research on animals shows that venom concentrations that work well *in vitro* are harmless. Breast cancer is the most frequent cancer among women globally, and the total amount of women receiving a breast cancer diagnosis is rising annually as a result of advancements in diagnostic technology and lifestyle modifications. Although anticancer medication and surgery are common therapies for breast cancer, patients' quality of life declines throughout treatment due to side effects.Inhibition of tumour and metastases growth, suppression of tumour proliferation, decreased angiogenesis, the decrease of tumour size, and induction cell apoptosis were shown in studies conducted primarily on mice and rats using either whole BV or To the best of our knowledge, there are currently no human clinical trials that could verify the clinical efficacy of bee venom and assess the safety of its delivery with regard to cancer treatment, despite the fact that a number of clinical trials have either been completed or are recruiting for other disorders [50].

Reference

1. Harvey A. From Demons to Darlings: Drugs from Venoms. Drug Discovery Today,1998:3:531–532.
2. von Reumont BM, Anderluh G, Antunes A, Ayvazyan N, Beis D, Caliskan F, *et al*. Modern Venomics-Current Insights, Novel Methods, and Future Perspectives in Biological and Applied Animal Venom Research. Gigascience,2022:11:048.
3. Sung HA, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, *et al*. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians,2021:71:209–449.
4. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics 2021. CA: A Cancer Journal for Clinicians,2021:71:7–33.
5. Mebs D. Venomous and Poisonous Animals: A Handbook for Biologists, Toxicologists and Toxinologists, Physicians and Pharmacists; CRC Press: Boca Raton, FL, USA, 2002. ISBN 0849312647.
6. Chen J, Lariviere WR. The Nociceptive and Anti-Nociceptive Effects of Bee Venom Injection and Therapy: A Double-Edged Sword. Progress in Neurobiology,2010:92:151–183.
7. Obeidat M, Al-khraisat IF, Jaradat DMM, Ghanim BY, Abdallah QM, Arqoub DA, *et al*. Mellitin Peptide Quantification in Seasonally Collected Crude Bee Venom and Its Anticancer Effects on Myelogenous K562 Human Leukaemia Cell Line. BMC Complementary Medicine and Therapies,2023:23:132.
8. Shier WT. Activation of High Levels of Endogenous Phospholipase A2 in Cultured Cells. Proceedings of the National Academy of Sciences of the United States of America,1979:76:195–199.
9. Lad PJ, Thomas Shier W. Activation of Microsomal Guanylate Cyclase by a Cytotoxic Polypeptide: Melittin. Biochemical and Biophysical Research Communications,1979:89:315–321.
10. Miao V, Coëffet-Le Gal MF, *et al*. Daptomycin biosynthesis in *Streptomyces roseosporus*: cloning and analysis of the gene cluster and revision of peptide stereochemistry. Microbiology,2005:151(5):1507–1523.
11. Habermann E. Apamin. Pharmacology and Therapeutics,1984:25:255–270.
12. Currie MG, *et al*. Guanylate Cyclase C Agonists: Genesis of Linaclotide. Proceedings of the National Academy of Sciences of the United States of America, 2005.
13. Buku A. Mast Cell Degranulating (MCD) Peptide: A Prototypic Peptide in Allergy and Inflammation. Peptides,1999:20:415–420.
14. Valentin E, Lambeau G. What Can Venom Phospholipases A2 Tell Us about the Functional Diversity of Mammalian Secreted Phospholipases A2? Biochimie,2000:82:815–831.
15. Taguchi H, Sankawa U, Shibata S. Biosynthesis of Usnic Acid and Isousnic Acid. Chemical and Pharmaceutical Bulletin,1969:17(10):2054–2060.
16. Salcido R. Honey, Is Apitherapy an Emergency? Advances in Skin and Wound Care,2008:21:552.
17. Doery HM, Pearson JE. Phospholipase B in Snake Venoms and Bee Venom. Biochemical Journal,1964:92:599–602.
18. Havas LJ. Effect of Bee Venom on Colchicine-Induced Tumours. Nature,1950:166:567–568.

19. Killion JJ, Dunn JD. Differential Cytolysis of Murine Spleen, Bone-Marrow and Leukemia Cells by Melittin Reveals Differences in Membrane Topography. Biochemical and Biophysical Research Communications,1986:139:222–227.
