



DOI: 10.32768/abc.202184267-276



An Insight into the Role of Bee Venom and Melittin Against Tumor Cells: A Review of Breast Cancer therapy

 Roha Tariq^a, Amna Liaqat^b, Usama Ahmed Khalid^{*c}
^a Department of Biotechnology, Lahore College for Women University, Lahore, Pakistan

^b Department of Healthcare Biotechnology, Atta ur Rahman School of Applied Biosciences, National University of Sciences and Technology, Islamabad, Pakistan

^c Department of Biotechnology & Genetic Engineering, Kohat University of Science and Technology, Kohat, Khyber Pakhtunkhwa, Pakistan

ARTICLE INFO

Received:
09 February 2021
Revised:
25 May 2021
Accepted:
04 June 2021

Keywords:
Breast cancer
Melittin,
combinational therapy,
Honeybee venom

ABSTRACT

Background: Breast cancer is the most common and life-threatening cancer in females characterized by the abnormal proliferation of tumor cells in lobules and ducts. For years, many anti-breast cancer drugs have been tested with some of them showing severe health problems and drug resistance. Recently, different biological and pharmacological actions of bee venom have been indicated to play anti-bacterial, anti-viral and anti-inflammatory role against different cancers especially breast cancer.

Methods: This review study is based on PubMed, Google Scholar and PubMed search. Search terms used were Melittin, Breast cancer and Honey Bee Venom.

Results: Many studies have shown that a positively charged C-terminal sequence of mellitin facilitates plasma membrane contact and antitumor action. Precise targeting and selective activity of melittin has been found in recent studies as it suppresses the activation of growth factor receptors in HER2-enriched and triple-negative breast cancer that are generally difficult to treat. Significantly, it leaves healthy cells intact. The most striking feature of melittin is the pore formation property. Monomers of melittin bind to the plasma membrane of cancer cells in a collective manner and start forming pores, ultimately bringing cell lysis.

Conclusion: Since melittin has a very selective action against the HER-2 related tumors, a combinational therapy of melittin and HER-2 targeted agents could be a very potent strategy in breast cancer. This review reflects the importance of honey bee venom and melittin as a potential therapy for aggressive breast cancer.

Copyright © 2021. This is an open-access article distributed under the terms of the [Creative Commons Attribution-Non-Commercial 4.0](https://creativecommons.org/licenses/by-nc/4.0/) International License, which permits copy and redistribution of the material in any medium or format or adapt, remix, transform, and build upon the material for any purpose, except for commercial purposes.

INTRODUCTION

Although advancements and innovations have calmed human lifestyles, this technological age is somehow responsible for emerging diseases which are

very difficult to deal with. Cancer is one of the leading, widespread, and lethal diseases with various complications.¹ When it comes to the most common cancers in women, breast cancer is predominant with high prevalence ratio² and ranks second in number worldwide.¹ Mostly, the cells in lobule and ducts divide in an uncontrolled manner resulting in breast cancer, while a few cells in other portions of the breast also contribute in this regard.³ However, in some cases, breast cancer cells from glandular portions cross the

* Address for correspondence:

Usama Ahmed Khalid, MD
 Department of Biotechnology & GE, Kohat University of
 Science and Technology, Pakistan
 Tel: +923434656343
 Email: usama.ahmed.khalid@gmail.com



duct and lobular wall barrier and their entrance into the surrounding tissues proves to be fatal.⁴ The severity of breast cancer depends on the analysis of the status of the cancer cells and then the "stage" of cancer is nominated. Declaration of breast cancer stages is based on the invasive and non-invasive manner of cells and ranges from 0-IV.⁵ As per report cases, it is an alarming situation that the breast cancer is strengthening its root in America, Africa and Asia.⁶ Majority of countries are on red line with high mortality rates in women and breast cancer is one of the causes of it.⁷ Mortality rate can be considerably reduced if breast cancer is detected in the initial stages and that is only possible when the patient instantly gets checked upon the appearance of visible symptoms.⁶ Multiple factors are directly or indirectly involved in the origin of breast cancer. Some women who had breast cancer in the past or have family history are susceptible to this disease.^{8,9} Family history is directly linked to abnormal genetic makeup. While considering the genetic causes, two genes, namely *BRCA1* and *BRCA2*, are the prominent ones. Mutations present in them are precursor to large-scale breast cancer.¹⁰ To tackle the different aspects of cancer, scientists and researchers are looking for novel and combined therapeutic approaches. Considering the usefulness of honeybee compounds at biological levels, its use to treat cancer is under research.

