Journal of Chemical Health Risks

www.jchr.org

JCHR (2026) 16(1), 1082-1105 | ISSN:2251-6727

Melittin: A Key Ingredient of Bee Venom with Potential Anticancer Activity

Adrima Kundu[1], Ankan Pandey[1], Sayandip Biswas[1], Sudip Kumar Mandal[1]*, Partha Sarathi Das[2], Ismail Mondal[1], Pralay Kumar Pahari[1], Soumyadip Mahato[1], Debjit Chakrabarti[1], Atyurmila Chakraborty[3]*

[1] *Dr. B. C. Roy College of Pharmacy and Allied Health Sciences, Durgapur-713212, West Bengal, India*

[2]*DmbH Institute of Medical Sciences, Dadpur, Hoogly-712305, West Bengal*

[3]*Anand College of Education, Department of Pharmacy, Kabilpur, Debra-721126, West Bengal, India*

(Received: 16 January 2026 Revised: 25 February 2026 Accepted: 17 March 2026)

KEYWORDS

Melittin,

Bee venom,

Anticancer activity,

Anti-inflammatory activity,

Toxicity study,

Mechanism of action

ABSTRACT:

Cancer remains one of the leading causes of morbidity and mortality worldwide, necessitating the continuous exploration of novel and effective therapeutic strategies. Natural bioactive compounds, particularly animal venom–derived peptides, have gained significant attention due to their diverse pharmacological properties. Melittin, a 26-amino-acid amphipathic peptide and the principal component of honey bee (*Apis mellifera*) venom, constitutes nearly 40–60% of the venom's dry weight and exhibits potent anticancer and anti-inflammatory activities. This review provides a comprehensive overview of the origin, biosynthesis, chemical composition, and therapeutic potential of melittin, with a special emphasis on its role in cancer therapy. The multifaceted mechanisms underlying its anticancer action—including membrane disruption, induction of apoptosis, inhibition of angiogenesis, suppression of metastasis, and modulation of key signaling pathways such as PI3K/Akt, JAK/STAT, NF-κB, and VEGF—are critically discussed. Additionally, the anti-inflammatory and immunomodulatory effects of melittin, mediated through downregulation of pro-inflammatory cytokines and oxidative stress pathways, are highlighted. Despite its promising preclinical efficacy, melittin's nonspecific cytotoxicity and hemolytic activity present major challenges to clinical translation. Recent advances in chemical modification, nanocarrier-based delivery systems, and tumor-targeting conjugation strategies aimed at improving its safety profile and therapeutic index are reviewed. Overall, melittin emerges as a potent bioactive peptide with significant potential in cancer treatment, warranting further investigation to overcome its limitations and enable clinical application.

1. Introduction

Cancer represents one of the most serious global health challenges of the 21st century, exerting profound effects not only on individuals and societies but also on the global healthcare system. It accounts for approximately one in every six deaths worldwide and nearly one in four deaths from non-communicable diseases**.** Among individuals aged 30–69 years, cancer ranks among the top three causes of mortality and is the leading cause of death in 177 of 183 countries**.** Beyond mortality, cancer significantly reduces life expectancy and imposes substantial economic burdens on healthcare systems and societies, with costs varying according to cancer type, geographic region, and gender [1]. The morbidity and mortality associated with cancer remain alarmingly high worldwide, underscoring the urgent need for effective prevention and management strategies [2]. According to GLOBOCAN 2020 estimates, approximately 19.3 million new cases and 10 million deaths were recorded globally in 2020 [3]. Projections suggest a substantial rise in cancer burden, with new cases expected to reach nearly 29.4 million annually and approximately 35 million cases by 2050 [1,4]. Without significant intervention, global cancer incidence could increase to 33 million cases with nearly 18 million deaths annually by 2050. In the United States alone, projections indicate approximately 1.9 million new cases and 618,000 deaths in 2025 [5].

Cancer is fundamentally a genetic disease characterized by uncontrolled cellular proliferation resulting from

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(1), 1082-1105 | ISSN:2251-6727

genetic and epigenetic alterations in somatic cells, with the potential to invade and metastasize to distant tissues [6]. It is a complex, multifactorial disorder influenced by genetic susceptibility and modifiable risk factors [5,6]. Lifestyle and environmental determinants play a major role in cancer incidence and mortality. Tobacco use, alcohol consumption, obesity, unhealthy diet, physical inactivity, and exposure to carcinogens collectively contribute to more than half of global cancer deaths [5, 6]. Several malignancies contribute substantially to global cancer incidence and mortality, with lung, colorectal, breast, and prostate cancers among the most prevalent and life-threatening types [5,6]. Epidemiological reports indicate that prostate cancer in men and breast cancer in women are the most commonly diagnosed cancers, accounting for approximately 29% and 31% of cases, respectively [7]. In recent years, an alarming rise in early-onset cancers among individuals younger than 50 years has been observed, particularly in younger generations [5]. This trend includes increasing incidence of breast and liver cancers, which are often diagnosed at advanced stages. Age-related genetic alterations, cumulative molecular damage, and progressive decline in immune surveillance are believed to contribute to the rising cancer burden [5]. Current cancer treatment strategies include both conventional and advanced therapeutic approaches. Traditional modalities such as surgery, chemotherapy, and radiotherapy remain fundamental components of cancer management, while newer approaches including targeted therapy, immunotherapy, and hormone therapy have significantly improved treatment outcomes [8,9]. These therapies act by targeting molecular pathways, cancer cells, tumor vasculature, immune responses, or endocrine mechanisms involved in tumor growth and progression [9]. Despite significant advances, limitations such as adverse effects, drug resistance, high costs, and incomplete therapeutic response persist, highlighting the ongoing need for novel and more effective treatment strategies. Natural bioactive compounds, particularly animal venom–derived peptides, have gained significant attention due to their diverse pharmacological properties [10].

Melittin is the principal bioactive peptide found in the venom of the *Apis mellifera* and constitutes nearly 40–60% of its dry weight. It is a small, amphipathic peptide known for its strong anti-inflammatory, antimicrobial, and anticancer properties. Melittin exerts cytotoxic effects on cancer cells by disrupting cell membranes, inducing apoptosis, and inhibiting tumor growth pathways. Due to these biological activities, melittin has gained increasing attention as a potential therapeutic agent in cancer research and drug development. Melittin has a diverse spectrum of pharmacological activity. The central aspect of its action is its membrane disruption by pore formation on lipid bi-layers and this is at the centre of its cytolytic and antimicrobial action [11-13]. This effect of melittin allows the antimicrobial effect to be broad-spectrum and effective against bacteria, fungi, and drug-resistant microbes, e.g., vancomycin-resistant Staphylococcus aureus [14-19]. In addition to antimicrobial, melittin has shown a strong anticancer property in different cancer cells such as breast cancer, leukemia, lung cancer, and prostate cancer [12, 20, 21-23]. Its anticancer effects include the induction of apoptosis, the inhibition of proliferation and metastasis, the suppression of inflammatory signal transduction pathways, such as IL-17, and the targeting of mitochondria to inhibit mitophagy flux [24, 25-28]. It has also been found that melittin is an anti-inflammatory agent that inhibits the production of pro-inflammatory cytokines, making it useful in conditions such as acute kidney injury and acne vulgaris [20, 21, 22, 29]. Although melittin has potential in therapy, its non-selective cytotoxic and hemolytic effects restrict its clinical use, with researchers dealing with this by introducing N- and C-terminal PEGylation, fatty-acid residues, and encapsulation, which increases selectivity and stability in niosomes [12, 14, 30, 31]. It is also capable of modulating ion channels, and synergism with phospholipase A2 is mediated by the liquid-liquid miscibility phase changes in membranes [32].

By providing an overview of cancer's epidemiology, underlying molecular processes, risk factors, and current therapy modalities, as well as pointing out the shortcomings of current therapies, this review aims to objectively investigate cancer as a significant worldwide health concern. Additionally, in order to facilitate the creation of safer and more efficient anticancer treatments, this work attempts to assess the therapeutic potential of honey bee-derived compounds as prospective natural agents for cancer prevention and

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(1), 1082-1105 | ISSN:2251-6727

therapy. A representative image of a honey bee and its hive is shown in **Figure 1**.

Figure 1: Portrait of a honey bee and a bee nest

1.1 The History of Melittin

The investigation of curative qualities of natural elements and especially elements of animal venom has exhausted a lengthy record [33,34]. Bee venom is a complicated biological product of secretes on which generations of scientists conduct research [34, 35, 36]. The analysis of the composition of the bee venom was conducted by Langer in 1897, and by Neumann and Habermann in 1954, who revealed that the peptides and proteins were the ones that caused the biological activity of the venom [37].

In the near future, melittin was identified as the major component of bee venom that constitutes 30-50 per cent of the dry weight [37, 38]. It possesses distinct structural and functional peculiarities, such as a high hemolytic activity and amphipathic character, which predetermine it as a very interesting research object [37, 39]. The study of the Nate structure, folding, and action of peptides and proteins in membranes has been of interest to scientists, and it is the use of melittin that has made the study easier because of its ability to bind to the lipid bilayer membrane, fold into empathetic helical secondary structure, and break up initial barriers [40,41].

Despite the scientific explanation of it, the bee venom, and consequently, melittin, developed into a therapeutic agent by conventional medicines. The use of bee products as a therapeutic agent can be traced to ancient Egypt, Greece, and China [42-44]. It received more official acceptance in the West when an Austrian physician by the name Philip Terc published an article in 1888, relating bee stings to rheumatism. This research is widely recognized to have given the bee venom therapy to rheumatic patients [43]. It is highly stressed by this historical application from the perspective of the recent attention attracting the medicinal quality of the bee venom constituents. The chemical structural of Melittin is represented in the **Figure 2.**

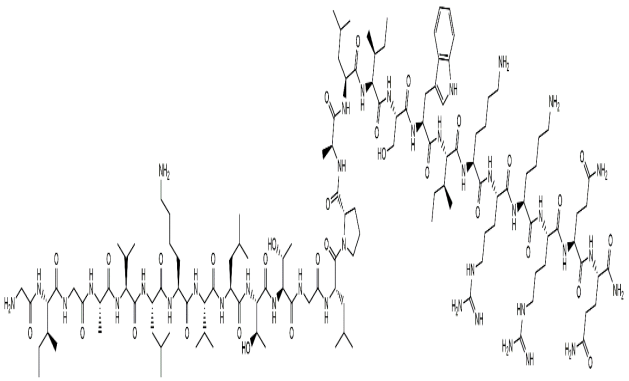


Figure 2: Structure of Melittin

1.2 Biosynthetic Pathway

Unlike synthesis in its mature form, Melittin is a 26-amino acid peptide synthesized by a complex process of biosynthesis in the honey bee venom glands. This is a select messenger RNA (mRNA) that is first transcribed in the venom glands of queen and worker bees out of deoxyribonucleic acid [45-47]. Melittin mRNA gives rise to the major structural product of pre-pro-melittin, a 70 amino acid polypeptide [41, 48-49]. This preproprotein has displayed an N-terminal signal peptide, which is needed in the regulation of its synthesis to the secretion pathways of the endoplasmic reticulum [41, 49].

In the course of passing through the endoplasmic reticulum membrane and into its lumen, the growing polypeptide chain is exposed to enzymes which break down signal peptides [49, 50]. This cleavage reaction transforms pre-pro-melittin to an intermediate, pro-melittin [46, 48]. The pro-melittin subsequently gets deteriorated further in the venom recipient through the enzyme of the dipeptidyl-peptidase IV, which splits the

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(1), 1082-1105 | ISSN:2251-6727

portion of the pro part to result in the physiologically active, complete sized melittin [50]. As the age of bees increases, pro-melittin is gradually digested to yield melittin [50].

