REVIEW ARTICLE

Anticancer Properties of Bee Venom Bioactive Compounds: A Scoping Review

Siti Nur Farisyah Abdul Rahim[1], Mohammad Syaiful Bahari Abdull Rasad[1,*]

[1]Department of Biomedical Sciences, Kulliyyah of Allied Health Sciences, International Islamic University Malaysia, 25200 Kuantan, Pahang, Malaysia

Keywords:
Bee venom; anticancer activity; melittin; bioactive compounds

ABSTRACT

Background: *Apis melliferra* (bee venom) has long been used in alternative medicine for its therapeutic effects and recently research highlights its anticancer potential. This scoping review aims to systematically gather and evaluate evidence on the anticancer properties of bee venom and its bioactive compounds. **Methods:** This review followed PRISMA-ScR guidelines using articles retrieved from PubMed, ScienceDirect and Scopus from 2010 to 2024. Studies were screened based on inclusion and exclusion criteria, focusing on the anticancer effects of bee venom components. A total of 240 articles were retrieved, with 35 meeting the eligibity criteria. Data on cancer type, model, compound, and mechanism were extracted and analyzed. **Results:** It was found that melittin was the most frequently investigated compound, showing anticancer activity in breast, lung, glioblastoma, and ovarian cancer models. Mechanisms include induction of apoptosis, inhibition of cell proliferation, suppression of NFκB and PI3K/Akt/mTOR pathways, and modulation of immune responses. Additionally, a number of studies documented synergistic effects when melittin was mixed with apamin and PLA2, two additional components of bee venom. **Conclusion:** Bee venom, particularly melittin, demonstrated strong anticancer potential by targeting multiple molecular pathways. However, further *in vivo* and clinical studies are required to validate its efficacy and safety as a therapeutic agent in addition to thorough examination of less well-known substances such as adolapin and MCD peptide.

INTRODUCTION

Nearly 20 million new cases of cancer in 2022 with 9.7 million deaths from cancer and its global incidence continues to rise despite major advances in diagnostics and therapeutics (Bray et al., 2024). Many conventional cancer treatments including surgery, chemotherapy and radiotherapy, often present significant limitations such as severe side effects, multidrug resistance and non-selective toxicity toward healthy issues. These challenges highlight the pressing need for new anticancer agents that are both selective and less harmful. In recent decades natural bioactive compounds derived from plants, marine organisms and animal venoms have gained attention as potential sources of novel anticancer drugs due to their ability to target multiple signaling pathways involved in tumour development and metastasis (Zhang et al., 2018). Among naturally derived agents, bee venom extracted from a bee species known as *Apis mellifera* has attracted considerable interest for its broad spectrum of pharmacological properties, including anti-inflammatory, antimicrobial, and also anticancer effects. Traditionally, bee venom therapy has been practiced for centuries in various cultures such as Chinese, Indian, and Malay medicine for the treatment of arthritis, pain, and inflammatory disorders (Pandey et al., 2023). Modern applications of bee venom, often referred to as apitherapy, have expanded into the management of chronic diseases, autoimmune conditions, and cancer. Bee venom is a complex mixture of peptides, enzymes, and biogenic amines, with melittin, phospholipase A2 (PLA2), apamin, adolapin, and mast cell degranulating (MCD) peptide as its principal bioactive components (Abd El-Wahed et al., 2019). Among these, melittin comprising approximately 40-60% of the venom's dry weight is the most studied and exhibits potent anticancer activity across a wide range of cancer types, including breast, lung, ovarian, liver, and glioblastoma. Melittin exerts its effects by inducing apoptosis, suppressing tumour cell proliferation, disrupting cellular membranes, and modulating key oncogenic signaling pathways such as PI3K/Akt and NF-κB (Wehbe et al., 2019). PLA2 facilitates melittin's entry into tumour cells and enhances its cytolytic effects, while adolapin and apamin exhibit anti-inflammatory and neuroprotective properties that may complement bee venom's anticancer potential (Cui et al., 2024).

At therapeutic dosages, several investigations have shown that bee venom and its constituents can specifically target cancerous cells while preserving healthy ones. However,

* *Corresponding author.*
E-mail address: syaiful@iium.edu.my

Journal homepage: https://journals.iium.edu.my/ijahs/index.php/IJAHS
EISSN NO 2600-8491

concerns about toxicity, delivery effectiveness, and a lack of knowledge about its molecular mechanisms continue to restrict the medicinal potential of bee venom, even in the face of encouraging preclinical results. Additionally, most of the research has concentrated on melittin, leaving other substances like adolapin and MCD peptide comparatively unexplored (Pandey et al., 2023).