Honeybee is widely being used for the welfare of human beings in the form of various products. The main usages of honeybee compounds include therapies of various diseases. Among different compounds of honeybee, "Honeybee venom" has shown promising effects in treatment. The term used for the treatment of various diseases by using bee compounds is "apitherapy". Important compounds of honeybee venom are Melittin, Apamin, peptides, Adolapin and Phospholipase A₂. Different diseases like Alzheimer, Parkinson, viral infection, bacterial infections, and different type of cancers have been treated by honeybee compounds.¹¹ Despite the many uses of bee venom, its molecular effects with respect to breast cancer treatment have not been properly understood. As breast cancer is prevailing in women worldwide, efficient strategy regarding its treatment is urgently needed.¹² Honeybee venom and its main compound melittin are proved to be good agents for cancer treatment by managing different conditions of tumor like initiation of apoptosis, inhibition of cell proliferation and cell growth and control of metastasis.¹³ Melittin is the essential component of bee venom. This can be inferred from the fact that dry weight of bee venom contains 40-50 % of melittin. Melittin is a cationic and amphipathic peptide which perform its activity by attaching onto the negatively charged membrane. On attaching, melittin forms pores in the membrane and destabilizes it.^{14, 15}

In this era of multifactorial diseases, a quick and efficient treatment strategy is utmost necessary. Breast cancer is the result of various complicated cellular processes, so understanding these complications is imperative for the discovery of new treatment and therapeutic strategies.¹⁶ This review paper will give insight regarding the novel therapeutic approaches to breast cancer by using bee venom and melittin.

METHODS

Search terms used for this review includes "cancer", "breast cancer", "honeybee venom", "melittin" and a combination of these terms. The data for this review was collected through different search databases including PubMed and Google Scholar. Collected data were correctly cited. Here, we have demonstrated, by a comprehensive literature review, the role of honeybee venom and its component named mellitin in effectively inducing cell death mainly in HER2-enriched and triple-negative breast cancer. All the images used in this review were retrieved from "Pixabay", an open source of non-copyrighted images.

RESULTS AND DISCUSSION

Therapies in use for Breast Cancer

Effective therapy and management of breast cancer are the two most crucial steps for its eradication. Surgical attempt depends upon the types of tumor and stage of breast cancer.¹⁷ Radiation therapy is sometimes linked with surgical attempts, as in some cases, it is necessary to irradiate the tumor site after surgery using radiation. In the case of breast cancer, radiation therapy is usually sought only after surgery. However, radiations should be strong enough to wipe out cancer cells.^{3, 18} In addition, chemotherapy is also used for treatment in the case of serious risk of cancer. This therapy can be attempted both before and after surgery depending on the type of cancer cells. Targeted drugs are also in practice for breast cancer therapy, but its repercussions cannot be ignored.¹⁷ As the days go by, science is leading the search to new techniques for diagnosing and treating the disease. Discovery of novel biomarkers and advancement in the genomics and transcriptomics assessment are giving an insight into the production of personalized therapies. Three prominent biomarkers of breast cancer, i.e., Estrogen Receptor (ER), Progesterone Receptor (PR) and Human Epidermal Growth Factor Receptor 2 (HER2), decide the nature and precise targeted therapy for breast cancer. However, based on these biomarkers, we can get an insight into the optimal therapeutic approach. In the case of Triple Negative Breast Cancers (TNBCs) which are lagging in the expression of these receptors still have no approved targeted treatment available.¹⁹ This indicates that new agents and treatment strategies that may increase the efficacy



of conventional chemotherapeutic drugs are instantly needed to acquire effectiveness against cancers. Some of the common therapeutic approaches that are in practice for breast cancer are shown in Figure 1.