20. Zhu H, Tayeh I, Israel L, Castagna M. Different Susceptibility of Lung Cell Lines to Inhibitors of Tumor Promotion and Inducers of Differentiation. Journal of Biological Regulators and Homeostatic Agents,1991:5:52–58.
21. Hamza AA, Lashin I. Melittin as a potential natural weapon against cancer: An updated review of its molecular mechanisms and therapeutic applications. Journal of Applied Pharmaceutical Science,2023:13(06):001–015.
22. Arora AS, de Groen PC, Croall DE, Emori Y, Gores GJ. Hepatocellular Carcinoma Cells Resist Necrosis during Anoxia by Preventing Phospholipase-Mediated Calpain Activation. Journal of Cellular Physiology,1996:167:434–442.
23. Wu YL, Jiang XR, Newland AC, Kelsey SM. Failure to Activate Cytosolic Phospholipase A2 Causes TNF Resistance in Human Leukemic Cells. Journal of Immunology,1998:160:5929–5935.
24. Saini SS, Chopra AK, Peterson JW. Melittin Activates Endogenous Phospholipase D during Cytolysis of Human Monocytic Leukemia Cells. Toxicon,1999:37:1605–1619.
25. Wang B, Wu L, Chen J, Zhao L, Yi R, Zhan Y, *et al*. Metabolism pathways of arachidonic acids: mechanisms and potential therapeutic targets. Signal Transduction and Targeted Therapy,2021:6(1):94.
26. Moon DO, Park SY, Heo MS, Kim KC, Park C, Ko WS, *et al*. Key Regulators in Bee Venom-Induced Apoptosis Are Bcl-2 and Caspase-3 in Human Leukemic U937 Cells through Downregulation of ERK and Akt. International Immunopharmacology,2006:6:1796–1807.
27. Jang MH, Shin MC, Lim S, Han SM, Park HJ, Shin I, *et al*. Bee Venom Induces Apoptosis and Inhibits Expression of Cyclooxygenase-2 MRNA in Human Lung Cancer Cell Line NCI-H1299. Journal of Pharmacological Sciences,2003:91:95–104.
28. Chen YQ, Zhu ZA, Hao YQ, Dai KR, Zhang C. Effect of Melittin on Apoptsis and Necrosis of U2OS Cells. Journal of Chinese Integrative Medicine,2004:2:208–209.
29. Wang C, Chen T, Zhang N, Yang M, Li B, Lu WP, *et al*. Melittin, a major component of bee venom, sensitizes human hepatocellular carcinoma cells to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-induced apoptosis by activating CaMKII-TAK1-JNK/p38 and inhibiting IκBα kinase-NF-κB. Journal of Biological Chemistry,2009:284(6):3804–3813.
30. Sharkawi FZ, Saleh SS, Sayed AFM. Potential anticancer activity of snake venom, bee venom and their components in liver and breast carcinoma. International Journal of Pharmaceutical Sciences and Research,2015:6:3224–3235.
31. Hematyar M, Soleimani M, Es-Haghi A, Rezaei Mokarram A. Synergistic co-delivery of doxorubicin and melittin using functionalized magnetic nanoparticles for cancer treatment: Loading and *in vitro* release study by LC-MS/MS. Artificial Cells, Nanomedicine, and Biotechnology,2018:46:S1226–S1235.
32. Evans VG. Multiple pathways to apoptosis. Cell Biology International,1993:17:461–476.
33. Shi L, Nishioka WK, Th'ng J, Bradbury EM, Litchfield DW, Greenberg AH. Premature p34cdc2 activation required for apoptosis. Science,1994:263:1143–1145.
34. Jung GB, Huh JE, Lee HJ, Kim D, Lee GJ, Park HK, Lee JD. Anti-cancer effect of bee venom on human MDA-MB-231 breast cancer cells using Raman spectroscopy. Biomedical Optics Express,2018:9:5703–5718.