The current scoping review fills these gaps by methodically mapping and synthesising scientific data in the anticancer effects of bee venom and its bioactive ingredients that were published between 2010 and 2024. This review aims to identify the mechanisms of action, summarize experimental findings across cancer models, and highlight research gaps to guide future exploration of bee venom-derived compounds as potential anticancer therapeutics. This review may represent the most up-to-date and comprehensive analysis of bee venom components and their anticancer properties.

METHODOLOGY

Study Design

This study adopted a scoping review design based on the methodological framework proposed by Arksey & O'Malley (2005) guided by the Prisma-ScR checklist, comprising five key stages: (1) identifying research questions, (2) identifying relevant studies, (3) study selection, (4) charting the data, and (5) collating, summarizing, and reporting the results (Arksey & O'Malley, 2005). The scoping approach was chosen to map and summarize the existing literature regarding the anticancer potential of bee venom and its bioactive components, including melittin, phospholipase A2 (PLA2), apamin, mast-cell degranulating (MCD) peptide, and hyaluronidase.

Search Strategy

A comprehensive and systematic search strategy was employed to retrieve relevant studies. Three electronic databases, PubMed, ScienceDirect, and Scopus were searched for publications between 2010 and 2024. The keywords were constructed using Medical Subject Headings (MeSH) terms and Boolean operators (AND, OR) are used to maximize sensitivity and specificity. The search terms included combinations of "bee venom", "anticancer activity", "bioactive compound" and "antineoplastic agents" were included. The search was limited to English language, peer-reviewed articles. All retrieved were exported into Microsoft Excel for organization and duplicate removal.

Inclusion and Exclusion Criteria

The inclusion criteria: (1) Studies investigating the anti-cancer effects and mechanisms of actions of bee venom or its bioactive compound, (2) full text articles, (3) peer-reviewed articles published in English from 2010 until 2024, and (4) experimental studies conducted *in vitro, in vivo,* or clinical studies involving both human and animal studies. Studies were excluded if the studies focus on non-bee venom toxins or those unrelated to cancer, articles without full text access, published before 2010 and after 2024, systematic reviews, meta-analyses, and other reviews lacking primary data or original research. These criteria ensured that only relevant and high-quality studies were included to provide reliable evidence on the anticancer mechanisms of bee venom.

Study Selection

The selection process followed the PRISMA-ScR guidelines. An initial total of 240 records were identified from the three selected databases. After removing 72 duplicates, 168 studies remained for title and abstract screening. Following this stage, 65 full-text articles were assessed for eligibility, and 35 met all inclusion criteria and were included in the final review. Screening was performed in two stages: (1) title and abstract screening to exclude irrelevant studies, (2) full-text screening to confirm eligibility based on inclusion and exclusion criteria. Discrepancies during screening were resolved through discussion to ensure consistency. The detailed process is illustrated in **Figure 1**, following the PRISMA-ScR flow structure.

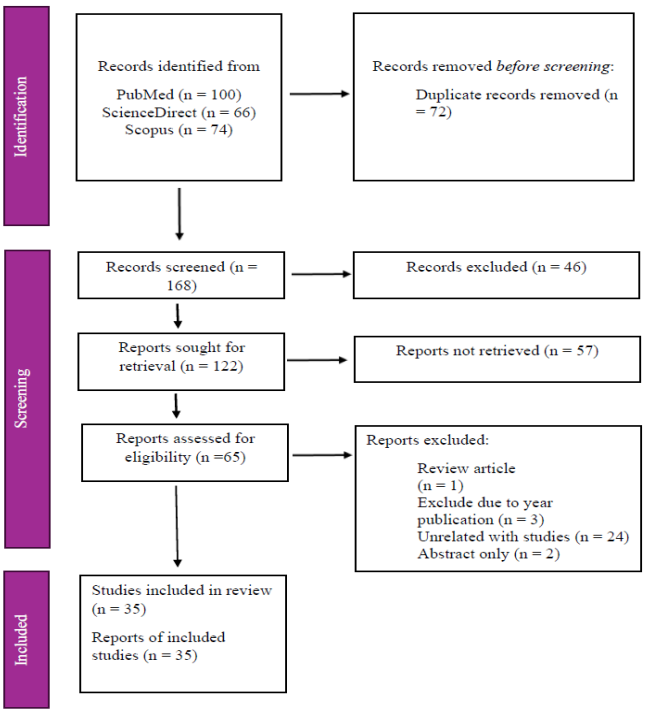

Figure 1: PRISMA-ScR flow diagram

Data Extraction and Charting

Data extraction and charting were performed systematically and summarized in the table form from the final full-text articles and journals. For each included article, the following information was extracted and organized: (1) author(s) and year of publication, (2) cancer type, (3) cancer model, (4) bioactive compound, (5) IC_{50}/LC_{50} values, and (6) reported anticancer activity from the study. Table 1 summarizes the data, presenting an overview of the included studies and highlighting the primary mechanisms through which bee venom and its components exert anticancer effects.

