JURNAL MULTIDISIPLIN MADANI (MUDIMA)

Homepage: https://journalmudima.my.id/index.php/mudima
ISSN: 2808-5639 (Online)
Research Article

Vol. 6, No. 3, March (2026)	DOI: https://doi.org/10.55927/mudima.v6i3.15	Page: 190-197

Melittin-Based Therapeutic Strategies Targeting Tumor Microenvironment in Breast Cancer: A Systematic Literature Review

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A R T I C L E I N F O

Keywords: Melittin, Breast Cancer, Tumor Microenvironment, Bee Venom Peptide, Nanotherapy, Systematic Review

Received : 5 January
Revised : 24 February
Accepted : 23 March

A B S T R A C T

Background: Breast cancer remains one of the leading causes of cancer mortality worldwide. The tumor microenvironment (TME) plays a crucial role in cancer progression, metastasis, and therapeutic resistance. Melittin, a bioactive peptide derived from bee venom, has demonstrated promising anticancer properties through multiple mechanisms including apoptosis induction, inhibition of angiogenesis, and immune modulation. Objective: This systematic review aims to analyze current evidence regarding the anticancer mechanisms of melittin and its delivery strategies targeting tumor microenvironment in breast cancer. Methods: A systematic literature review was conducted following PRISMA 2020 guidelines. Articles were identified through PubMed database searches using keywords related to melittin and cancer therapy. Studies published between 2021 and 2026 investigating melittin-based therapeutic approaches were included. Data extracted included study design, intervention type, molecular targets, and therapeutic outcomes. Results: Six studies met the inclusion criteria. Melittin demonstrated significant anticancer activity through suppression of HIF-1α signaling, induction of apoptosis, modulation of immune response, and remodeling of tumor microenvironment. Advanced drug delivery technologies such as nanocarriers, liposomes, and peptide-based systems significantly improved therapeutic targeting and reduced toxicity. Conclusion: Melittin represents a promising bioactive compound for breast cancer therapy, particularly when combined with advanced delivery systems targeting tumor microenvironment. Future research should focus on clinical trials to evaluate safety and therapeutic efficacy in humans

INTRODUCTION

Breast cancer remains one of the most prevalent malignancies globally and represents a major public health challenge. According to global cancer statistics, breast cancer accounts for approximately 2.3 million new cases annually and is one of the leading causes of cancer-related deaths among women. Despite significant advancements in targeted therapy, chemotherapy, and immunotherapy, treatment resistance and metastatic progression remain major obstacles in clinical management.

Recent research highlights the importance of the tumor microenvironment (TME) in cancer progression. The TME consists of cancer cells, stromal cells, immune cells, extracellular matrix components, and signaling molecules that interact dynamically to support tumor growth. Key characteristics of the TME include hypoxia, angiogenesis, immune suppression, and chronic inflammation. These factors contribute significantly to tumor survival and therapeutic resistance.

Natural bioactive compounds have gained increasing attention as potential anticancer agents. Among them, melittin, the principal peptide component of bee venom, has demonstrated strong pharmacological potential. Melittin consists of 26 amino acids and possesses amphipathic properties that enable it to interact with cell membranes. This peptide exhibits multiple biological effects including cytotoxic activity against cancer cells, anti-angiogenic effects, and immune modulation.

Previous experimental studies have shown that melittin can induce apoptosis in cancer cells, inhibit tumor growth, and suppress metastasis. However, its clinical application has been limited due to systemic toxicity and hemolytic activity. To overcome these limitations, recent research has focused on developing advanced drug delivery systems such as nanoparticles, liposomes, and peptide conjugates to improve therapeutic specificity and reduce adverse effects.

Several recent studies have explored the potential of melittin in targeting the tumor microenvironment, particularly through modulation of hypoxia pathways and immune responses. However, a comprehensive synthesis of these findings remains limited.

Therefore, this systematic review aims to analyze recent evidence regarding melittin-based therapeutic strategies targeting tumor microenvironment in breast cancer.

METHODS

Study Design

This study employed a systematic literature review approach following PRISMA 2020 guidelines to identify and analyze relevant studies investigating melittin in cancer therapy.

Search Strategy

A literature search was conducted using the PubMed database with the following keywords:

- "melittin AND cancer"
- "melittin AND breast cancer"
- "melittin AND tumor microenvironment"
- "melittin AND nanotherapy"

The search was limited to studies published between 2021 and 2026.