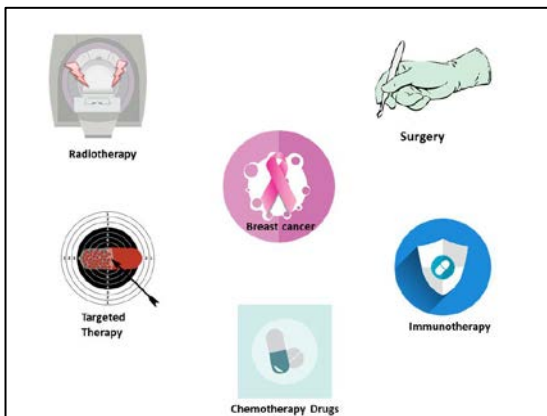


Figure 1. Main therapeutic approaches currently in practice for breast cancer treatment

Alternative way for treatment of breast cancer

High prevalence and death rate of breast cancer have placed this disease at the top of life threatening diseases in women.²⁰ About 80% of the patients' treatment ultimately fail due to the side effects and resistance developed against the anticancer drugs administered to them.²¹ A promising way to impede the development of cancer cells without any side effects is to use oriental medicine such as bee venom (BV).²² Several studies have discussed the anti-cancer effects of BV on lung, liver, renal, prostate, breast, and cervical-cancer cells.²³

Biotoxins: A Natural Remedy

In recent years, a substantial growth has been witnessed in the treatment of breast cancer using natural substances especially biotoxins.²⁴ It is also supported by an extensive investigation carried out by a group of scientists that various animal toxins have demonstrated an exceptional antitumor activity against innumerable illnesses.²⁵ These venoms include scorpion venom²⁶, Bee Venom (BV)²⁷, sea anemone toxin²⁸, snake venom²⁹, and some other animal toxins. The factor which makes these biotoxins a valuable biological resource is that they are produced and secreted in the venom gland of the living organisms comprising pharmacologically functional constituents that might be having potential therapeutic significance.³⁰ Through complex pathways, these resources employ outstanding anticancer properties exerted by their novel compounds and play a key part in regression of the cancer.³¹

Anticancer role of Bee Venom (BV)

One such natural resource is a Bee Venom (BV), produced from the venom gland of the honey bee (*Apis mellifera*) containing approximately eighteen

bioactive compounds.³² These include peptides (melittin, adolapin, apamin, polamines, histamine, and mast cell-degranulation peptide), enzymes (phospholipase A2, hyaluronidase), and other amines and non-peptide components.^{27, 33} In Asian countries especially Korea, BV has been used to treat various human diseases.³⁴ Furthermore, in other countries it is widely used for various skin problems, rheumatism³⁵, arthritis³⁶, and chronic pain.³⁷ Many researchers have depicted amazing effects of BV on diverse range of human cancerous cells such as breast cancer³⁸, lung cancer³⁹, ovarian cancer⁴⁰, melanoma⁴¹, bladder cancer⁴², leukemia⁴³, and so on. For that reason, biotoxins present great potential as antitumor pharmaceutical products in cancer therapy.

Melittin and its anticancer properties

Melittin (MEL) is the primary active component of bee venom, responsible for 40–60% of its dry weigh.⁴⁴⁻⁴⁶ It is a linear, strong, cationic and amphiphilic peptide entailing 26 amino acids with 6 positive charges at physiological pH.⁴⁷ Its chemical formula is C131H228N38O32, weighing 2847.5 Da and is hemolytic and strongly cardiotoxic.⁴⁸ The most extensive literature on MEL has reported that it performs several biological functions such as antibacterial⁴⁹, antifungal¹⁹, antiviral⁵⁰, and anti-parasitic.^{51, 52} Apart from that, a large number of research studies emphasize its antitumor effect in glioblastoma⁵³, leukemia⁵⁴, cervical cancer⁵⁵, non-small-cell lung cancer⁵⁶, and pancreatic cancers with a greater cytotoxic strength in cancer cells in comparison to non-transformed cells.⁵⁷ Moreover, it has an exponential role in inhibition of cancer cell growth and clonogenicity, inducing apoptosis or suppressing tumor metastasis, signifying that it might be an excellent substitute for managing cancer.¹³