Table 1: Extraction of data of the bioactive compounds of bee venom and their anticancer effects.

Cancer Type	Cancer Model	Bioactive Compound	IC_{50}/LC_{50}	Reported Anticancer Activity	Ref.
Glioblastoma	8-MG-BA, GAMG (human glioblastoma cell lines)	• Melittin • PLA2 • Apamin	Not specified	Inhibit cell viability, inhibit MMP-2 and MMP-9 secretion (anti-metastatic)	Malek et al., 2022
	U87 human glioblastoma cells in nude mice	• Apamin • Melittin • PLA2 • MCD-peptide	IC_{50}: 14.32 µg/mL (melittin *in vitro*)	Apoptosis (EGFP+/Caspase-3+), necrosis	Chahla et al., 2024
	A127 (human glioblastoma cell lines)	• Melittin • PLA2	IC_{50}: 28.5 µg/mL	Induced apoptosis, inhibits MMP-2 expression and activity	Sisakh et al., 2017
Chronic Myelogenous Leukaemia (CML)	K562 cells (human leukaemia cell line)	• Melittin	IC_{50}: 1.84 µg/mL	Induced apoptosis, induced necrosis, and cell cycle arrest at G0/G1 phase	Obeidat et al., 2023
Acute Lymphoblastic Leukaemia (ALL)	CCRF-CEM (Human leukaemia cell lines)	• Melittin	Not specified	Induced apoptosis	Ceremuga et al., 2020
Breast cancer	SUM159	• Melittin	IC_{50}: 0.94 µM	Induced apoptosis, inhibits EGFR/HER2 activation	Duffy et al., 2020
	MDA-MB-231	• Melittin	IC_{50}: 5.86 µg/mL	Inhibit metastasis, suppression of SDF-1α/CXCR4 signalling cell, induces apoptosis	Salimian et al., 2022
	MCF-7 (*in vitro*)	• Melittin • PLA2 • Apamin	IC_{50}: 1.8 µg/mL	Induced apoptosis, increase p53 and 8-OHdG levels, inhibit tumour growth	Plasay et al., 2022
				Inhibits metastasis, downregulating CD147 and MMP-9 expression	Shaw et al., 2019, Wang et al., 2017
				Inhibit NF-kB pathway	Kim et al., 2015
Cervical cancer	HeLa	• Melittin	IC_{50}: 1.8 µg/mL	Induced apoptosis, increase p53 and 8-OHdG	Zarrinnahad et al., 2017

				levels	
	C33A	• Melittin	IC_{50}: 21.59-23.12 µg/mL	Cytotoxicity, ROS generation	Shasuvar et al., 2023
Malignant melanoma	B16F10	• Melittin	IC_{50}: 12.67 µg/mL	Inhibit cell growth, inhibits migration, induced apoptosis	Lim et al., 2019
Colon cancer	HT-29 (*in vitro*)	• Melittin • PLA2 • Apamin	IC_{50}: 5.86 µg/mL	Induced apoptosis, inhibit proliferation	Duarte et al., 2022
	HCT116	• Melittin • PLA2	IC_{50}: 101.0-194.9 µg/mL	Cytotoxicity, synergistic activity of melittin and PLA2, inhibits proliferation	Yaacoub et al., 2021
		• Melittin	IC_{50}: 3.8 µg/mL	Induced apoptosis, activates autophagy pathways	El-Didamony et al., 2024
			IC_{50}: 14.05 µg/mL	Cytotoxicity	Zamani et al., 2024
	COLO205	• Melittin	Not specified	Induced apoptosis	Soliman et al., 2019
	HCT-15	• Melittin	Not specified	Induced apoptosis	Soliman et al., 2019
Gastric cancer	AGS (Human gastric cancer cell line)	• Melittin	Not specified	Inhibits cell viability, Induced necrosis at higher dose	Mahmoodzadeh et al., 2015
		•		Induced apoptosis, inhibit proliferation	Soliman et al., 2019
Hepatocellular carcinoma cancer (HCC)	HepG2	• Melittin	Not specified	Inhibit proliferation, inhibit migration, induces demethylation of ADAMTS9-AS2	Lv et al., 2023
	SMMC-7721	• Melittin	Not specified	Increases INF-γ, promote tumor cytotoxicity, enhances immune responses	Liu et al., 2016
	Huh-7	• Melittin	IC_{50}: 129.5-272.6 µg/mL	Inhibits cancer cell proliferation	El-Didamony et al., 2024
	Hepa 1-6	• Melittin	IC_{50}: 6.39 µg/mL	Induced apoptosis	Hematyar et al., 2018
Non-small cell lung cancer (NSCLC)	A549 cell (human NSCLC cell lines)	• Melittin	IC_{50}: 1 µg/mL	Inhibit migration, suppresses VEGF expression	Zhang & Chen, 2017
			IC_{50}: 2 µg/mL	Induced apoptosis, inhibits glycolysis, increase cisplatin sensitivity	Zhang et al., 2021