It is also interesting to add that the levels of productions are not produced in the pupal period but during the first week of adulthood, the levels of melittin levels rise to a high extent of about 95 ug per worker bee and the level does not change thereafter, but instead, it undergoes gradual decline [50].The levels of productions are also found to take the first week of adulthood, and on the other hand, the levels of productions decrease during the second week to a low of about 95 µg per worker bee and cease The expression is controlled on the transcriptional level [50]. Recent researchers have indicated that honey bees can synthesize melittin in fat cells and venom gland. Interestingly enough, such cells are no longer under the influence of the harmful effects of the peptide [51]. This complex biosynthetic process guarantees that an important uniform of protection in bee venom is produced (melittin). Biosynthetic pathway of Melittin & its development with the time is shown in the **Figure 3.**

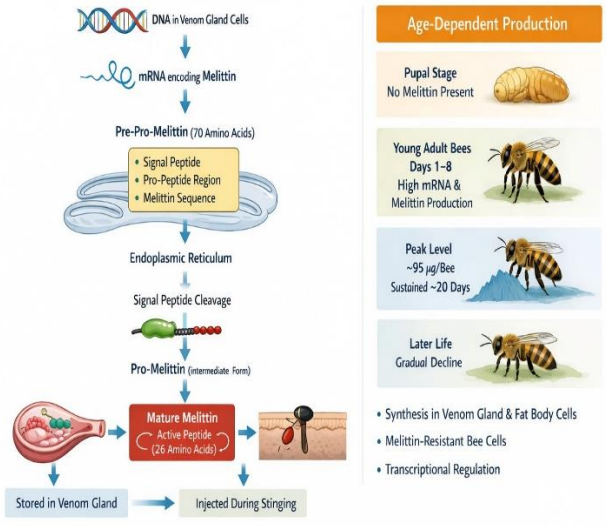


Figure 3: Biosynthetic pathway of Melittin and its development with time

1.3. The composition of Bee Venom Melittin

Honey bee venom from the *Apis mellifera* is a protein-rich, biologically active secretion that plays an essential role in defence and survival. It is a complex mixture composed of enzymes, biogenic amines, peptides, and other non-peptide components that contribute to its diverse biological activities [45, 52-53].

Melittin is the principal component of bee venom, accounting for approximately 40–60% of its dry weight [51-52, 54]. It is a 26-amino-acid amphiphilic peptide responsible for the pain, inflammation, and hemolytic effects associated with bee stings. Melittin interacts with and disrupts cell membranes, triggering the release of inflammatory mediators and ultimately leading to cell death [39, 52-54]. Other biologically active peptides present in bee venom are summarized in **Table 1.**

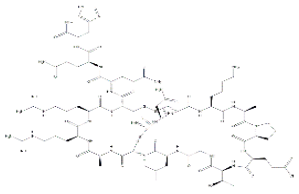
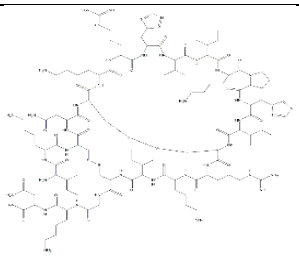
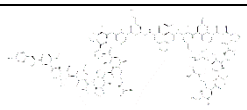
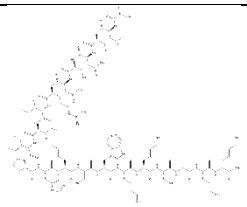
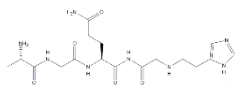
Another important component of bee venom from the Apis mellifera is its enzymatic fraction, which facilitates the spread of venom through tissues and enhances its biological and toxic effects. These enzymes increase membrane permeability, promote local tissue damage, and intensify inflammatory responses. The principal enzymes present in bee venom are summarized in **Table 2.**

Bee venom from the *Apis mellifera* contains a complex mixture of biologically active constituents, including peptides, enzymes, and physiologically active amines such as norepinephrine, histamine, and epinephrine [60, 61]. These components are responsible for the pain, inflammatory reactions, and vasoconstrictive effects associated with envenomation. In addition, bee venom comprises lipids, carbohydrates (including fructose and glucose), and free amino acids, all of which contribute to its distinctive pharmacological profile [43].

The synergistic interaction of these constituents underlies the diverse biological activities of bee venom, including antibacterial, anti-inflammatory, and notably anticancer properties [53, 56, 62]. A thorough understanding of this complex composition is essential to harness its full therapeutic potential [60, 61].

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(1), 1082-1105 | ISSN:2251-6727

Table 1. List of biologically active peptides of Bee venom

Peptide	Approximate content in Bee venom	Biological activity	Structure	Mechanism	Reference
Apamin	1-3% of dry venom	Neurotoxic coma anti-inflammatory		Blocks the Ca^{2+} activated K^{+} channel, affecting neuronal excitability	[52, 55-56]
Mast degranulating peptide (MCD)	Minor component	Induce histamine, shows anti-inflammatory effects		Stimulates mast cell degranulation, leading to inflammatory mediator release	[54, 56]
Adolapin	0.1-0.8% of dry venom	Anti-inflammatory, anti-rheumatic, antipyretic, and anti-analgesic	NA	Inhibits prostaglandin synthesis and cyclooxygenase activity	[55-57]
Secapin	Trace amounts	Antimicrobial activity		Exhibits activity against the bacterial membrane	[53, 54, 57]
Tertiapin	Trace amounts	Parasympathomimetic effect		Blocks the inward rectifier potassium (Kir) channel	[53, 54, 57]
Procamine	Trace amounts	Limited characterized biological activity		Minor venom pip died with reported psychological effects	[53, 54, 57]
Cardiopep	Trace amounts	Antiarrhythmic activity	NA	Modulates cardiac electrical activity	[57]
Bombolittins	Present in bumblebee venom	Cytolytic activity	NA	Structurally related to melittin	[41]

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(1), 1082-1105 | ISSN:2251-6727

Table: 2 List of enzymes present in bee venom

Component	Approximate amount	Malfunction	Allergen status	References
Phospholipase A 2 (PLA_2)	10 to 12 percent of dry venom second most abundant	Breaks down phospholipids in cell membranes, damages cells, releases fatty acids and lysophospholipids, causes hemolysis and inflammation	Major allergen	[45, 54, 58]
Hyaluronidase	Enzyme minor component	Brake hyaluronic acid in the extracellular matrix, increased tissue permeability, helps venom spread	Major allergen	[45, 53, 56]
Acid phosphatase (alpha-glucosidase)	Enzyme	Contributes to overall venom activity by breaking phosphate containing molecule	Major allergen	[45, 55, 59]
Phospholipase B	Enzyme	Supports venom pharmacological effects by acting on membrane lipids	NA	[55, 59]

Bee venom from the *Apis mellifera* contains a complex mixture of biologically active constituents, including peptides, enzymes, and physiologically active amines such as norepinephrine, histamine, and epinephrine [60, 61]. These components are responsible for the pain, inflammatory reactions, and vasoconstrictive effects associated with envenomation. In addition, bee venom comprises lipids, carbohydrates (including fructose and glucose), and free amino acids, all of which contribute to its distinctive pharmacological profile [43].

The synergistic interaction of these constituents underlies the diverse biological activities of bee venom, including antibacterial, anti-inflammatory, and notably anticancer properties [53, 56, 62]. A thorough understanding of this complex composition is essential to harness its full therapeutic potential [60, 61].

2. METHODOLOGY

This review is based on a comprehensive evaluation of published literature from 1990 to 2025. In extensive literature search was performed using major scientific databases, including PubMed, Scopus, SciFinder, ScienceDirect, MEDLINE, and Google Scholar. The search strategy focused on studies related to bee venom, melittin, and their pharmacological activities. Databases were queried using combinations of keywords such as "bee venom," "*Apis mellifera*," "melittin," "cancer therapy," "pharmacological activity," and "biological activity."

3. MECHANISM OF ACTION OF MELITTIN: ANTI-CANCER AND ANTI-INFLAMMATORY EFFECTS

Melittin, the principal peptide component of bee venom, has attracted significant scientific interest due to its broad spectrum of biological activities, particularly its potent anti-inflammatory and anticancer effects. These therapeutic properties arise from multiple pharmacological mechanisms involving complex biochemical interactions and modulation of cellular functions at different levels. This section integrates chemical and pharmacological perspectives to describe the mechanisms through which melittin exerts its anti-inflammatory and anticancer actions.

3.1 Mechanisms Underlying Anticancer Activity

The anticancer mechanism of melittin is complex and continues to be elucidated. Its activity is primarily attributed to direct cytolytic effects, induction of programmed cell death, and interference with key signaling pathways involved in oncogenesis. These actions are closely related to its amphipathic structure and its interactions with cellular membranes and intracellular targets [63-65].

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(1), 1082-1105 | ISSN:2251-6727

3.1.1 Chemical-Physical Mechanism of Membrane Disruption and Pore Formation

One of the most rapid and effective anticancer mechanisms of melittin is its ability to disrupt cellular membranes, resulting in cell lysis. This chemical-physical process is mainly governed by the amphipathic nature and positive charge of the peptide [38, 64].

Chemical and Structural Basis of Melittin

Melittin is a linear peptide composed of 26 amino acids [66]. Structurally, it possesses a net positive charge of approximately +6 at physiological pH due to positively charged residues such as lysine and arginine [38, 63]. The molecule consists of a hydrophobic N-terminal region and a hydrophilic C-terminal region, creating an amphiphilic configuration that facilitates insertion into lipid bilayers [38].

3.1.1.1. Mechanism of Interaction with Cell Membranes

Electrostatic attraction and insertion

The positively charged C-terminal region of melittin is attracted to negatively charged phospholipid head groups present on cell membranes. Cancer cells often exhibit a higher negative surface charge than normal cells, which may enhance melittin selectivity. Upon binding, melittin undergoes conformational change into an amphipathic α-helical structure [67, 68].

Oligomerization of monomers

At low concentrations, melittin monomers align parallel to the membrane surface and remain relatively inactive. At higher concentrations, the monomers aggregate and oligomerize within the membrane [67, 69, 70].

Pore formation models

Melittin aggregates form membrane pores through barrel-stave or toroidal pore mechanisms. In these models, peptides insert perpendicularly into the lipid bilayer, forming a hydrophilic channel lined by peptide monomers while interacting with lipid acyl chains externally. This creates a continuous pathway for water and ions [63, 70].

Detergent-like mechanism

At high peptide-to-lipid ratios, melittin may act similarly to a detergent, solubilizing membrane lipids and forming micelle-like structures that disrupt membrane integrity [71].

Conformational transition

A critical step in pore formation involves reorientation of melittin from a parallel alignment to a perpendicular insertion within the membrane. This transition is essential for pore formation and subsequent cell lysis [67].

3.1.1.2. Pharmacological Consequences of Membrane Disruption

Formation of membrane pores results in rapid and uncontrolled ion flux and leakage of essential intracellular components, leading to loss of cellular homeostasis [64].

Oncotic necrosis

Unregulated influx of ions and water causes cell swelling and eventual necrotic death. Membrane disruption can occur within seconds following melittin exposure, with intracellular debris released over several minutes. Melittin-induced necrosis has been observed in several cancer cell lines, including gastric cancer [69, 71, 41, 42].