Role of Honeybee venom in treating aggressive Breast Cancer cells

Recently, a detailed and comprehensive study carried out by Duffy *et al.* has been published in the Journal, *Precision Oncology*. It establishes the role of bee venom and melittin in suppressing the activation of growth factor receptors in HER2-enriched and triple-negative breast cancer. Irrespective of many years into study for the exact functioning and preciseness of this venom, molecular mechanism and selectivity for the bio molecular constituents of honeybee venom are still unclear to an extent especially in breast cancer, the most widespread cancer in women across the globe.^{12, 58} It is all about the depiction of the powerful and effective induction of cell death by melittin specifically in the aggressive triple-negative and HER2-enriched breast cancer subtypes. Research reveals the actual system



supporting the anticancer selectivity of melittin and summarizes the management approaches used to tackle aggressive breast cancers.⁵⁸ As a thorough understanding of the molecular basis and preciseness of bee venom action against cancer cells is crucial, it is important to manufacture and optimize new active

therapeutics from a natural product that are not only readily available but also economical to develop in different countries worldwide. The anticancer effect of mellitin and bee venom on different cancer cells has been studied previously which is shown in Table 1.

Table 1. Anticancer effects of mellitin and bee venom on different cancer cells

Treatment condition	Cancers	Cell lines	Dose	Results/ Mechanisms	References
	Lung cancer	NCI-H1299 cells	1, 10 µg/mL	Induction of apoptosis in NCI-H1299 human lung carcinoma cells	39
	Mammary carcinoma	MCF7 cells	7.5, 12.5 µg/mL	Apoptosis induction by mitochondria-dependent pathway	38
	Prostate cancer	LNCaP cells, DU145 cells, PC-3 cells	1, 5, 10 µg/mL (in vitro)	Decreasing cell growth via activation of caspase pathway	59
	Melanoma	A2058 cells	0.5, 1, 2, 4 µg/mL	Apoptosis induction through calcium reliant & caspase-independent pathway	41
	Ovarian cancer	A2780cp cells 4	8 µg/mL 8 µg/mL (24 h)	Induction of apoptosis	60
	Gastric cancer	KI735M2	2.8,11,14.2 µg/mL 10 µg/mL (24 h)	Repressed cell multiplication in vitro Initiating apoptosis with Bcl-2 and caspase-3 as key regulators	61
	Leukemia	U937 cells	0.5, 1, 2, 3 µg/mL	by down-regulation of ERK and Akt signal pathway	43
	Cervical carcinoma	HeLa cells	0.7125, 1.425, 2.85, 7.125 or 14.25 µg/mL (72 h)	Impeding cell growth, cell propagation, and clonogenicity of HeLa cells, via inhibition of calmodulin	62
	Osteosarcoma	MG63 cells	0.5, 1, 2 µM	Induction of cell apoptosis by phospholipase A2-independent Ca ²⁺ entry	63
	Prostate cancer	LNCaP cells, DU145 cells, PC-3 cells	0.5,1, 2.5 µg/mL 2.9, 1.5 and cancer 1.8 µg/mL (72 h)	Suppressing cell growth by activation of caspase pathway through inactivation of NF-kB	59