				Inhibits cell growth, inhibits invasion, induced TGF-β-mediated ERK pathway	Yu et al., 2021
	LLC (mouse NSCLC cell lines)	• Melittin	Not specified	Reduced M2 macrophages, increased M1/M2 ratio	Lee et al., 2017
	NCI_H460	• Melittin	IC_{50}: 3 µg/mL	Inhibit NF-kB pathway	Choi et al., 2014
	HCC1833 cell	• Melittin	IC_{50}: 0.94 to 1.49 µM for HER2-enriched cells	Inhibit proliferation, induction of autophagy cell	Wang et al., 2024
Bronchogenic carcinoma (Lung Cancer)	ChaGo-K1 (Human bronchogenic carcinoma cell line)	• Melittin	ChaGo-K1; IC_{50}: 2.5 µM	Inhibit lung cancer cell proliferation, apoptosis, inhibition of TAM	Tipgomut et al., 2018
Ovarian cancer	A2780 and A2780CR	• Melittin	A2780: Melittin IC_{50}: 5 µg/mL + Cisplatin IC_{50}: 2 µg/mL A2780CR: Melittin IC_{50}: 2 µg/mL Cisplatin: IC_{50}: 10 µg/mL	Synergistic cytotoxic effects with cisplatin, metabolic changes, induced apoptosis	Alonezi et al., 2017
	SKOV3	• Melittin	Not specified	Increases INF-γ, promote tumor cytotoxicity, enhances immune responses,	Liu et al., 2016
			IC_{50}: 80 µg/mL	Inhibits proliferation, induces cell cycle arrest (G1 phase), induced apoptosis	Su et al., 2014
Osteosarcoma	UMR-106	• Melittin	IC_{50}: 6.33 µg/mL	Inhibit angiogenesis via SDF-1α/CXCR4	Qin et al., 2016
Esophageal Squamous Cell Carcinoma (ESCC)	TE1 (human esophageal carcinoma cell line)	• Melittin	Not specified	Induced apoptosis in TE1 cells, inhibit cell proliferation in time-dependent manner	Zhou et al., 2021
Hodgkin Lymphoma (HL)	KM-H2, L-428 cell lines	• Melittin	IC_{50}: 0.93µM for KM-H2, 0.75µM for L-428	Induced apoptosis, inhibit growth, increase cisplatin sensitivity	Kreinest et al., 2020

RESULTS

A total of 35 studies met the inclusion criteria and were included in this scoping review. The selected articles investigated the anticancer activities of whole bee venom and its bioactive compounds melittin, phospholipase A2 (PLA2), apamin, adolapin, mast cell degranulating (MCD) peptide, and hyaluronidase using both *in vitro* and *in vivo* cancer models. Among 35 studies, melittin was the most extensively studied compound.

Anticancer Activity of Bee Venom and its Bioactive Compounds

The 35 included studies collectively revealed that bee venom and its bioactive components exhibit strong anticancer, antiproliferative, and pro-apoptotic activites. Most studies focused on melittin, followed by PLA2 and apamin, while fewer examined adolapin, MCD peptide, and hyaluronidase. These bioactive compounds act through multiple mechanisms involving apoptosis induction, inhibition of metastasis, and modulation of oncogenic signaling pathways.

DISCUSSION

The findings from this scoping review confirm that bee venom possesses remarkable anticancer potential, primarily attributed to its peptide and enzymatic constituents. Melittin emerged as the principal compound responsible for direct cytotoxicity through apoptosis induction and mitochondrial disruption. PLA2, apamin, adolapin, MCD peptide, and hyaluronidase complement melittin's effects by enhancing membrane permeability, modulating immune responses, and supporting intracellular signaling regulation. The multi-targeted nature of bee venom distinguishes it from conventional chemotherapeutic agents, which often act through single pathways. By influencing multiple signaling cascades such as PI3K/Akt and NF-κB, bee venom compounds not only suppress proliferation but also impede metastasis and angiogenesis.

Comparison between bioactive compounds of bee venom

Melittin demonstrates the strongest and most consistent anticancer efficacy. It triggers apoptosis, inhibits migration, and alters the tumour microenvironment (Obeidat et al., 2023). It interacts directly with the lipid bilayer of cancer cell membranes, forming pores that disrupt cellular homeostasis and lead to apoptosis (Lim et al., 2019). In addition, melittin modulates key regulatory proteins such as caspase-3, for further promoting programmed cell death. However, despite its strong efficacy, melittin's non-selective toxicity poses a major limitation such as toxicity towards both normal and cancer cells as well as other adverse effects. Studies have emphasized the need for nanoparticle-based or targeted delivery systems to minimize damage to healthy cells while maximizing therapeutic potential (Oršolić, 2011).