Disruption of intracellular organelles

Melittin's membrane-lytic action also damages intracellular organelles, particularly mitochondria, leading to metabolic dysfunction and enhanced cell death. Cancer cells are especially susceptible due to differences in membrane composition and membrane potential [68, 70-71].

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(1), 1082-1105 | ISSN:2251-6727

3.1.2. Programmed Cell Death Modulation: Apoptotic Signaling

Melittin is a potent inducer of apoptosis, a tightly regulated form of programmed cell death. Its pro-apoptotic activity involves both membrane disruption and modulation of intracellular signaling pathways. This mechanism represents one of the key anticancer actions of melittin.

3.1.2.1. Pharmacological Routes

Caspase-dependent apoptosis

Melittin activates caspase cascades that execute apoptosis. Activation of caspases has been demonstrated in various malignancies, including leukemia (U937, Jurkat), melanoma (A2058), hepatocellular carcinoma (SMMC7721, Hep3B, HepG2, BEL7402), prostate cancer (PC3, LNCaP, DU145), and cervical cancer cells [73]. Melittin promotes the upregulation of pro-apoptotic proteins while downregulating anti-apoptotic proteins such as Bcl-2, Bcl-xL, and members of the inhibitor of apoptosis protein [74]. In gastric cancer SGC7901 cells, melittin induces mitochondrial-mediated apoptosis, resulting in cytochrome-c release and activation of caspase-3 [71, 75].

Inhibition of the PI3K/Akt pathway

Melittin suppresses the Akt signaling pathway by inhibiting Akt phosphorylation. The PI3K/Akt/mTOR pathway is frequently overactivated in cancers and promotes cell growth, survival, and proliferation. By blocking this pathway, melittin suppresses survival signaling and promotes apoptotic cell death [74].

Downregulation of the JAK2/STAT3 pathway

Melittin inhibits cancer cell proliferation by suppressing the JAK2/STAT3 signaling pathway and activating death receptor pathways [68, 76]. STAT3 is commonly overexpressed in cancers and promotes angiogenesis, cell survival, and tumor progression [76].

Induction of death receptors

Melittin enhances the expression of cell-surface death receptors, thereby activating the extrinsic apoptotic pathway upon ligand binding [68, 71].

Activation of p38 MAPK signaling

Melittin has been shown to increase phosphorylation of p38 MAPK [74]. This pathway regulates stress responses, cell cycle arrest, and apoptosis in cancer cells [81].

3.1.3 Impact on Cell Proliferation and Metastasis

Melittin exhibits significant inhibitory effects on tumor progression by suppressing cancer cell proliferation, angiogenesis, invasion, and metastasis [33, 46]. These activities are essential for limiting tumor growth and preventing the spread of malignant cells.

Mechanisms of Pharmacological Action

3.1.3.1. Cell Cycle Arrest

Melittin interferes with regulatory signaling molecules that control cell cycle progression. By arresting the cell cycle at specific checkpoints, it prevents uncontrolled cellular proliferation and inhibits tumor growth [77-79]

3.1.3.2. Inhibition of Angiogenesis

Melittin dramatically inhibits angiogenesis (development of new blood vessels needed in the promotion of tumor growth and metastasis). This is done through suppression of Veg2 and VEGFR2. Melittin suppresses/ decreases Vascular Endothelial Growth Factor (VEGF) and Vascular Endothelial Growth Factor receptor (VEGFR-2) [78, 80-81].

Suppression of VEGF and VEGFR-2

Melittin suppresses vascular Endothelial Growth Factor and receptor [46]. VEGF is also one of the proangiogenic factors [73, 82-83].

Inhibition of VEGFR-2/Ras/Raf/MEK1/ERK1/2 signaling

Melittin blocks activation of MEK1/ERK1/2 pathways, thereby disrupting VEGFR-2 downstream signaling essential for endothelial cell proliferation and neovascularization [73, 82-83].

HIF-1α suppression

Melittin is in a position to suppress epidermal Growth Factor-stimulated Hypoxia inducible factor-1alpha, a transcription factor that increases VEGF expression

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(1), 1082-1105 | ISSN:2251-6727

under hypoxic conditions, which are known to be induced by malignancies [82-83]. It reduces the half-life of HIF1 and inhibits the interaction of DNA with the VEGF promoter [80, 82].

3.1.3.3. Anti-metastatic Activity

Melittin inhibits cancer cell invasion and metastatic potential through multiple mechanisms:

Inhibition of MMP-9 expression

Melittin suppresses matrix metalloproteinase-9 (MMP-9), an enzyme responsible for extracellular matrix degradation and tumor invasion. It interferes with AP-1 and NF-κB transcription factors involved in MMP-9 gene expression [73].

Modulation of ERK and JNK pathways

Melittin inhibits PMA-induced phosphorylation of ERK and JNK signaling pathways, which regulate cancer cell migration, survival, and proliferation [80, 82].

Overall, melittin restricts tumor progression by halting cell division, suppressing angiogenesis, and preventing metastatic dissemination. The comprehensive mechanisms of melittin's anticancer activity are summarized in **Figure 4.**

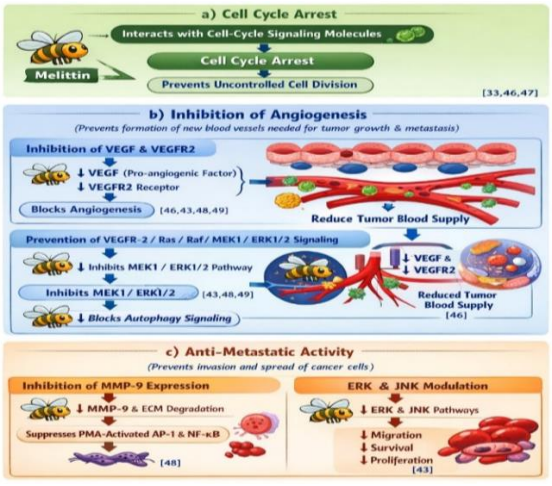


Figure 4: Summary of mode of action of Melittin in Anti-Cancer action

3.2 Mechanisms of Anti-Inflammatory action

Melittin exhibits potent anti-inflammatory activity at low, non-toxic concentrations. This dual behavior reflects its complex pharmacological nature, as bee venom can produce pro-inflammatory effects such as pain and irritation during stings, while demonstrating significant anti-inflammatory properties under controlled therapeutic conditions [84-85]. The anti-inflammatory potential of bee venom has been recognized since ancient medical practices and has been applied in the management of chronic inflammatory disorders [84].

3.2.1 Modulation of the NF-κB Signaling Pathway: A Central Regulator of Inflammation

The NF-κB signaling pathway plays a pivotal role in regulating inflammatory responses by controlling the expression of numerous pro-inflammatory genes. Inhibition of this pathway is a major mechanism underlying the anti-inflammatory effects of melittin [86-87].

Pharmacological Mechanisms

Inhibition of p65 and p50 Nuclear Translocation

Melittin prevents the translocation of NF-κB subunits p65 and p50 from the cytoplasm into the nucleus. Nuclear translocation is essential for NF-κB binding to DNA and initiating transcription of inflammatory mediators. By blocking this step, melittin suppresses inflammatory gene expression [87, 88].

Prevention of IκB Degradation

Melittin inhibits phosphorylation and subsequent degradation of IκB (inhibitor of NF-κB). Under inflammatory stimuli, IκB is normally phosphorylated, ubiquitinated, and degraded, allowing NF-κB to translocate to the nucleus. By stabilizing IκB, melittin retains NF-κB in the cytoplasm and prevents activation of inflammatory pathways [88, 89].

Direct Interaction with NF-κB p50 Subunit

Melittin can directly bind to the dimerization interface and C-terminal nuclear localization sequence of the NF-κB p50 subunit. This interaction may inhibit NF-κB activation by preventing p50 nuclear translocation and blocking p50–p65 dimer formation [90].

Suppression of IKK Phosphorylation

Melittin inhibits IκB kinase (IKK), the enzyme responsible for phosphorylating IκB. This action further

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(1), 1082-1105 | ISSN:2251-6727

prevents NF-κB activation and reduces inflammatory mediator production [89].

Chemical–Pharmacological Link in NF-κB Modulation

The anti-inflammatory activity of melittin is closely linked to its chemical structure and its ability to interact with key components of the NF-κB signaling pathway. Melittin is an amphipathic α-helical peptide containing positively charged residues that facilitate electrostatic and hydrophobic interactions with intracellular proteins. These structural features enable melittin to interact with NF-κB components such as p50 and IκB, thereby interfering with inflammatory signaling [88].

Melittin and bee venom have been shown to inhibit NF-κB activation by preventing the nuclear translocation of the p50 subunit. This inhibition is believed to occur through interaction with sulfhydryl (–SH) groups of the p50 protein and by suppressing IκB kinase (IKK) activation. As a result, phosphorylation and degradation of IκB are prevented, allowing NF-κB to remain sequestered in the cytoplasm and blocking transcription of pro-inflammatory genes.

Figure 5a illustrates the mechanism of NF-κB pathway modulation by melittin, highlighting its role in suppressing inflammatory responses.

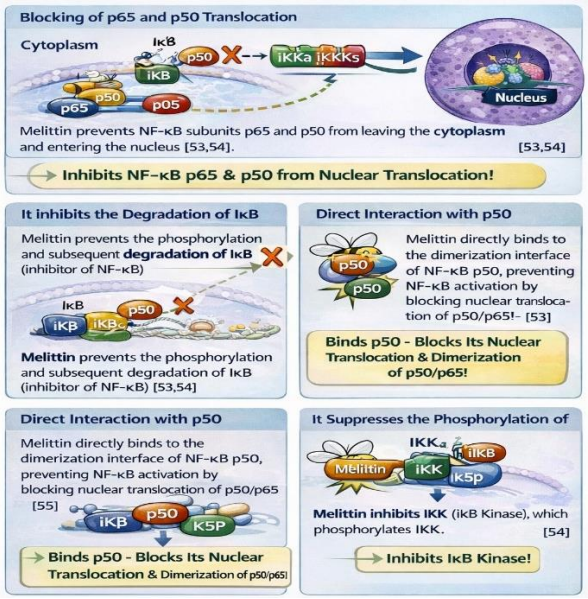


Figure 5a: NF-kB Pathway Modulation to show anti-inflammatory activity.

3.2.2 Downregulation of Cytokines and Pro-Inflammatory Mediators

Melittin attenuates the inflammatory cascade by suppressing the synthesis and release of key pro-inflammatory mediators and cytokines, thereby reducing tissue inflammation and immune overactivation.

Mechanism of Pharmacological Action

Inhibition of COX-2 and iNOS Expression

Melittin significantly inhibits the expression of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS). Prostaglandins produced via COX-2 and nitric oxide generated by iNOS are potent mediators of pain, fever, and inflammation. By suppressing these enzymes, melittin reduces inflammatory mediator production. Experimental studies have shown that melittin (≈1 g/mL) decreases COX-2 expression and nitric oxide production in lipopolysaccharide (LPS)-stimulated macrophages [88, 91].

Decreased Production of Pro-Inflammatory Cytokines

Melittin suppresses the production of major pro-inflammatory cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) [89, 91]. These cytokines play critical roles in initiating and sustaining inflammatory responses. Melittin has been reported to reduce LPS-induced mRNA expression of TNF-α and IL-1β, thereby limiting inflammatory signaling.

Inactivation of the JNK Pathway

Melittin inhibits the c-Jun N-terminal kinase (JNK) signaling pathway, which regulates cellular responses to stress and inflammation. Suppression of JNK signaling contributes to the anti-inflammatory and anti-arthritic effects of melittin by reducing inflammatory gene expression [88, 91].