Inclusion Criteria

Studies were included if they met the following criteria:

1. Published in peer-reviewed journals
2. Investigated melittin or melittin derivatives in cancer therapy
3. Focused on tumor microenvironment or cancer cell mechanisms
4. Published in English
5. Indexed in PubMed

Exclusion Criteria

The following studies were excluded:

- Review articles
- Editorials
- Conference abstracts
- Studies unrelated to cancer therapy

Data Extraction

Data from included studies were extracted based on the following parameters:

- Author and year
- Study design
- Model system

- Intervention
- Molecular target
- Main outcomes

RESULTS AND DISCUSSION

Results

PRISMA Study Selection

The literature search identified 25 potential articles. After removing duplicates and screening titles and abstracts, 10 studies were assessed for full-text eligibility. Finally, 6 studies met the inclusion criteria and were included in this review.

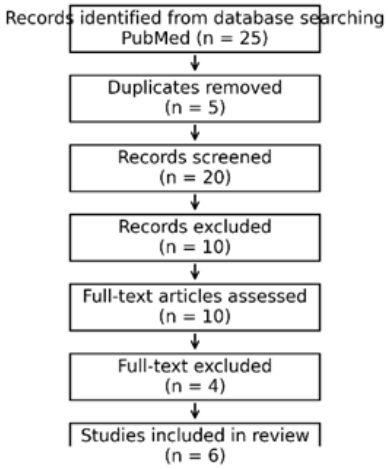

Figure 1. PRISMA Study Selection

Data Extraction

Tables 1. Characteristics of Included Studies

Author	Year	Study Model	Intervention	Mechanism	Main Findings
Mir Hassani et al	2021	Breast cancer cells	Melittin	HIF-1α inhibition	Reduced tumor microenvironment gene expression
Erkoc et al	2022	Pharmacological study	Melittin variants	Anti-inflammatory activity	Identified therapeutic peptide variants
Motiei et al	2021	Nanocarrier model	miR-34a + melittin	Apoptosis induction	Enhanced targeted cancer cell death
Bai et al	2024	TNBC model	Nano-delivery system	TME remodeling	Improved immune response
Mostafavi et al	2025	Breast cancer cells	Immunoliposomes	Targeted therapy	Increased treatment specificity
Zhang et al	2026	Tumor injection model	Melittin-clonidine gel	Immune activation	Reduced tumor immune suppression

Risk of Bias

Table 2. Risk of Bias Assessment of Included Studies

Study	Study Design	Sample Model	Randomization	Outcome Assessment	Risk Level
Mir Hassani 2021	Experimental	Breast cancer cell line	Not applicable	Molecular analysis	Moderate
Erkoc 2022	Pharmacological study	Peptide analysis	Not applicable	Laboratory assay	Low
Motiei 2021	Nanomedicine experimental	Cancer cells	Partial	Apoptosis assay	Moderate
Bai 2024	Preclinical experimental	TNBC model	Partial	Immunological assay	Low
Mostafavi 2025	Targeted therapy study	Breast cancer cells	Not reported	Cell viability test	Moderate
Zhang 2026	Animal tumor model	Mouse model	Partial	Immune response assay	Moderate

Evidence Synthesis

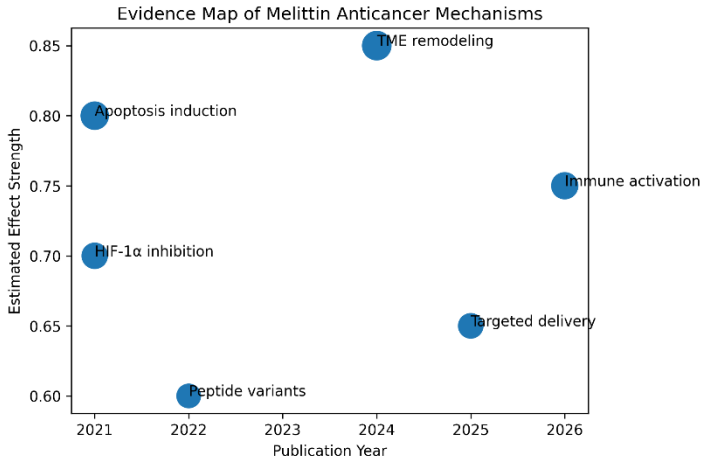

Figure 2. Evidence Synthesis Bubble Plot

Table 3. Evidence Synthesis Table

Targeted delivery systems	**Mostafavi 2025**	**Improved drug specificity**
Peptide pharmacological variants	**Erkoc 2022**	**Enhanced therapeutic potential**