PLA2 plays a supporting role by enhancing melittin's cytolytic activity. It hydrolyzes phospholipids in cancer cell membranes, facilitating melittin penetration and enhancing its apoptotic effect (Yaacoub et al., 2021). Moreover, PLA2 exhibits immune-regulatory functions by activating macrophages and dendritic cells, thereby promoting antitumour immunity. Despite these benefits, its intrinsic hemolytic activity restricts its standalone use and necessities formulation refinement (Hematyar et al., 2018).

Apamin, a small neuropeptide, interferes with calcium-activated potassium channels that influence tumour cell motility. It inhibits epithelial-mesenchymal transition (EMT) a crucial step in metastasis by downregulating mesenchymal markers such as *vimentin* and *N-cadherin* (Plassay et al., 2022). Adolapin, on the other hand, exhibits strong anti-inflammatory properties that indirectly contribute to its anticancer effects by suppressing tumour-promoting cytokines like TNF-α and COX-2 (Wehbe et al., 2019). These two compounds, which exhibit lower cytotoxicity, act synergistically to reduce metastatic potential and inflammation-driven tumor progression. The MCD peptide primarily influences immune response by promoting cytokine release from mast cells, thereby enhancing immune-mediated tumour suppression (Zhang et al., 2021). Hyaluronidase, commonly referred to as the "spreading factor", enhances tissue permeability and improves the diffusion of other active peptides such as melittin and PLA2 into tumour sites (Wehbe et al., 2019). While their direct anticancer effects are limited, both components serve as important enhancers of bee venom's overall antitumour efficacy.

Comparison of Bee Venom's Anticancer Effects across Different Cancer Types

Studies on breast cancer (MCF-7 and MDA-MB-231 cells) demonstrated that melittin effectively inhibits cell proliferation and migration through suppression of the PI3K/Akt and MAPK signaling pathways (Lim et al., 2019). Apamin also contributed to reduced metastatic activity by inhibiting EMT, while hyaluronidase improved melittin diffusion within tumour tissues (Plassay et al., 2022). These findings support the potential of bee venom peptides as complementary agents in breast cancer therapy. In lung cancer (A549) models, melittin triggered apoptosis via mitochondrial disruption, while apamin inhibited EMT and cell migration (Wang et al., 2021). PLA2 enhanced these effects through synergistic membrane lysis and immune activation. Collectively, these findings suggest that combining melittin with other bee venom

components could improve therapeutic outcomes for lung carcinoma.

Melittin induced apoptosis in colon cancer cells (HT-29) through death receptor activation and NF-kB pathway inhibition, leading to reduced cell survival and inflammation (Duarte et al., 2022). PLA2 was shown to induce oxidative stress-mediated apoptosis in colon carcinoma cells. These mechanisms underline the potential of bee venom compounds as effective agents for targeting colorectal malignancies. Although limited studies are available, melittin has demonstrated potential to cross the blood-brain barrier and induce apoptosis in glioblastoma cells through activation of caspase pathways and mitochondrial disruption (Kim et al., 2015). The unique ability of melittin to penetrate neural tissue highlights its promise for future therapeutic development against brain tumors.

Collectively, the evidence presented in this review supports the hypothesis that bee venom and its bioactive constituents possess multifaceted anticancer activities through apoptosis induction, anti-metastatic effects, and immune modulation (Wehbe et al., 2019). Among these melittin remains the most potent and extensively characterized, while the synergistic effects of PLA2, apamin, adolapin, MCD peptide, and hyaluronidase enhance its overall therapeutic impact. Future research should emphasize *in vivo* models, nanocarriers formulations, and toxicity profiling to ensure selective and safe clinical applications. Bee venom therefore represents a promising, natural-based approach for the development of novel anticancer therapies.

CONCLUSION

This scoping review provides comprehensive evidence that bee venom and its bioactive compounds particularly melittin, phospholipase A2 (PLA2), apamin, adolapin, MCD peptide, and hyaluronidase exhibit significant anticancer potential through diverse biological mechanisms. Melittin emerged as the principal active compound, inducing apoptosis and suppressing tumour growth via inhibition of multiple oncogenic pathways, while other peptides contribute synergistically by modulating inflammation, enhance immune activity, and improving compound penetration into tumour tissues. Despite promising *in vivo* and clinical data highlight the need for further investigation to ensure safety, efficacy, and selectivity in therapeutic applications. Future research should focus on standardized extraction, toxicity evaluation, and the development of targeted delivery systems such as melittin-based nanoparticles. Collectively, bee venom represents a promising natural source for anticancer drug discovery and warrants continued exploration in translational cancer research.