Chemical–Pharmacological Interconnection

The regulation of NF-κB and JNK signaling by melittin directly influences the expression of iNOS, COX-2, and pro-inflammatory cytokines. The amphipathic structure and charged residues of melittin enable interactions with key components of these signaling pathways, leading to

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(1), 1082-1105 | ISSN:2251-6727

suppression of inflammatory mediator gene expression and overall reduction of inflammation.

Inhibitory effect of melittin on the COX and LOX inflammatory pathways is shown in **Figure 5b.**

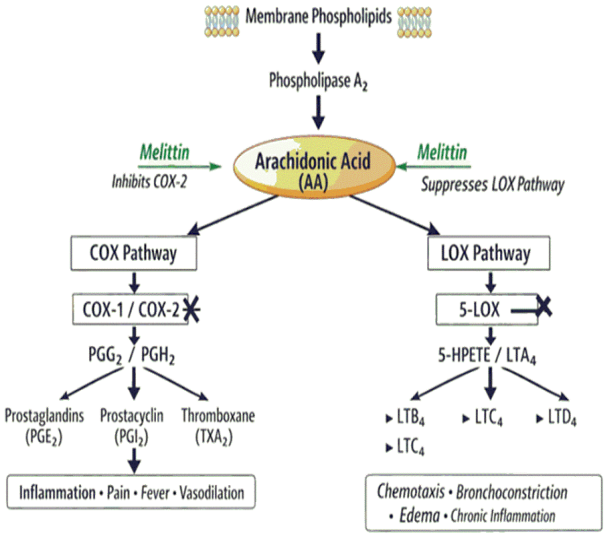


Figure 5b: Inhibitory Effect of Melittin on the COX and LOX Inflammatory Pathways

3.2.3 Immunomodulatory and Antioxidant Effects

The anti-inflammatory activity of melittin is further strengthened by its antioxidant properties and its ability to modulate immune cell function. By regulating oxidative stress and immune responses, melittin contributes to the control of chronic inflammatory conditions.

Mechanism of Pharmacological Action

Activation of the Nrf2/HO-1 Pathway

Melittin promotes the nuclear translocation of nuclear factor erythroid 2–related factor 2 (Nrf2), leading to the expression of antioxidant defense genes such as heme oxygenase-1 (HO-1). This activation enhances cellular antioxidant capacity and reduces oxidative stress, a key contributor to chronic inflammation. Molecular docking studies suggest that melittin may directly interact with Kelch-like ECH-associated protein 1 (Keap1), the negative regulator of Nrf2, thereby facilitating Nrf2 activation [92-94].

Modulation of Immune Cell Function

As a therapeutic agent, at low doses, melittin can be used to control the activity of immune cells (macrophages) to minimize hyper-irritation of immune responses, but at high doses, it results in an inflammatory response (e.g., NLRP3 inflammasome activation and discharging IL1b at lytic concentrations) [95-96]. Finally, due to the distinct set of physicochemical characteristics, melittin permits the development of a variety of interrelated anticancer and anti-inflammatory effects. Its amphipathic nature and positive charge make it cause cell lysis (a rapid chemical-physical activity), which can occur through direct membrane lysis [84].

Non Membrane Disruptive Mechanisms

Beyond its membrane-lytic activity, melittin can exert biological effects through non-lytic pathways. It may directly interact with intracellular signaling proteins such as calmodulin and other regulatory molecules, influencing inflammatory signaling cascades and immune responses [83].

Integrated Pharmacological Significance

Melittin's amphipathic structure and positive charge enable diverse biological interactions. While membrane disruption contributes to rapid cytolytic effects, its antioxidant activation and immune modulation pathways support broader anti-inflammatory and anticancer actions. **Figure 6** illustrates the immunomodulatory and antioxidant mechanisms of melittin.

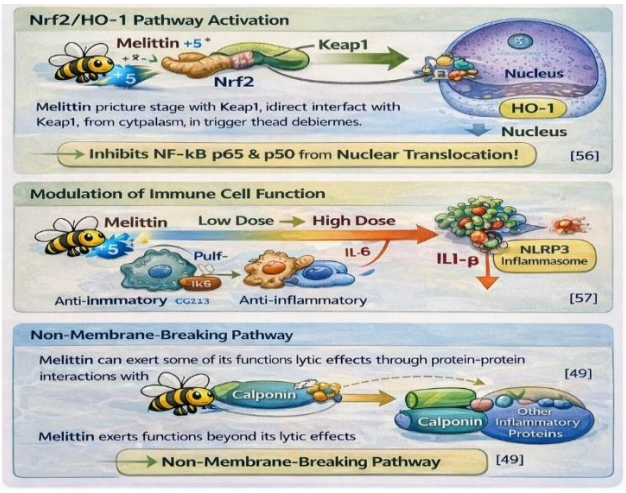


Figure 6: MOA of Immunomodulatory and Antioxidant Effects

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(1), 1082-1105 | ISSN:2251-6727

4. TOXICOLOGICAL PROFILING OF MELITTIN

Despite its promising therapeutic potential, the toxicity of melittin presents significant challenges for clinical application. A comprehensive understanding of its toxicological profile—from chemical properties to pharmacological effects—is essential to minimize adverse effects and improve its therapeutic index [97].

4.1. Chemical Basis: Non-Specific cytotoxicity and haemolytic Activity

The strong hemolytic and nonselective cytotoxicity of Melittin is the main toxicological concern [73, 98]. These effects are directly related to its physicochemical properties, especially its amphipathic nature and positive charge. Melittin can interact directly with cell membranes, forming pores [83]. This is possible with virtually any type of cell because of the presence of positively charged amino acids, making it highly effective and leading to the destruction of phospholipid bilayers and subsequent pore formation [73, 87].

The light-activated melittin can cause hemolysis, or the bursting of RBCs and the release of hemoglobin, which is especially dangerous to erythrocytes [73, 87]. Melittin was found to have a median of volatility concentration of 16.28 ± 0.17 ug/mL in the human RBC (2% suspension) [83]. The strong lytic activity of melittin is related directly to the fact that it permeabilizes cell membranes and causes loss of the intercellular contents and the death of the cell [99]. The cationic property of Melittin facilitates the first electrostatic interaction of Melittin with the negatively charged phospholipid head groups on the cell membrane surface. This property is found in both normal and cancerous (including erythrocytes) cells [87].

4.2. In Vivo Safety, Toxicity, and Adverse Effects

In vivo experiments have shown that melittin has other broader deleterious effects than cell cytotoxicity. Systemic toxicity would be evidenced with higher dosages by a median lethal dose of 4.98 mg/kg, which Melittin depicts, when fed high concentrations of melittin orally into the peritoneal cavity of BALBc mice [100]. Melittin is not long-lived and, due to the effect of high dosage, a high dosage is necessary to reach treatment dosages, as it is quickly broken down in the biological fluids, and is a nonspecific lytic agent which aggravates its side effects [73, 101].

As melittin is active on a broad spectrum of psychological systems, it can cause local inflammation, discomfort, pruritus and more serious diseases, it can cause system wide reactions leading to its entrapping in the mails, e.g. can cause heart and mechanical hyperalgesia, or of primary damage, and it can cause heat hypersensitivity by potentiating sodium channels in primary sensory neurons which are not vulnerable to some form of tetrodotoxin inflammatory and can cause serious pathological diseases [20, 102]. These releases of tissue-injurious compounds, such as lysosomal enzymes, serotonin, and histamine, following migraine disruption, also contribute to inflammatory and painful responses [99]. This systemic toxicity significantly limits its direct clinical acceptability.

4.3. Pharmacological and chemical strategies for toxicity mitigation

For successful clinical translation, melittin must be engineered to reduce toxicity while preserving therapeutic efficacy. Current strategies aim to enhance tumor specificity and minimize off-target effects [87, 103].

4.3.1. Chemical modification approaches

4.3.1.1. PEGylation

Conjugation with polyethylene glycol (PEG) increases hydrodynamic size, improves enzymatic stability, reduces renal clearance, and significantly decreases hemolytic activity while maintaining anticancer efficacy.

4.3.1.2. Amino acid substitution

Targeted amino acid substitutions can modify peptide charge, hydrophobicity, and secondary structure, improve cancer cell selectivity and reduce damage to normal cells.

4.3.1.3. Fusion protein formation

Fusion of melittin with carrier molecules (e.g., glutathione or targeting peptides) reduces systemic toxicity while preserving anti-inflammatory and anticancer activity.

Melittin must be successfully translated to clinical use to become non-toxic. To increase its therapeutic index, researchers have reviewed its pharmacological and

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(1), 1082-1105 | ISSN:2251-6727

chemical alternatives, mainly through the increase of tumor specificity and decrease of off-target effects. The Techniques of Chemical modification of melittin is shown in the **Figure 7.**

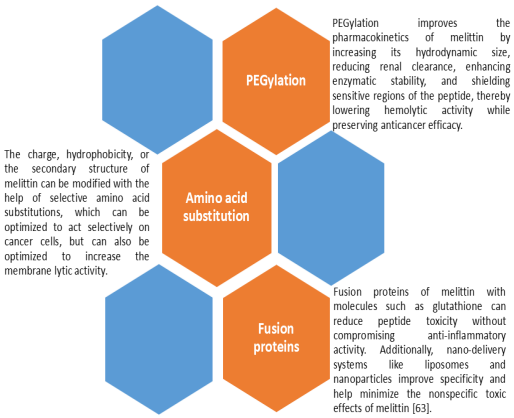


Figure 7: Techniques for chemical modification and delivery of melittin

4.3.2. Nanotechnology based delivery systems

4.3.2.1. Liposomes

Encapsulation of melittin in lipid vesicles protects normal cells—especially erythrocytes—thereby reducing hemolysis [63, 103].

4.3.2.2. Polymeric nanoparticles

Biodegradable polymeric carriers enable controlled release and protect melittin from premature degradation [103].

4.3.2.3. Perfluorocarbon nanoparticles

These nanoparticles interact with lipid monolayers and facilitate targeted delivery to tumor vasculature by binding angiogenic endothelial integrins and exploiting enhanced permeability and retention (EPR) effects. This improves tumor inhibition while reducing systemic toxicity [104].

4.3.3. Tumor-Targeting ligand conjugation of Melittin or its nano-formulations

Melittin or melittin-loaded nanocarriers can be conjugated with tumor-targeting ligands that recognize receptors overexpressed on cancer cells to achieve active targeting.

4.3.3.1. Antibodies/ peptides

Ligands, which include antibodies or tumor-homing peptides, can be used to address melittin-loaded nanoparticles and increase treatment in the cancer site and tumor sparing in healthy tissues. One such instance is that a bifunctional melittin within a peptide containing an RGD peptide motif (arginine, glycine, aspartic acid) has since been designed to get the target to triple-negative breast cancer (TNBC) cells to have a charged melittin C-terminus sequence. The approach minimizes non-therapeutic effects and increases specificity to a considerable extent [20].

These are the more intricate chemical and pharmacological engineering approaches that are needed in the conversion of melittin into a strong yet toxic peptide to a useful clinical drug.

5. TRIPLE NEGATIVE BREAST CANCER (TNBC): THERAPY OUTCOME

Triple-negative breast cancer presents a serious problem in cancer treatment as it is highly invasive; it lacks adequate therapeutic options; and in most cases, its prognosis is low, in comparison to other types of this cancer [105]. The active targeting is possible through conjugation with tumor-targeting ligands such as melittin in a nano-formulation, as well as ligands specific to receptors (which are highly expressed on the cancer cells). Peptides loaded in nanoparticles can be directed to a specific region of the human body (e.g., cancer cells) using ligands like antibodies or tumor-homing peptides to maximize treatment in the tumor location and to avoid normal tissues [106].