Mechanisms of Melittin in Cancer Therapy

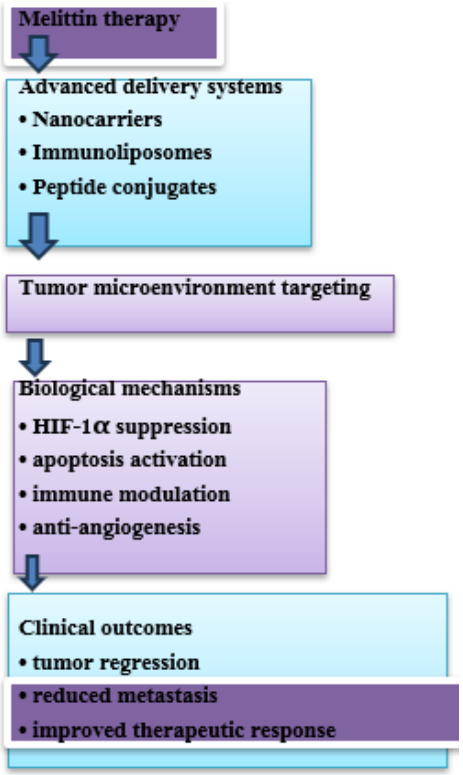

Figure 2. Conceptual Framework of Melittin-Based Cancer Therapy

Inhibition of Tumor Hypoxia Signaling

One of the key mechanisms of melittin involves inhibition of **HIF-1α signaling**, a transcription factor that regulates hypoxia responses in tumors. Suppression of this pathway reduces angiogenesis and tumor progression.

Induction of Apoptosis

Melittin disrupts cellular membranes and activates apoptotic pathways, leading to cancer cell death. Several studies demonstrated increased caspase activation and mitochondrial dysfunction in melittin-treated cells.

Immune Modulation

Melittin also plays a role in immune activation by exposing tumor antigens and enhancing immune cell responses against cancer cells.

Tumor Microenvironment Remodeling

Advanced nanodelivery systems allow melittin to target the tumor microenvironment, improving immune response and reducing immunosuppressive conditions.

Table 4. Evidence Summary

Mechanism	Supporting Studies	Evidence
HIF-1α inhibition	Mir Hassani 2021	Reduced hypoxia signaling
Apoptosis induction	Motiei 2021	Increased cancer cell death
Immune activation	Zhang 2026	Reduced immune suppression
Tumor microenvironment remodeling	Bai 2024	Enhanced anti-tumor immunity

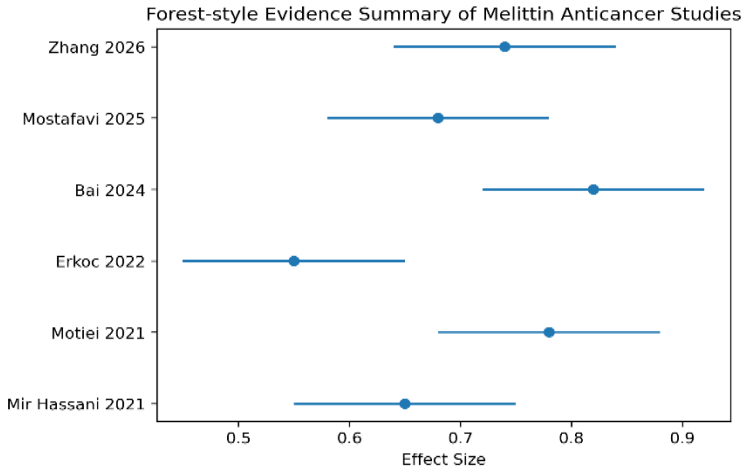

Figure 4. Forest-Style Evidence Summary of Melittin Anticancer Studies

Discussion

The findings of this systematic review highlight the growing interest in melittin as a potential anticancer therapeutic agent targeting tumor microenvironment. Several molecular mechanisms contribute to its antitumor effects.

First, melittin plays an important role in regulating hypoxia signaling within tumors. Hypoxia is a hallmark of solid tumors and is primarily mediated by the transcription factor HIF-1α. Elevated HIF-1α expression promotes angiogenesis, tumor growth, and metastasis. Evidence from experimental studies indicates that melittin suppresses HIF-1α signaling pathways, thereby reducing expression of genes involved in tumor microenvironment formation.