ACKNOWLEDGEMENT

The authors would like to acknowledge the Department of Biomedical Science, Kulliyyah of Allied Health Sciences, International Islamic University Malaysia (IIUM).

REFERENCES

Abd El-Wahed, A. A., Khalifa, S. A. M., 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. F., Algethami, A. F., Büttner, S., & El-Seedi, H. R. (2019). Bee venom composition: From chemistry to biological activity. *Studies in Natural Products Chemistry*, 459–484. https://doi.org/10.1016/b978-0-444-64181-6.00013-9

Alonezi, S., Tusiimire, J., Wallace, J., Dufton, M. J., Parkinson, J. A., Young, L. C., Clements, C. J., Park, J. K., Jeon, J. W., Ferro, V. A., & Watson, D. G. (2017). Metabolomic profiling of the synergistic effects of melittin in combination with cisplatin on ovarian cancer cells. *Metabolites*, *7*(2). https://doi.org/10.3390/metabo7020014

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 Cancer Journal Clinical*, *74*(3), 229–263. https://doi.org/10.3322/caac.21834

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). https://doi.org/10.3390/biom10020247

Chahla, C., Rima, M., Mouawad, C., Roufayel, R., Kovacic, H., El Obeid, D., Sabatier, J. M., Luis, J., Fajloun, Z., & El-Waly, B. (2024). Effect of *Apis mellifera* syriaca bee venom on glioblastoma cancer: *In vitro* and *in vivo* studies. *Molecules*, *29*(16), 3950. https://doi.org/10.3390/molecules29163950

Choi, K., Hwang, C., Gu, S., Park, M., Kim, J., Park, J., Ahn, Y., Kim, J., Song, M., Song, H., Han, S.-B., & Hong, J. (2014). Cancer cell growth inhibitory effect of bee venom via increase of death receptor 3 expression and inactivation of NF-kappa B in NSCLC cells. *Toxins*, *6*(8), 2210–2228. https://doi.org/10.3390/toxins6082210

Cui, Z., Zhou, Z., Sun, Z., Duan, J., Liu, R., Qi, C., & Yan, C. (2024). Melittin and phospholipase A2: Promising anti-cancer candidates from bee venom. *Biomedicine &*

Pharmacotherapy, 179, 117385. https://doi.org/10.1016/j.biopha.2024.117385

Duarte, D., Falcão, S. I., El Mehdi, I., Vilas-Boas, M., & Vale, N. (2022). Honeybee venom synergistically enhances the cytotoxic effect of CNS drugs in HT-29 colon and MCF-7 breast cancer cell lines. *Pharmaceutics*, *14*(3), 511. https://doi.org/10.3390/pharmaceutics14030511

Duffy, C., Sorolla, A., Wang, E., Golden, E., Woodward, E., Davern, K., Ho, D., Johnstone, E., Pfleger, K., Redfern, A., Iyer, K. S., Baer, B., & Blancafort, P. (2020). Honeybee venom and melittin suppress growth factor receptor activation in HER2-enriched and triple-negative breast cancer. *NPJ Precision Oncology*, *4*(1). https://doi.org/10.1038/s41698-020-00129-0

El-Didamony, S. E., Kalaba, M. H., Sharaf, M. H., El-Fakharany, E. M., Osman, A., Sitohy, M., & Sitohy, B. (2024). Melittin alcalase-hydrolysate: A novel chemically characterized multifunctional bioagent; antibacterial, anti-biofilm and anticancer. *Frontiers in Microbiology*, *15*. https://doi.org/10.3389/fmicb.2024.1419917

Hematyar, M., Soleimani, M., Es-Haghi, A., & Rezaei Mokarram, A. (2018). Synergistic co-delivery of doxorubicin and melittin using functionalized magnetic nanoparticles for cancer treatment: Loading and *in vitro* release study by LC-MS/MS. *Artificial Cells, Nanomedicine, and Biotechnology*, *46*(sup3), S1226–S1235. https://doi.org/10.1080/21691401.2018.1536063

Kim, Y. W., Chatirvedi, P. K., Chun, S. N., Lee, Y. G., & Ahn, W. S. (2015). Honeybee venom possesses anticancer and antiviral effects by differential inhibition of HPV E6 and E7 expression on cervical cancer cell line. *Oncology Reports*, *33*(4), 1675–1682. https://doi.org/10.3892/or.2015.3760

Kreinest, T., Volkmer, I., & Staege, M. S. (2020). Melittin increases cisplatin sensitivity and kills KM-H2 and L-428 Hodgkin lymphoma cells. *International Journal of Molecular Sciences*, *22*(1), 343. https://doi.org/10.3390/ijms22010343