A case in point is targeting TNBC cells using a bifunctional melittin modified with a charged C-terminus and an RGD (arginine–glycine–aspartic acid) motif, which reduces off-target effects and enhances specificity. Advanced chemical and pharmacological engineering is required to develop melittin into a clinically useful drug. TNBC is highly aggressive, has limited treatment options, poor prognosis, lacks estrogen, progesterone, and HER2 receptors, and does not respond to HER2-targeted or hormonal therapies [105, 107]. It is this desperate nature of lacking any molecular target that the desperate methods are aimed at [67, 105]. This is because of its chemical specialty and pharmacological

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(1), 1082-1105 | ISSN:2251-6727

multimodality, which gives melittin an important part of the bee venom therapeutic potential in TNBC in a preclinical study. It still is not an established medical treatment but has good preclinical results in animal models and cell lines, and there have been several hurdles to its use in humans [73, 108].

5.1. Chemical basis of selective action at TNBC

This selective mechanism and the ability of Melittin to select and affect TNBC cells is largely attributed to the nature of the chemical aspects [65, 109].

5.1.1. Surface linked to the charge

Melittin is a 26-amino-acid linear peptide (~2847.5 Da) with an amphipathic structure and a net positive charge of +6 at physiological pH due to arginine- and lysine-rich regions. Its hydrophobic N-terminal region and overall positive charge enable initial electrostatic interaction with cell membranes. Cancer cells, including TNBC cells, are more negatively charged than normal cells because of higher levels of negatively charged phospholipids (e.g., phosphatidylserine) in the outer membrane leaflet, promoting selective melittin binding with relatively less damage to healthy tissues [67, 70, 73, 110].

5.1.2. Chemical - Physical mechanism of membrane disruption by pore formation

The binding of Melittin to the cell membrane leads to the penetration of those monomers into the lipid bilayer. It is conformationally changed by changes in the chemical environment of the membrane, where such monomers are clustered and form transmembrane holes in the shape of toroidal pores [70, 73, 110]. Such pores destroy the physical integrity of the membrane, and, as a rule, their diameter is 4.4 nm. This causes an unduly rapid influx of ions and loss of intracellular elements of vital usage [70, 110]. It is necrotic cell death and osmotic lysis that led to the breakdown of cellular equilibrium [73].

It is important that the pore size and peculiarities of the ages of the membrane by melittin could be highly different based on the nature of the experiments and could be conditional on the character of the membranes [11]. In addition, the lytic activity and the pore formation of melittin depend much on the alignment of the melittin molecules on the margin of their parallel or perpendicular pose to the surface of the membrane [63]. Although the fast effects of complete cell studies are not reported most of the time, studies using lipid monolayers have confirmed apparent pore development and specific morphological changes [71]. The activity of melittin is more effective against cancer cells than in normal cells due to the increased membrane potential of the cancer cells [67].

5.2. Pharmacology efficacy in TNBC

Along with the production of direct membrane-lytic effects, Melittin possesses a pharmacological profile in TNBC, such as activation of programmed cell death, and a range of other major intracellular signaling pathways. These have been found in animal models and pre-clinical cell culture to a great extent [73].

5.2.1. Basic mechanisms: apoptosis and direct cytotoxicity induction

Melittin has a convenient effect of decreasing the viability of TNBC cell lines, including human SUM159 cells, under the pharmacological mode [85, 109]. A more controlled process is termed apoptosis, and is usually triggered together with this cytotoxicity. Cells treated with melittin have a significant increase in the proteins that are apoptotic-related, as indicated by cleaved caspase-3 in TNBC cells [85, 109-110]. In addition, the 4T1 TNBC cancer cell study has attributed the melittin-induced apoptosis to an elevation in the concentrations of dynamin-related protein 1 and mitochondrial fusion protein 2, which indicates that it affects the dynamics of mitochondria and activation of intrinsic apoptotic programs [85].

5.2.2. Signaling interference of growth factor receptors

There is signaling interference of growth factor receptors, which results in desensitization and downregulation of the receptors during handling. The anti-receptor activity of Melittin to inhibit the activity of developmental factor receptors holds a valuable pharmacological ground against its effectiveness in TNBC and HER2-positive breast tumors [110]. Melittin does this by inhibiting epidermal growth factor and HER2 Phosphorylation of the plasma membrane of

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(1), 1082-1105 | ISSN:2251-6727

breast cancerous cells. It has mutational analyses that positively charged C-terminal melittin sequence mediates this plasma membrane connection that directly affects its anticancer action [110]. Such interference results in an abnormal pharmacological down-regulation of the PI3K/Akt signaling pathways that are often abnormally stimulated in TNBC and required to warrant cell survival, proliferation, and growth [67, 85, 110].

5.2.3. Anti-Proliferative effects

Melittin generates a direct anti-proliferative impact on cells, and this attribute adds to its efficacy on TNBC. The combination of all the above-mentioned ways, including the membrane rupture, apoptotic induction, and the inhibition of pro-survival signaling pathways, is cooperative in the prevention of the unrestricted growth of the TNBC cells and can be attributed to this treatment effect [77].

5.3. Strategies to improve therapeutic effectiveness

Other strategies to enhance the effectiveness of melittin in the therapy of TNBC by chemical modification and the adoption of complex delivery methods to offset the non-specific toxicity of melittin, particularly its potent hemolytic effect and quick degradation, are being researched [73, 77, 112]. There is the imminent necessity to stress that the questions of delivery and safety are under research, and the alternative to the problem is not yet capable of being implemented at a clinical level [64, 73]. The challenges are associated with its non-specific cytotoxicity, high rate of metabolism, poor absorption, and allergy [63, 112].

5.3.1. Targeted delivery via chemical conjugation

Melittin, in its turn, may be attached to certain targeting ligands through chemical conjugation to become more successful in its delivery to TNBC cells. To illustrate this, in order to make sure that the melittin only acts on the malignant cells with minimum effects on the normal cells, a bifunctional melittin peptide including a charged sequence in its C-terminus to contain an RGD motif (arginine, glycine, and aspartic acid) has been engineered. The combinations of Coupled Pharmacology are known as Coupled Pharmacology Combinations [20, 110].

5.3.2. Synergistic pharmacology

Melittin demonstrates a certain degree of synergistic effectiveness with the traditional chemotherapy therapies that are typically applied to the treatment of TNBC, such as docetaxel and epirubicin [20]. Melittin has been shown to effectively decrease tumors that are resistant to docetaxel in vivo TNBC xenograft models and, therefore, may be of use in treating chemoresistance, and thus the combination of the two is of interest [62,70]. This synergy reduces the side effects, may reduce the toxicity of melittin internally, and also leads to some treatment outcomes, and could reduce individual drug dosage [20].

5.3.3. Nano-Delivery systems for targeting and pharmacokinetic enhancement

Nanocarrier systems are a complicated chemical procedure of delivering that can not only protect against its undesirable effects but also provide tumor-targeting delivery [63, 112]. These are some of the cationic polymers, nanodiamond, perfluorocarbon nanoparticles, and liposomes [63, 103-104]. Such systems would reduce toxicity and improve the efficacy of tumor treatment by improving stability and controlled release [63-64, 73, 103]. To illustrate this, the use of the anti-cancer property of melittin-loaded niosomes has been shown to be superior to melittin [70, 106].

Passive Targeting: These nanoparticles can also target the location of tumors, including TNBC, passively, because of the higher permeability and retention. This is because the tumor microenvironments contain leaky vasculatures and insufficient lymphatic drainage that permit extravasation of the nanoparticles and their preferential retention in the tumor [103, 113].

Active Targeting: This is dynamic and very specific to the TNBC cells by further modification of nanocarriers with specific ligands. In order to improve the drug delivery and raise the levels within the tumor bed and lower the levels in the systemic circulation, e.g., nanoparticles can be coated with receptors on the cancer cells or other over expresses on the angiogenic endothelial cells [104].

It is established that the anticancer activity of free melittin is weaker in comparison with the application of these melittin-loaded nanocarriers [70]. To minimize the

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(1), 1082-1105 | ISSN:2251-6727

overly negative side-effects and maximize the stability, scientists have continuously tried to make the systems more simplified [63, 104].

6. DISCUSSION

Melittin, the principal bioactive peptide of honey bee venom, has emerged as a promising multifunctional anticancer agent due to its diverse and complementary mechanisms of action. Unlike conventional chemotherapeutic agents that often target a single molecular pathway, melittin exerts cytotoxicity through both direct membrane disruption and modulation of multiple intracellular signaling cascades. Its amphipathic α-helical structure and strong cationic charge enable selective electrostatic interaction with negatively charged cancer cell membranes enriched in phosphatidylserine and other anionic phospholipids. This physicochemical preference partly explains the enhanced susceptibility of malignant cells compared to normal tissues. Rapid pore formation induces ionic imbalance, mitochondrial dysfunction, membrane destabilization, and ultimately necrotic or apoptotic cell death. Importantly, this membrane-lytic mechanism reduces the probability of resistance development, a significant limitation associated with many targeted therapies. The overall percentage of research work reported of Mellitin is shown in **Figure 8.**

Beyond its direct cytolytic effects, melittin interferes with several oncogenic signaling pathways involved in tumor proliferation, survival, angiogenesis, and metastasis. Inhibition of the PI3K/Akt/mTOR axis suppresses proliferative and anti-apoptotic signaling, while downregulation of JAK/STAT and NF-κB pathways attenuates inflammation-mediated tumor progression. Furthermore, suppression of VEGF and VEGFR signaling impairs angiogenesis, thereby limiting tumor vascularization and metastatic spread. These pleiotropic effects highlight melittin as a multi-target therapeutic candidate capable of disrupting tumor biology at multiple regulatory levels. Such broad-spectrum activity may be particularly advantageous in aggressive and heterogeneous malignancies that frequently develop resistance to single-target therapies.

In addition to its anticancer properties, melittin exhibits notable anti-inflammatory and immunomodulatory activities. Chronic inflammation is increasingly recognized as a critical contributor to carcinogenesis, tumor progression, and immune evasion. By inhibiting pro-inflammatory mediators such as TNF-α, IL-1β, COX-2, and iNOS, melittin may indirectly suppress tumor growth within an inflammatory microenvironment. Activation of antioxidant defense pathways, particularly Nrf2/HO-1 signaling, further enhances cellular protection against oxidative stress, a key driver of genomic instability and cancer development. However, the dual pro- and anti-inflammatory behavior of melittin—dependent on concentration and biological context—underscores the complexity of its pharmacological profile and necessitates controlled delivery strategies.

Despite its strong therapeutic potential, significant challenges remain regarding safety and clinical translation. The nonspecific cytotoxicity, pronounced hemolytic activity, rapid enzymatic degradation, and systemic toxicity resulting from indiscriminate membrane disruption limit its direct clinical application. Recent advances in chemical modification and nanotechnology-based delivery systems, including PEGylation, tumor-targeted conjugation, and nanoparticle encapsulation, have substantially improved tumor selectivity, reduced off-target toxicity, and enhanced pharmacokinetic stability. Passive targeting through enhanced permeability and retention (EPR) effects and active targeting via ligand modification further increase therapeutic precision.