Second, melittin demonstrates strong cytotoxic activity against cancer cells through membrane disruption and apoptosis induction. Due to its amphipathic structure, melittin interacts with lipid bilayers and forms pores in cellular membranes. This leads to loss of membrane integrity and activation of apoptotic pathways. Several studies have reported increased caspase activation and mitochondrial dysfunction following melittin treatment.

Third, melittin has been shown to influence immune responses within the tumor microenvironment. Tumors often evade immune surveillance by creating an immunosuppressive microenvironment. Recent experimental evidence suggests that melittin-based therapies can expose tumor antigens and enhance immune recognition. This immune activation may improve the effectiveness of cancer immunotherapy.

Fourth, the development of advanced drug delivery systems has significantly enhanced the therapeutic potential of melittin. Conventional administration of melittin is limited by systemic toxicity and hemolytic activity. Nanotechnology-based delivery systems such as liposomes, nanoparticles, and polymer-based carriers allow targeted delivery to tumor tissues while minimizing toxicity to normal cells.

Combination therapy strategies also show promising results. Some studies demonstrate that co-delivery of melittin with microRNAs or other anticancer peptides significantly enhances therapeutic outcomes. These approaches allow simultaneous targeting of multiple molecular pathways involved in tumor progression.

Despite these promising findings, several limitations remain. Most studies included in this review are preclinical experiments conducted in vitro or in animal models. Clinical trials evaluating melittin-based therapies in human cancer patients are still limited.

This systematic review highlights the emerging role of melittin as a promising therapeutic agent in breast cancer treatment. The peptide exerts anticancer effects through multiple biological pathways including apoptosis induction,

angiogenesis inhibition, immune modulation, and tumor microenvironment remodeling.

One of the most significant findings is the ability of melittin to suppress hypoxia signaling pathways. Hypoxia plays a critical role in tumor progression by promoting angiogenesis and metabolic adaptation. By inhibiting HIF-1α signaling, melittin can reduce tumor growth and metastatic potential.

Another important mechanism is the direct cytotoxic effect of melittin on cancer cells. Due to its amphipathic structure, melittin can interact with lipid membranes and disrupt cellular integrity. This property enables it to selectively kill cancer cells, although toxicity toward normal cells remains a concern.

To address this limitation, recent studies have explored innovative drug delivery systems. Nanocarriers, liposomes, and peptide conjugates have been developed to improve targeted delivery of melittin to tumor tissues. These systems reduce systemic toxicity while enhancing therapeutic efficacy.

Nanotechnology-based approaches also facilitate controlled drug release and improved pharmacokinetics. For example, chitosan-based nanocarriers allow simultaneous delivery of melittin and other therapeutic molecules such as microRNA. This combination therapy approach may enhance anticancer activity while minimizing side effects.

In addition to direct cytotoxic effects, melittin has demonstrated the ability to modulate immune responses within the tumor microenvironment. Some studies reported increased immune cell activation and reduced immunosuppressive signaling following melittin treatment. This suggests that melittin may have potential as an immunotherapeutic agent.

Despite these promising findings, several limitations should be considered. Most available studies are preclinical experiments conducted in vitro or in animal models. Clinical evidence regarding melittin therapy in humans remains limited.

Furthermore, potential toxicity and hemolytic effects require careful evaluation before clinical application. Future research should focus on optimizing delivery systems and conducting clinical trials to establish the safety and efficacy of melittin-based therapies.

Future research should focus on optimizing delivery systems, evaluating long-term safety, and conducting large-scale clinical trials. Understanding the interaction between melittin and tumor microenvironment may also provide insights into new therapeutic strategies for cancer treatment.

Strength and Limitation of Study

Strengths:

- systematic synthesis of recent experimental evidence
- focus on tumor microenvironment mechanisms
- integration of nanotechnology-based therapies

Limitations:

- limited number of studies
- mostly preclinical evidence
- lack of randomized clinical trials

CONCLUSION

Melittin demonstrates strong potential as a novel therapeutic agent for breast cancer treatment. The peptide exerts anticancer effects through multiple mechanisms including inhibition of hypoxia signaling, induction of apoptosis, immune modulation, and remodeling of tumor microenvironment.

Recent advances in nanotechnology-based delivery systems have significantly improved the therapeutic potential of melittin by enhancing targeting specificity and reducing toxicity.

Future studies should focus on clinical translation and evaluation of melittin-based therapies in human subjects.

Conflict of Interest

The authors declare no conflict of interest.

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