Lee, C., Bae, S. J. S., Joo, H., & Bae, H. (2017). Melittin suppresses tumor progression by regulating tumor-associated macrophages in a Lewis lung carcinoma mouse model. *Oncotarget*, *8*(33), 54951–54965. https://doi.org/10.18632/oncotarget.18627

Lim, H., Baek, S., & Jung, H. (2019). Bee venom and its peptide component melittin suppress growth and migration of melanoma cells via inhibition of PI3K/AkT/MTOR and MAPK pathways. *Molecules*, *24*(5), 929. https://doi.org/10.3390/molecules24050929

Liu, M., Wang, H., Liu, L., Wang, B., & Sun, G. (2016). Melittin-MIL-2 fusion protein as a candidate for cancer immunotherapy. *Journal of Translational Medicine*, *14*(1), 155. https://doi.org/10.1186/s12967-016-0910-0

Lv, C., Chen, J., Huang, F., Fang, F., & Li, B. (2023). Melittin inhibits the proliferation migration and invasion of HCC cells by regulating ADAMTS9-AS2 demethylation. *Toxicon*, *222*(2023), 106996–106996. https://doi.org/10.1016/j.toxicon.2022.106996

Mahmoodzadeh, A., Zarrinnahad, H., Bagheri, K. P., Moradia, A., & Shahbazzadeh, D. (2015). First report on the isolation of melittin from Iranian honey bee venom and evaluation of its toxicity on gastric cancer AGS cells. *Journal of the Chinese Medical Association*, *78*(10), 574–583. https://doi.org/10.1016/j.jcma.2015.06.008

Małek, A., Kocot, J., Mitrowska, K., Posyniak, A., & Kurzepa, J. (2022). Bee venom effect on glioblastoma cells viability and gelatinase secretion. *Frontiers in Neuroscience*, *16*(792970). https://doi.org/10.3389/fnins.2022.792970

Obeidat, M., Al-Khraisat, I. F., Jaradat, D. M. M., Ghanim, B. Y., Abdallah, Q. M., Duaa Abu Arqoub, D. A., Sabbah, D., Al-Sanabra, O. M., Arafat, T., & Qinna, N. A. (2023). Mellitin peptide quantification in seasonally collected crude bee venom and its anticancer effects on myelogenous K562 human leukaemia cell line. *BMC Complementary Medicine and Therapies*, *23*(1), 1-11. https://doi.org/10.1186/s12906-023-03897-x

Oršolić, N. (2011). Bee venom in cancer therapy. *Cancer and Metastasis Reviews*, 31(1-2), 173–194. https://doi.org/10.1007/s10555-011-9339-3

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. https://doi.org/10.3390/nu15143111

Plasay, M., Natzir, R., Cangara, M. H., Hardjo, M., Syahrijuita, & Soraya, G. V. (2022). Melittin-Induced cell death through p53 and 8-OHdG in breast cell cancer MCF-7. *Biomedical and Pharmacology Journal*, *15*(2), 979–983. https://biomedpharmajournal.org/vol15no2/melittin-induced-cell-death-through-p53-and-8-ohdg-in-

breast-cell-cancer-mcf-7/

PRISMA. (2020). PRISMA 2020 Flow Diagram. *PRISMA*. https://www.prisma-statement.org/prisma-2020-flow-diagram

Qin, G., Chem, Y., Li, H., Xu, S., Li, Y., Sun, J., Rao, W., Chen, C., Du, M., He, K., & Ye, Y. (2016). Melittin inhibits tumor angiogenesis modulated by endothelial progenitor cells associated with the SDF-1α/CXCR4 signaling pathway in a UMR-106 osteosarcoma xenograft mouse model. *Molecular Medicine Reports*, *14*(1), 57–68. https://doi.org/10.3892/mmr.2016.5215

Sahsuvar, S., Guner, R., Gök, Ö., & Can, O. (2023). Development and pharmaceutical investigation of novel cervical cancer-targeting and redox-responsive melittin conjugates. *Scientific Reports*, *13*(1). https://doi.org/10.1038/s41598-023-45537-x

Salimian, F., Nabiuni, M., & Salehghamari, E. (2022). Melittin prevents metastasis of epidermal growth factor-induced MDA-MB-231 cells through the inhibition of the sdf-1α/cxcr4 signalling pathway. *Cell Journal*, *24*(2), 85–90. https://doi.org/10.22074/cellj.2022.7626

Shaw, P., Kumar, N., Hammerschmid, D., Privat-Maldonado, A., Dewilde, S., & Bogaerts, A. (2025). Synergistic effects of melittin and plasma treatment: A promising approach for cancer therapy. *Cancers*, *11*(8), 1109. https://doi.org/10.3390/cancers11081109