Treatment condition	Cancers	Cell lines	Dose	Results/ Mechanisms	References
Melittin	Hepatocellular cancer	MHCC97L cells, MHCC97H cells	4, 8 µg/mL (in vitro), 80 µg/kg (in vivo) respectively	Inhibiting cell metastasis by suppressing Rac1-dependent pathway	64
	Breast cancer	MCF-7 cells	0.5, 1, 2 µg/mL	Inhibiting cell proliferation and attack by inhibiting PI3K/Akt/mTOR signaling pathway Suppressing PMA-induced	65
	Renal cancer	Caki-1 cells	1, 2, 3 µg/mL	invasion and migration by inhibiting MMP-9 expression Radio-sensitizing	66
	Esophageal cancer	ECA109 cells, TE13 cells	0.5, 1 µM 1.88, 1.64 µM (24 h) respectively	esophageal squamous cell carcinoma with induction of apoptosis	67
	Skin cancer	SCC12	1–10 µM	Inhibited cell proliferation in vivo	19
	Retinoblastoma MEL	Y79	10–500 ng/mL	Induced cell apoptosis via AA pathway	68

Effect of melittin and combined compounds in triple negative breast cancer and HER-2 enriched cell lines

Triple negative breast cancer and HER-2 enriched tumors are among the most aggressive forms of tumors. These tumors do not express genes such as estrogen receptors or progesterone receptors but show high level of genomic instability, invasiveness and repetition in comparison to other cells of breast cancer. Mutations in tumor suppressor genes are most prevalent.⁶⁹ For this reason, treatment against such cancer cells is very difficult to attain. TNBC and HER-2 cells show the absence of a lot of important molecular targets.⁷⁰ It also shows poor prognosis as compared to other subtypes of cancers in females.⁷¹ Melittin extracted from honeybee venom shows a very targeted and selective action in TNBC and HER-2 aggressive cancer cells. It attacks the cell surface by disturbing the phosphorylation process at receptors. Ligand induced phosphorylation is especially targeted. This compound also suppresses the activation of HER-2 which is over-expressed in breast cancer.⁵⁸

Melittin displays a wide range of effective properties such as being anti-fungal, anti-bacterial and anti-cancerous. The most striking feature of

melittin is its ability to form pores. This compound binds with the negatively charged phospholipids present in the membrane. Binding forms pores through which atomic ions can easily pass. It also shows the surfactant activity in creating pores. The usual problem in treating cells is the non-targeted attack on body cells with no differentiation between normal cells and undifferentiated cells. Melittin is nearly a 100% target specific treatment strategy. However, in both TNBC and HER-2 cancer cells, melittin targets cancer cells and even aggressive cancer cells. As compared to other compounds, melittin causes a minimum damage to the normal cells because the membrane potential of cancerous cells is larger due to the outflow of ions and molecules through pores.²⁴

Signaling pathways are also disturbed in triple negative breast cancer and HER-2 cancer cells such as the P13K/AKT as well as mTOR. Alterations in these pathways disturb a lot of downstream gene expression in cascades. Resultant genomic instability is at its peak, causing aggressive cancer cells. Melittin has auspicious potential in normalizing the expression levels of genes involved in progression of tumor formation.⁵⁸



Mechanism of action of melittin in TNBC and HER-2 breast cancer cell lines

Melittin is known to have remarkable positive effects against cancers especially breast cancer using different mechanisms to initiate cancer cells killing. Among many strategies, one of the most accepted mechanisms is “model for pore forming peptides” on cancer cells surfaces. According to this model, monomers of melittin get attached to the cell membrane. However, these monomers do not act independently but show a collective action where all the monomers attack the receptors simultaneously. Moreover, melittin has the capacity of acting upon the cell membrane at even lower concentrations. In such conditions, melittin forms pores that allow the conduction of only atomic ions.⁷²

Structural conformation of melittin alters while binding to the cell membrane. Binding occurs within no less than milliseconds and results in amphipathic alpha helical confirmation. The resulting structure settles with parallel or perpendicular to plane of membrane. In the parallel conformation, melittin does

not get activated, while perpendicular confirmation is of particular importance to anti-cancerous effect.⁷³