Notably, melittin has demonstrated promising preclinical efficacy against aggressive malignancies such as triple-negative breast cancer (TNBC), a subtype lacking established molecular targets. Its ability to synergize with conventional chemotherapeutic agents suggests additional clinical value in overcoming drug resistance and reducing required dosages. However, challenges related to immunogenicity, optimal dosing strategies, large-scale manufacturing, and the absence of robust clinical trials continue to impede its translation into routine clinical practice.

Future research should focus on improving melittin's safety and tumor selectivity through advanced drug delivery systems such as nanoparticles, liposomes, and ligand-targeted formulations. Structural modifications, including PEGylation and peptide engineering, may enhance stability and reduce hemolytic effects.

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(1), 1082-1105 | ISSN:2251-6727

Exploration of combination therapies and comprehensive pharmacokinetic and clinical studies will be essential to establish melittin as a safe and effective therapeutic agent in oncology.

In summary, melittin represents a compelling lead compound for future anticancer drug development due to its multi-mechanistic action profile. Continued refinement of targeted delivery systems and comprehensive clinical evaluation will be essential to balance safety with therapeutic efficacy and to fully harness its potential in oncology.

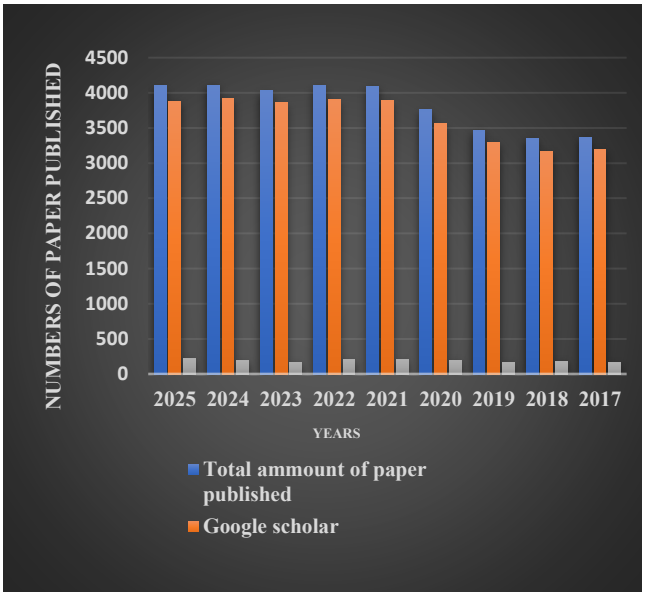


Figure 8: Proportion of research done every year on the Melittin (Google scholar, Pubmed, etc)

7. CONCLUSION

Melittin, the dominant bioactive peptide of honey bee venom, has emerged as a compelling prototype molecule in the pursuit of next-generation anticancer therapeutics. The collective evidence from studies published between 1990 and 2025 highlights its capacity to function as a multi-target anticancer agent, exerting cytotoxic effects through coordinated mechanisms that include rapid membrane permeabilization, mitochondrial dysfunction, apoptosis induction, suppression of proliferative signaling, inhibition of angiogenesis, and attenuation of metastatic progression. Its regulatory influence on pivotal oncogenic pathways—PI3K/Akt/mTOR, JAK/STAT, NF-κB, MAPK, and VEGF/VEGFR—underscores a systems-level mode of action that distinguishes it from conventional single-target chemotherapeutics. Moreover, its anti-inflammatory, immunomodulatory, and antioxidant activities suggest an additional capacity to remodel the tumor microenvironment, thereby amplifying therapeutic efficacy.

Despite these promising attributes, the intrinsic limitations of melittin—including nonspecific membrane lysis, hemolytic toxicity, rapid proteolytic degradation, and systemic adverse effects—pose significant barriers to direct clinical application. These challenges, however, have catalyzed innovative advances in peptide engineering and nanomedicine. Chemical modifications (e.g., PEGylation, amino acid substitutions, and fusion constructs) and targeted delivery platforms (liposomes, polymeric nanoparticles, ligand-conjugated systems) have demonstrated substantial improvements in stability, tumor selectivity, and therapeutic index in preclinical models, particularly in aggressive and treatment-resistant malignancies.

Taken together, melittin represents a potent and versatile lead scaffold with the potential to redefine peptide-based anticancer therapy. Future translational success will depend on rational molecular redesign, precision-targeted delivery systems, rigorous pharmacokinetic optimization, and well-structured clinical investigations. With continued interdisciplinary integration across chemistry, oncology, pharmacology, and nanotechnology, melittin may transition from a naturally derived cytolytic peptide to a clinically viable, precision-guided anticancer therapeutic.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

ACKNOWLEDGEMENTS

Authors are grateful to the management of Dr. B. C. Roy College of Pharmacy and Allied Health Sciences, Durgapur; DmbH Institute of Medical Sciences, Dadpur, Hoogly; and Anand College of Education, Department of Pharmacy, Debra for providing various reprographic sources for executing this review article successfully.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2026) 16(1), 1082-1105 | ISSN:2251-6727

REFERENCE

1. Bray F., Laversanne M., Sung H., Ferlay J., Siegel R. L., Soerjomataram I., Jemal A., 2024. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians. 74(3), 229–263.
2. Hanahan D., 2022. Hallmarks of cancer: new dimensions. Cancer Discovery. 12(1), 31–46.
3. Deo S. V., Sharma J., Kumar S., 2022. GLOBOCAN 2020 report on global cancer burden: challenges and opportunities for surgical oncologists. Annals of Surgical Oncology. 29(11), 6497–6500.
4. Danjuma M. I., Entonu M. E., Emmanuel E., 2022. Drug repurposing: Recent advancements, challenges, and future therapeutics for cancer treatment. J Bacteriol Mycol Open Access. 10(2), 26–30.
5. Mengistu B. A., Demessie Y., Kinde M. Z., Getnet K., Bitew A. B., Berrie K., Sendeku W., Berihun A. M., Abat A. S., Mebratu A. S., Feleke M. G., 2025. Biology of stem cell paradox: a double-edged sword-implications for cancer therapy. Cancer Cell International. 25(1), 380.
6. Saini A., Kumar M., Bhatt S., Saini V., Malik A., 2020. Cancer causes and treatments. Int J Pharm Sci Res. 11(7), 3121–3134.
7. Sharma V., Chaudhary A. A., Bawari S., Gupta S., Mishra R., Khan S. U., Ali M. A., Shahid M., Srivastava S., Verma D., Gupta A. Unraveling cancer progression pathways and phytochemical therapeutic strategies for its management. Frontiers in Pharmacology, 2024. 15, 1414790.
8. Kayal S., 2019. Cancer therapy: A brief outline. Annals of the National Academy of Medical Sciences (India). 55(3), 138–144.
9. Ostios-Garcia L., Perez D. M., Castelo B., Herradon N. H., Zamora P., Feliu J., Espinosa E., 2024. Classification of anticancer drugs: an update with FDA- and EMA-approved drugs. Cancer and Metastasis Reviews. 43(4), 1561–1571.
10. Mandal S. K., Debnath U., Kumar A., Thomas S., Mandal S. C., Choudhury M. D., Palit P., 2020. Natural sesquiterpene lactones in the prevention and treatment of inflammatory disorders and cancer: A systematic study of this emerging therapeutic approach based on chemical and pharmacological aspect. Letters in Drug Design & Discovery. 17(9), 1102–1116.
11. Guha S., Ferrie R. P., Ghimire J., Ventura C. R., Wu E., Sun L., Kim S. Y., Wiedman G. R., Hristova K., Wimley W. C. Applications and evolution of melittin, the quintessential membrane active peptide. Biochemical Pharmacology, 2021. 193, 114769.
12. Jin G., Yang Z., Wang L., Zhang S., Lin S., Bi Z., Yu B., Su Y., Xiang S., Veselova I. A., Liu H. pH-responsive polymeric-peptide complex enhances tumor immunogenic cell death by membrane disruption. Journal of Controlled Release, 2026. 114660.
13. Chen H., Dong Y., Shi F., Li F., 2025. Modulation of membrane-disruptive activity of melittin via N- and C-terminal PEGylation strategies. Bioconjugate Chemistry. 36(7), 1438–1447.
14. Ko S. J., Park E., Asandei A., Choi J. Y., Lee S. C., Seo C. H., Luchian T., Park Y., 2020. Bee venom-derived antimicrobial peptide melectin has broad-spectrum potency, cell selectivity, and salt-resistant properties. Scientific Reports. 10(1), 10145.
15. Memariani M., Memariani H., 2024. Anti-biofilm effects of melittin: Lessons learned and the path ahead. International Journal of Peptide Research and Therapeutics. 30(3), 29.
16. Bevalian P., Pashaei F., Akbari R., Bagheri K. P. Eradication of vancomycin-resistant Staphylococcus aureus on a mouse model of third-degree burn infection by melittin: an antimicrobial peptide from bee venom. Toxicon, 2021. 199, 49–59.
17. Maitip J., Mookhploy W., Khorndork S., Chantawannakul P., 2021. Comparative study of antimicrobial properties of bee venom extracts and melittins of honey bees. Antibiotics. 10(12), 1503.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2026) 16(1), 1082-1105 | ISSN:2251-6727

18. Radhakrishnan N., Kumar S. D., Shin S. Y., Yang S., 2024. Enhancing selective antimicrobial and antibiofilm activities of melittin through 6-aminohexanoic acid substitution. Biomolecules. 14(6), 699.
19. Chen Q. C., Liu L., Yu T. Y., Tang L., Yin M. L., Zhu W. H., Jiang X. Y., Wang H. Y., 2021. High-level expression and purification of melittin in Escherichia coli using SUMO fusion partner. International Journal of Peptide Research and Therapeutics. 27(1), 9–15.
20. Zhang H. Q., Sun C., Xu N., Liu W. The current landscape of the antimicrobial peptide melittin and its therapeutic potential. Frontiers in Immunology, 2024. 15, 1326033.
21. Pawar A., 2024. Exploring the therapeutic promise of melittin: anti-inflammatory and anti-cancer applications of bee venom. Journal of Internal Medicine and Pharmacology (JIMP). 1(4), 01–9.
22. Zade A., 2024. The therapeutic potential of melittin, the main component of bee venom: From inflammation to cancer treatment. Journal of Internal Medicine and Pharmacology (JIMP). 1(1), 01–8.
23. Gunathilaka N., Wimalasiri U., Wijerathna T., 2023. Therapeutic potential of melittin peptide: Major pain-producing substance of European honeybee (Apis mellifera) venom against several communicable and non-communicable diseases. Journal of Desk Research Review and Analysis. 1(2).
24. Pandey P., Khan F., Khan M. A., Kumar R., Upadhyay T. K., 2023. An updated review summarizing the anticancer efficacy of melittin from bee venom in several models of human cancers. Nutrients. 15(14), 3111.
25. Ceremuga M., Stela M., Janik E., Gorniak L., Synowiec E., Sliwinski T., Sitarek P., Saluk-Bijak J., Bijak M., 2020. Melittin—a natural peptide from bee venom which induces apoptosis in human leukaemia cells. Biomolecules. 10(2), 247.
26. Li X., Li Z., Meng Y. Q., Qiao H., Zhai K. R., Li Z. Q., Wei S. L., Li B., 2023. Melittin kills A549 cells by targeting mitochondria and blocking mitophagy flux. Redox Report. 28(1), 2284517.
27. Yan R., Dai W., Mao Y., Yu G., Li W., Shu M., Xu B., 2023. Melittin inhibits tumor cell migration and enhances cisplatin sensitivity by suppressing IL-17 signaling pathway gene LCN2 in castration-resistant prostate cancer. The Prostate. 83(15), 1430–1445.
28. Xu P., Zhou J., Xing X., Hao Y., Gao M., Li Z., Li X., Li M., Xiao Y., 2024. Melitoxin inhibits proliferation, metastasis, and invasion of glioma U251 cells by down-regulating F2RL1. Applied Biochemistry and Biotechnology. 196(9), 6234–6252.
29. Gu H., An H. J., Gwon M. G., Bae S., Leem J., Lee S. J., Han S. M., Zouboulis C. C., Park K. K., 2022. Bee venom and its major component melittin attenuated Cutibacterium acnes- and IGF-1-induced acne vulgaris via inactivation of Akt/mTOR/SREBP signaling pathway. International Journal of Molecular Sciences. 23(6), 3152.
30. Huang S., Su G., Jiang S., Chen L., Huang J., Yang F., 2024. New N-terminal fatty-acid-modified melittin analogs with potent biological activity. International Journal of Molecular Sciences. 25(2), 867.
31. Doltchinkova V., Vitkova V., Kitanova M., Shkodrova M., Lozanova S., Ivanov A., Roumenin C., 2025. On the effect of melittin on surface properties of erythrocyte and mitochondrial membranes. Membranes. 16(1), 11.
32. Min S., Picou C., Jeong H. J., Bower A., Jeong K., Chung J. K., 2024. Melittin–phospholipase A2 synergism is mediated by liquid–liquid miscibility phase transition in giant unilamellar vesicles. Langmuir. 40(14), 7456–7462.
33. Bose S., Mandal S. K., Hossain P., Das A., Das P., Nandy S., Giri S. K., Chakraborti C. K., 2019. Phytochemical and pharmacological potentials of Agaricus bisporus. Research Journal of Pharmacy and Technology. 12(8), 3811–3817
34. Abbasi E., 2025. The role of insects in future medicine: Diagnostic and therapeutic potential of insect-derived biomolecules and microbiota.