Sisakht, M., Mashkani, B., Bazi, A., Ostadi, H., Zare, M., Avval, F. Z., Sadeghnia, H. R., Mojarad, M., Nadri, M., Ghorbani, A., & Soukhtanloo, M. (2017). Bee venom induces apoptosis and suppresses matrix metaloprotease-2 expression in human glioblastoma cells. *Revista Brasileira de Farmacognosia*, *27*(3), 324–328. https://doi.org/10.1016/j.bjp.2016.11.006

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. https://doi.org/10.1371/journal.pone.0224028

Su, M., Chang, W., Cui, M., Lin, Y., Wu, S., & Xu, T. (2014). Expression and anticancer activity analysis of recombinant human uPA1–43-melittin. *International Journal of Oncology*, *46*(2), 619–626. https://doi.org/10.3892/ijo.2014.2750

Tipgomut, C., Wongprommoon, A., Takeo, E., Ittiudomrak, T., Puthong, S., & Chanchao, C. (2018). Melittin induced G1 cell cycle arrest and apoptosis in chago-k1 human bronchogenic carcinoma cells and inhibited the differentiation of THP-1 cells into tumour- associated macrophages. *Asian Pacific Journal of Cancer Prevention: APJCP*, *19*(12), 3427–3434. https://doi.org/10.31557/APJCP.2018.19.12.3427

Wang, Y., Yuan, T., He, L., Huang, J., Wilfred, N., Yang, W., Jin, M., Huang, G., & Lu, C. (2024). Melittin treatment suppressed malignant NSCLC progression through enhancing CTSB-mediated hyperautophagy. *Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie*, *180*(2024), 117573. https://doi.org/10.1016/j.biopha.2024.117573

Wehbe, R., Frangieh, J., Rima, M., El Obeid, D., Sabatier, J.M., & Fajloun, Z. (2019). Bee venom: Overview of main compounds and bioactivities for therapeutic interests. *Molecules*, 24(16). https://doi.org/10.3390/molecules24162997

Yaacoub, C., Rifi, M., El Obeid, D., Mawlawi, H., Sabatier, J. M., Coutard, B., & Fajloun, Z. (2021). The cytotoxic effect of *Apis mellifera* venom with a synergistic potential of its two main components—melittin and pla2—on colon cancer HCT116 cell lines. *Molecules*, *26*(8), 2264. https://doi.org/10.3390/molecules26082264

Yu, R., Wang, M., Wang, M., & Han, L. (2021). Melittin suppresses growth and induces apoptosis of non-small-cell lung cancer cells via down-regulation of TGF-β-mediated ERK signal pathway. *Brazilian Journal of Medical and Biological Research*, *54*(2). https://doi.org/10.1590/1414-431x20209017

Zamani, M., Bozorg-Ghalati, F., & Mokarram, P. (2024). Melittin as an activator of the autophagy and unfolded protein response pathways in colorectal HCT116 cell line. *Iranian Biomedical Journal*, *28*(1), 46–52. https://doi.org/10.61186/ibj.3993

Zarrinnahad, H., Mahmoodzadeh, A., Hamidi, M. P., Mahdavi, M., Moradi, A., Bagheri, K. P., & Shahbazzadeh, D. (2017). 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. https://doi.org/10.1007/s10989-017-9641-1

Zhang, S., Lv, X., Li, L., Luo, Y., Xiang, H., Wang, L., & Li, Y. (2021). Melittin inhibited glycolysis and induced cell apoptosis in cisplatin resistant lung adenocarcinoma cells via TRIM8. *BIOCELL*, *45*(1), 167–175. https://doi.org/10.32604/biocell.2021.013636

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. https://doi.org/10.3892/mmr.2017.6970

Zhang, S., Liu, Y., Ye, Y., Wang, X. R., Lin, L. T., Xiao, L. Y., Zhou, P., Shi, G. X., & Liu, C. Z. (2018). Bee venom therapy: Potential mechanisms and therapeutic applications. *Toxicon*, 148, 64–73. https://doi.org/10.1016/j.toxicon.2018.04.012

Zheng, J., Lee, H. L., Ham, Y. W., Song, H. S., Song, M. J., & Hong, J. T. (2015). Anti-cancer effect of bee venom on colon cancer cell growth by activation of death receptors and inhibition of nuclear factor kappa B. *Oncotarget*, 6(42), 44437–44451. https://doi.org/10.18632/oncotarget.6295

Zhou, C., Ma, J., Lu, Y., Zhao, W., Xu, B., Lin, J., Ma, Y., Tian, Y., Zhang, Q., Wang, W., Yan, W., & Jiao, P. (2021). TERT promoter regulating melittin expression induces apoptosis and G_0/G_1 cell cycle arrest in esophageal carcinoma cells. *Oncology Letters*, *21*(1), 16. https://doi.org/10.3892/ol.2020.12277