35. Xia Q, Zhang FF, Geng F, Liu CL, Xu P, Lu ZZ, *et al*. Anti-tumor effects of DNA vaccine targeting human fibroblast activation protein α by producing specific immune responses and altering tumor microenvironment in the 4T1 murine breast cancer model. Cancer Immunology, Immunotherapy,2016:65:613–624.
36. De Melo Gagliato D, Jardim DL, Marchesi MS, Hortobagyi GN. Mechanisms of resistance and sensitivity to anti-HER2 therapies in HER2+ breast cancer. Oncotarget,2016:7:64431–64446.
37. Shah SP, Roth A, Goya R, Oloumi A, Ha G, Zhao Y, *et al*. The clonal and mutational evolution spectrum of primary triple-negative breast cancers. Nature,2012:486:395–399.
38. Duffy C, Sorolla A, Wang E, Golden E, Woodward E, Davern K, *et al*. Honeybee venom and melittin suppress growth factor receptor activation in HER2-enriched and triple-negative breast cancer. npj Precision Oncology,2020:4:24.
39. Putz T, Ramoner R, Gander H, Rahm A, Bartsch G, Thurnher M, *et al*. Antitumor action and immune activation through cooperation of bee venom secretory phospholipase A2 and phosphatidylinositol-(3,4)-bisphosphate. Cancer Immunology, Immunotherapy,2006:55:1374–1383.
40. Jang S, Kim KH. Clinical effectiveness and adverse events of bee venom therapy: A systematic review of randomized controlled trials. Toxins,2020:12(9):558.
41. Sabry E, Zayed HM, Ezzatt OM, Fathy I, Elsayeh HAS, El-Khazragy N, *et al*. Bee venom exhibits anti-cancer effects on tongue carcinoma cells by arresting cell cycle, inducing apoptosis, and suppressing cell migration. Journal of Applied Oral Science,2025:33:20250188.
42. Al Shammari BA, Al Junaidi HS, Alasmari MM, Alshaeri HK, Hock M, Talib WH, *et al*. Bee venom and thymoquinone combination inhibits cancer cells by inducing cell cycle arrest and apoptosis. Scientific Reports,2025:15:28733.
43. Zheng J, Lee HL, Ham YW, Song HS, Song MJ, Hong JT, *et al*. Anti-cancer effect of bee venom on colon cancer cell growth by activation of death receptors and inhibition of nuclear factor kappa B. Oncotarget,2015:6(42):44437–44451.
44. Zhao J, Hu W, Zhang Z, Zhou Z, Duan J, Dong Z, *et al*. Bee venom protects against pancreatic cancer via inducing cell cycle arrest and apoptosis with suppression of cell migration. Journal of Gastrointestinal Oncology,2022:13(5):2388–2399.
45. Duffy C, Sorolla A, Wang E, Golden E, Woodward E, Davern K, *et al*. Honeybee venom and melittin suppress growth factor receptor activation in HER2-enriched and triple-negative breast cancer.npj Precision Oncology,2020:4:24.

46. Obeidat WM, Bataineh MA, Al-Quraan NA, Al-Thunibat OY. Mellitin peptide quantification in seasonally collected crude bee venom and its anticancer effects on myelogenous K562 human leukaemia cell line. BMC Complementary Medicine and Therapies,2023:23:132.
47. Othman EM, Hamada HA, Mohamed GI, Abdallah GA, Ahmed ZS, Al-Shenqiti AM, *et al*. Clinical and histopathological responses to bee venom phonophoresis in treating venous and diabetic ulcers: a single-blind randomized controlled trial. Frontiers in Medicine,2023:10:1085544.
48. Liu B, Zhang L, Wang Z, Liu X, Guo W. Risk associated with bee venom therapy: A systematic review and meta analysis. International Journal of Clinical Practice,2015:69(8):977–987.
49. Wattenberg LW. Chemoprevention of Cancer. Cancer Research,1985:45:1–8.
50. Chatzi Memet B, Demirpolat E, Yildirim T, Aydin O. Development of Polymer-Based Nanoparticles for the Reduction of Melittin Toxicity. In Mediterranean Conference on Medical and Biological Engineering and Computing; Springer: Cham, Switzerland, 2024, 45–50. ISBN 978-3-031-49068-2.