Entomologia Experimentalis et Applicata. DOI: 10.1111/eea.70033.

35. Dantas C. G., Nunes M., Nunes M., Oliveira A., Reis F. P., de W., Cardoso J. C., Gomes M. Z., Gramacho K. P., 2014. Pharmacological evaluation of bee venom and melittin. Revista Brasileira de Farmacognosia. 24(1), 67–72. DOI: 10.1590/0102-695x20142413365.
36. Lee K. S., Kim B. Y., Yoon H. J., Jin B.-R., 2023. Proteases and protease inhibitors in bee venoms. Journal of Apiculture. 38(4), 391–396. DOI: 10.17519/apiculture.2023.11.38.4.391.
37. Hanson J. M., Morley J., Soria-Herrera C., 1974. Anti-inflammatory property of 401 (MCD-peptide), a peptide from the venom of the bee Apis mellifera (L.). British Journal of Pharmacology. 50(3), 383.
38. Huang S., Jianhua W. A., Xiaozhong W. A., Chenghong L. I., 2016. Melittin: A key composition of honey bee venom with diverse pharmaceutical function. In International Conference on Biological Engineering and Pharmacy (BEP 2016),. 193–197. Atlantis Press.
39. Raghuraman H., Chattopadhyay A., 2007. Melittin: a membrane-active peptide with diverse functions. Bioscience Reports. 27(4–5), 189–223.
40. Bishop D. G., Kenrick J. R., 1980. Melittin: an inhibitor of chloroplast photochemical reactions. Biochemical and Biophysical Research Communications. 97(3), 1082–1090.
41. Taruna, Simran, Mishra A., 2024. Anticancer activity of bee venom and its components against breast cancer: a review. Plant Archives. 24(1), 217–222.
42. Moreno M., Giralt E., 2015. Three valuable peptides from bee and wasp venoms for therapeutic and biotechnological use: melittin, apamin and mastoparan. Toxins. 7(4), 1126–1150.
43. Chen J., Lariviere W. R., 2010. The nociceptive and anti-nociceptive effects of bee venom injection and therapy: a double-edged sword. Progress in Neurobiology. 92(2), 151–183.
44. Zou X., Dong Y., Alhaskawi A., Zhou H., Abdullah Ezzi S. H., Kota V. G., Abdulla Hasan Abdulla M. H., Abdalbary S. A., Liu Z., Wang C., Lu H., 2025. Bee venom acupuncture in the treatment of musculoskeletal system disorders: A comprehensive review. Pain Research and Management. 2025(1). DOI: 10.1155/prm/1766393.
45. Kang I., Kim W., Lim J. Y., Lee Y., Shin C., 2021. Organ-specific transcriptome analysis reveals differential gene expression in different castes under natural conditions in Apis cerana. Scientific Reports. 11(1), 11267
46. Akram A. B., McCann G. Antimicrobial peptides and chemicals produced by animals, Vol. 5, Innovations in Microbiology and Biotechnology, 2022. pp.122–134.
47. Vijayakumar K. K., Rajandran A., Lumumba S., Harshavardhan S. In silico characterization of melittin from Apis cerana indica and evaluation of melittin intron for transgene expression in mammalian cells. Journal of Applied Biology & Biotechnology, 2022. DOI: 10.7324/jabb.2023.101771.
48. Jáuregui D., Blasco M., Mafla S. Cloning and identification system of Apis mellifera melittin cDNA in. Insights on Antimicrobial Peptides, 2022. 105..
49. Suchanek G., Kreil G., Hermodson M. A., 1978. Amino acid sequence of honeybee prepromelittin synthesized in vitro. Proceedings of the National Academy of Sciences. 75(2), 701–704.
50. Li J. H., Zhang C. X., Tang Z. H., 2005. Expression of melittin gene in the venom gland of the Chinese honeybee, Apis cerana cerana. Apidologie. 36(4), 533–541.
51. Hejníková M., Tomčala A., Černý J., Kodrík D. Melittin—The principal toxin of honeybee venom—Is also produced in the honeybee fat body. Comparative Biochemistry and Physiology Part C: Toxicology & Pharmacology, 2024. 281, 109928.
52. Kim W., 2021. Bee venom and its sub-components: characterization, pharmacology, and therapeutics. Toxins. 13(3), 191.
53. Abd El-Wahed A. A., Khalifa S. A., Sheikh B. Y., Farag M. A., Saeed A., Larik F. A., Koca-Caliskan U., AlAjmi M. F., Hassan M., Wahabi

H. A., Hegazy M. E. Bee venom composition: From chemistry to biological activity. Studies in Natural Products Chemistry, 2019. 60, 459–484.

54. Klupczynska A., Plewa S., Dereziński P., Garrett T. J., Rubio V. Y., Kokot Z. J., Matysiak J., 2020. Identification and quantification of honeybee venom constituents by multiplatform metabolomics. Scientific Reports. 10(1), 21645.
55. Pucca M. B., Cerni F. A., Oliveira I. S., Jenkins T. P., Argemí L., Sørensen C. V., Ahmadi S., Barbosa J. E., Laustsen A. H. Bee updated: current knowledge on bee venom and bee envenoming therapy. Frontiers in Immunology, 2019. 10, 2090.
56. Samancı T., Kekeçoğlu M., 2019. Comparison of commercial and anatolian bee venom in terms of chemical composition. Uludag Bee Journal. 19(1), 61–68.
57. Sig A. K., Güney M., Sig Ö. Ö., Şan H., 2019. Bee venom: A medical perspective. Turkish Journal of Clinics and Laboratory. 10(3), 414–421.
58. Peiren N., de Graaf D. C., Vanrobaeys F., Danneels E. L., Devreese B., Van Beeumen J., Jacobs F. J., 2008. Proteomic analysis of the honey bee worker venom gland focusing on the mechanisms of protection against tissue damage. Toxicon. 52(1), 72–83.
59. Pak S. C. Chemical composition of bee venom. In Bee Products—Chemical and Biological Properties. Springer International Publishing, 2017. 279–285.
60. Otręba M., Marek Ł., Stojko J., Rzepecka-Stojko A., 2025. Bee products as alternatives in the treatment of viral infections. Journal of the Science of Food and Agriculture. 106(1), 33–54. DOI: 10.1002/jsfa.70017.
61. Sanlier N., Kaya E. Y., Yucel I. I., 2026. Health effects of bee products: A comprehensive review. Food Science & Nutrition. 14(2). DOI: 10.1002/fsn3.71165.
62. Bose S., Mandal S. K., Das P., Nandy S., Das A., Dutta D., Chakraborti C. K., Sarkar D., Dey S., 2020. Comparative evaluation of anti-inflammatory, antipyretic and analgesic properties of Ixora coccinea and Mussaenda frondosa (Rubiaceae) leaves. Jordan Journal of Pharmaceutical Sciences. 13(3)
63. Wang A., Zheng Y., Zhu W., Yang L., Yang Y., Peng J., 2022. Melittin-based nano-delivery systems for cancer therapy. Biomolecules. 12(1), 118.
64. Yu X., Jia S., Yu S., Chen Y., Zhang C., Chen H., Dai Y., 2023. Recent advances in melittin-based nanoparticles for antitumor treatment: from mechanisms to targeted delivery strategies. Journal of Nanobiotechnology. 21(1), 454.
65. Li Y., 2025. Mechanism of melittin for anti-tumor effects: Research status and future perspectives. Journal of Clinical Technology and Theory. 2(1), 33–37. DOI: 10.54254/3049-5458/2025.21076.
66. Xing X., Zhang X., Fan J., Zhang C., Zhang L., Duan R., Hao H., 2024. Neuroprotective effects of melittin against cerebral ischemia and inflammatory injury via upregulation of MCPIP1 to suppress NF-κB activation in vivo and in vitro. Neurochemical Research. 49(2), 348–362.
67. Tariq R., Liaqat A., Khalid U. A. An insight into the role of bee venom and melittin against tumor cells: a review of breast cancer therapy. Archives of Breast Cancer, 2021. 267–276.
68. Misra S. K., Ye M., Kim S., Pan D., 2015. Defined nanoscale chemistry influences delivery of peptido-toxins for cancer therapy. PLoS One. 10(6), e0125908.
69. Shaw P., Kumar N., Hammerschmid D., Privat-Maldonado A., Dewilde S., Bogaerts A., 2019. Synergistic effects of melittin and plasma treatment: A promising approach for cancer therapy. Cancers. 11(8), 1109.
70. Dabbagh Moghaddam F., Akbarzadeh I., Marzbankia E., Farid M., Khaledi L., Reihani A. H., Javidfar M., Mortazavi P., 2021. Delivery of melittin-loaded niosomes for breast cancer treatment: an in vitro and in vivo evaluation of anti-cancer effect. Cancer Nanotechnology. 12(1), 14.
71. Soliman C., Eastwood S., Truong V. K., Ramsland P. A., Elbourne A., 2019. The

membrane effects of melittin on gastric and colorectal cancer. PLoS One. 14(10), e0224028.

72. Zarrinnahad H., Mahmoodzadeh A., Hamidi M. P., Mahdavi M., Moradi A., Bagheri K. P., Shahbazzadeh D., 2018. Apoptotic effect of melittin purified from Iranian honey bee venom on human cervical cancer HeLa cell line. International Journal of Peptide Research and Therapeutics. 24(4), 563–570.
73. Rady I., Siddiqui I. A., Rady M., Mukhtar H. Melittin, a major peptide component of bee venom, and its conjugates in cancer therapy. Cancer Letters, 2017. 402, 16–31.
74. Moon D. O., Park S. Y., Choi Y. H., Kim N. D., Lee C., Kim G. Y., 2008. Melittin induces Bcl-2 and caspase-3-dependent apoptosis through downregulation of Akt phosphorylation in human leukemic U937 cells. Toxicon. 51(1), 112–120.
75. Icriverzi M., Florian P. E., Bonciu A., Dumitrescu L. N., Moldovan A., Pelinescu D., Ionescu R., Avram I., Munteanu C. V., Sima L. E., Dinca V., 2024. Hybrid bio-nanoporous peptide loaded-polymer platforms with anticancer and antibacterial activities. Nanoscale Advances. 6(8), 2038–2058.
76. Jo M., Park M. H., Kollipara P. S., An B. J., Song H. S., Han S. B., Kim J. H., Song M. J., Hong J. T., 2012. Anti-cancer effect of bee venom toxin and melittin in ovarian cancer cells through induction of death receptors and inhibition of JAK2/STAT3 pathway. Toxicology and Applied Pharmacology. 258(1), 72–81. DOI: 10.1016/j.taap.2011.10.009.
77. Haque S., Hussain A., Joshi H., Sharma U., Sharma B., Aggarwal D., Rani I., Ramniwas S., Gupta M., Tuli H. S., 2023. Melittin: a possible regulator of cancer proliferation in preclinical cell culture and animal models. Journal of Cancer Research and Clinical Oncology. 149(19), 17709–17726.
78. Liu C. C., Hao D. J., Zhang Q., An J., Zhao J. J., Chen B., Zhang L. L., Yang H., 2016. Application of bee venom and its main constituent melittin for cancer treatment. Cancer Chemotherapy and Pharmacology. 78(6), 1113–1130.
79. Denk B., 2024. Structural insights and anticancer potential of melittin in CD147 interaction. Journal of Faculty of Pharmacy of Ankara University. 48(3), 912–919.
80. Park S.-H., Cho H.-J., Jeong Y.-J., Shin J.-M., Kang J.-H., Park K.-K., Choe J.-Y., Park Y.-Y., Bae Y.-S., Han S.-M., Moon S.-K., Kim W.-J., Choi Y. H., Chang Y.-C., 2014. Melittin inhibits TGF-β-induced pro-fibrotic gene expression through the suppression of the TGFβRII-Smad, ERK1/2 and JNK-mediated signaling pathway. The American Journal of Chinese Medicine. 42(5), 1139–1152. DOI: 10.1142/s0192415x14500712.
81. Huh J.-E., Kang J. C., Nam D., Baek Y.-H., Choi D.-Y., Park D.-S., Lee J.-D., 2012. Melittin suppresses VEGF-A-induced tumor growth by blocking VEGFR-2 and the COX-2-mediated MAPK signaling pathway. Journal of Natural Products. 75(11), 1922–1929. DOI: 10.1021/np300446c.
82. Shin J. M., Jeong Y. J., Cho H. J., Park K. K., Chung I. K., Lee I. K., Kwak J. Y., Chang H. W., Kim C. H., Moon S. K., Kim W. J., 2013. Melittin suppresses HIF-1α/VEGF expression through inhibition of ERK and mTOR/p70S6K pathway in human cervical carcinoma cells. PLoS One. 8(7), e69380.
83. Zhang S. F., Chen Z., 2017. Melittin exerts an antitumor effect on non small cell lung cancer cells. Molecular Medicine Reports. 16(3), 3581–3586.
84. Lee G., Bae H., 2016. Anti-inflammatory applications of melittin, a major component of bee venom: detailed mechanism of action and adverse effects. Molecules. 21(5), 616.
85. Zhang H. Q., Sun C., Xu N., Liu W. The current landscape of the antimicrobial peptide melittin and its therapeutic potential. Frontiers in Immunology, 2024. 15, 1326033.
86. Xing X., Zhang X., Fan J., Zhang C., Zhang L., Duan R., Hao H., 2024. Neuroprotective effects of melittin against cerebral ischemia and inflammatory injury via upregulation of MCPIP1 to suppress NF-κB activation in vivo and in vitro. Neurochemical Research. 49(2), 348–362.

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(1), 1082-1105 | ISSN:2251-6727

87. Huang H., Chen T., Zheng W., Cui Y., Peng T., Liu S., Wen X., Xu J., Wang L., Zhang S. Structure-guided synthesis of melittin analogs with reduced hemolysis and enhanced anti-inflammatory activity. Arabian Journal of Chemistry, 2025. 19, 5892025. DOI: 10.25259/ajc_589_2025.

88. Park H. J., Lee H. J., Choi M. S., Son D. J., Song H. S., Song M. J., Lee J. M., Han S. B., Kim Y., Hong J. T., 2008. JNK pathway is involved in the inhibition of inflammatory target gene expression and NF-kappaB activation by melittin. Journal of Inflammation. 5(1), 7.

89. Kim S. J., Park J. H., Kim K. H., Lee W. R., Kim K. S., Park K. K., 2011. Melittin inhibits atherosclerosis in LPS/high-fat treated mice through atheroprotective actions. Journal of Atherosclerosis and Thrombosis. 18(12), 1117–1126.

90. Gu S. M., Park M. H., Hwang C. J., Song H. S., Lee U. S., Han S. B., Oh K. W., Ham Y. W., Song M. J., Son D. J., Hong J. T., 2015. Bee venom ameliorates lipopolysaccharide-induced memory loss by preventing NF-kappaB pathway. Journal of Neuroinflammation. 12(1), 124.

91. Mandal S. K., Pal H., Pal I., Bose S., Roy B. C., 2018. Biological potential of Elephantopus scaber Linn. International Journal of Pharmaceutical Sciences Review and Research. 50(2), 130–134.

92. Nguyen C. D., Yoo J., Jeong S. J., Ha H. A., Yang J. H., Lee G., Shin J. C., Kim J. H., 2024. Melittin—the main component of bee venom: a promising therapeutic agent for neuroprotection through Keap1/Nrf2/HO-1 pathway activation. Chinese Medicine. 19(1), 166.

93. Wang T., Zhang J., Xiao A., Liu W., Shang Y., An J., 2016. Melittin ameliorates CVB3-induced myocarditis via activation of the HDAC2-mediated GSK-3β/Nrf2/ARE signaling pathway. Biochemical and Biophysical Research Communications. 480(1), 126–131. DOI: 10.1016/j.bbrc.2016.09.135.

94. Shahsavari S., Sarkar S., Sen D. J., Mandal S. K., 2022. Determination of the total antioxidant activity of methanolic extract of Falcaria vulgaris. Journal of Biochemicals and Phytomedicine. 1(1), 8–12.

95. Martín-Sánchez F., Martínez-García J. J., Muñoz-García M., Martínez-Villanueva M., Noguera-Velasco J. A., Andreu D., Rivas L., Pelegrín P., 2017. Lytic cell death induced by melittin bypasses pyroptosis but induces NLRP3 inflammasome activation and IL-1β release. Cell Death & Disease. 8(8), e2984.

96. Li D., Xue F., Wu Y., Chang L., Song Y., Du X., Wu J., Liu Q., Wang T. Efficacy and spinal noradrenergic mechanisms of contralateral melittin acupuncture against paclitaxel-induced peripheral neuropathic pain in rats. Journal of Pain Research, 2026. 19, 1–16. DOI: 10.2147/jpr.s584909.

97. Bhattacharya S. O., Mandal S. K., Akhtar M. S., Dastider D. I., Sarkar S. I., Bose S. A., Bose A. N., Mandal S. A., Kolay A. R., Sen D. J., Kumar A., 2020. Phytochemicals in the treatment of arthritis: Current knowledge. International Journal of Current Pharmaceutical Research. 12(4), 1–6.

98. Erkoc P., von Reumont B. M., Lüddecke T., Henke M., Ulshöfer T., Vilcinskas A., Fürst R., Schiffmann S., 2022. The pharmacological potential of novel melittin variants from the honeybee and solitary bees against inflammation and cancer. Toxins. 14(12), 818.

99. Cornara L., Biagi M., Xiao J., Burlando B. Therapeutic properties of bioactive compounds from different honeybee products. Frontiers in Pharmacology, 2017. 8, 261216.

100. Askari P., Namaei M. H., Ghazvini K., Hosseini M., 2021. In vitro and in vivo toxicity and antibacterial efficacy of melittin against clinical extensively drug-resistant bacteria. BMC Pharmacology and Toxicology. 22(1), 42.

101. Zu Y., Zhang Z. Three monoterpenoids eucommiol from the leaves of Eucommia ulmoides protect against neurotoxicity in PC12 cells. In International Conference on Biological Engineering and Pharmacy (BEP 2016), 2016. 143–145. Atlantis Press.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2026) 16(1), 1082-1105 | ISSN:2251-6727

102. Wang Y., Lu Y., Li C. L., Sun W., Li Z., Wang R. R., He T., Yang F., Yang Y., Wang X., Guan S., Chen J., 2016. Involvement of Rac1 signalling pathway in the development and maintenance of acute inflammatory pain induced by bee venom injection. British Journal of Pharmacology. 173(5), 937–950. DOI: 10.1111/bph.13413.
103. Das A., Raja Sheikh R., Pandey A., Biswas S., Sarkar A., Mondal I., Mandal S. K., 2026. Formulation and evaluation of lipid micro-particle based on mosquito repellent cream. Plant Biotechnology Persa. 8, 0–.
104. Pudelka L., Janovska S., Malis J., Sleha R., Bostik P., 2025. Bee venom–friend or enemy. MMSL. 94(2), 79–93.
105. Xiong N., Wu H., Yu Z. Advancements and challenges in triple-negative breast cancer: a comprehensive review of therapeutic and diagnostic strategies. Frontiers in Oncology, 2024. 14, 1405491.
106. Amin A., Singh J. P., Singh R., 2024. From bee venom to drug: A short review. Environmental Science Archives. 3(2), 124–130. DOI: 10.5281/zenodo.13898756.
107. Zagami P., Carey L. A., 2022. Triple negative breast cancer: Pitfalls and progress. NPJ Breast Cancer. 8(1), 95.
108. Prince G., Assi A., Aoude M., Kourie H. R., Haddad F. Melittin, a potential game-changer in the fight against breast cancer: a systematic review. Anti-Cancer Agents in Medicinal Chemistry, 2025.
109. Adel Abbas R., Attia M. N. T., Mohammed H. E., Tawfik M. M., 2026. Comprehensive evaluation of the anticancer activity of Egyptian bee venom (Apis mellifera): Cytotoxic effects on diverse human cancer cell lines and tumor suppression in EAC mice. Beni-Suef University Journal of Basic and Applied Sciences. 15(1). DOI: 10.1186/s43088-026-00743-0.
110. Duffy C., Sorolla A., Wang E., Golden E., Woodward E., Davern K., Ho D., Johnstone E., Pfleger K., Redfern A., Iyer K. S., 2020. Honeybee venom and melittin suppress growth factor receptor activation in HER2-enriched and triple-negative breast cancer. NPJ Precision Oncology. 4(1), 24.
111. Pandidan S., Mechler A., 2019. Nano-viscosimetry analysis of the membrane disrupting action of the bee venom peptide melittin. Scientific Reports. 9(1), 10841.
112. Zhou J., Wan C., Cheng J., Huang H., Lovell J. F., Jin H., 2021. Delivery strategies for melittin-based cancer therapy. ACS Applied Materials & Interfaces. 13(15), 17158–17173.
113. Soman N. R., Baldwin S. L., Hu G., Marsh J. N., Lanza G. M., Heuser J. E., Arbeit J. M., Wickline S. A., Schlesinger P. H., 2009. Molecularly targeted nanocarriers deliver the cytolytic peptide melittin specifically to tumor cells in mice, reducing tumor growth. The Journal of Clinical Investigation. 119(9), 2830–2842.