The action of melittin is accomplished in two steps. Firstly, the melittin monomers at low concentration bind to the cell membrane in the parallel fashion, and during this process the compound is kept in the inactive state. Secondly, the arrangement is shifted from parallel to perpendicular manner, and hence causing the activation as shown in the Figure 2. Activation leads to pores formation. Mechanism of conversion of parallel to perpendicular conformation is yet to be understood clearly. Another important aspect is that melittin has a strong affinity towards the phosphatidylcholine of membranes due to the cationic form of melittin. Concentration of melittin is crucial for estimating the action rate; however, the strong interactions towards phosphatidylcholine PC heads suggest that ratio of concentration of melittin to lipid molecules is a determining factor for anti-cancerous activity and studies have been conducted to understand this aspect of melittin.^{73, 74}

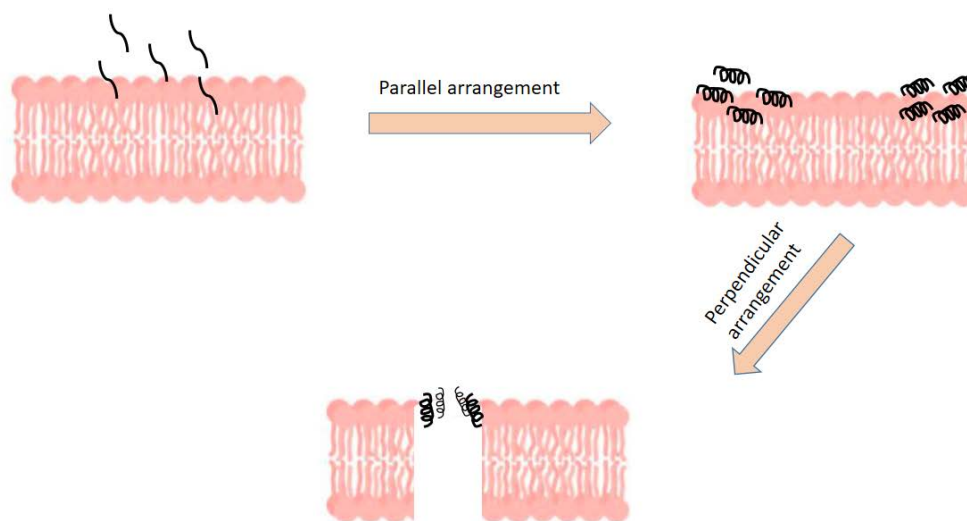


Figure 2. This model represents pore formation by melittin in membrane. Monomers of melittin accumulate on cell membrane and orient in parallel arrangement. Upon reaching a threshold concentration, it undergoes a shift from parallel to perpendicular arrangement. This perpendicular arrangement is crucial for pore formation activity. Figure 2 is adapted with permission from van den Bogaart *et al.* (2008).

Meanwhile, scientists are working to get a detailed insight into the binding mechanism of melittin to cell membrane. Since melittin has strong affinity towards selective regions of membrane, Duffy *et al.* conducted a study to identify those segments of melittin that show maximum potential for binding. The results showed that melittin forms the attraction and bond with the negatively charged cell membrane through its positively charged C terminus. The binding is facilitated as the C terminus is carrying a positive charge which assists in the formation of an

alpha helix. Binding leads to the creation of pores and ultimately the lysis of the cancerous cells. The evidence of functional involvement of C terminus of melittin in anti-cancerous pore formation was confirmed when the scientist designed a negatively charged C terminus of melittin and checked for pore formation ability. None of the cells appeared to show any signs of cell lysis and the effect can be reused by replacing the negatively charged terminus again by positively charged C terminus and formation of alpha helix.⁵⁸



Melittin and Combinational therapy

Effectiveness of a treatment depends upon two factors; maximum efficacy along with minimum side effects and targeted action. The precise and careful combination of therapeutic strategy can provide the patient with maximum desirable benefits, giving least recurrence and toxicity.⁷⁵ One recent combinational therapy involves the robust and synergistic anti-

cancerous effect of melittin and docetaxal, showing favorable effects on breast cancer cell lines. Melittin in combination with docetaxal causes the down regulation of PD-L1 and lessens the immune evasion process of cancerous cell. It also causes the levels of tumor associated macrophages to decrease.⁷⁶ Combinational therapeutic strategy is shown in Figure 3.

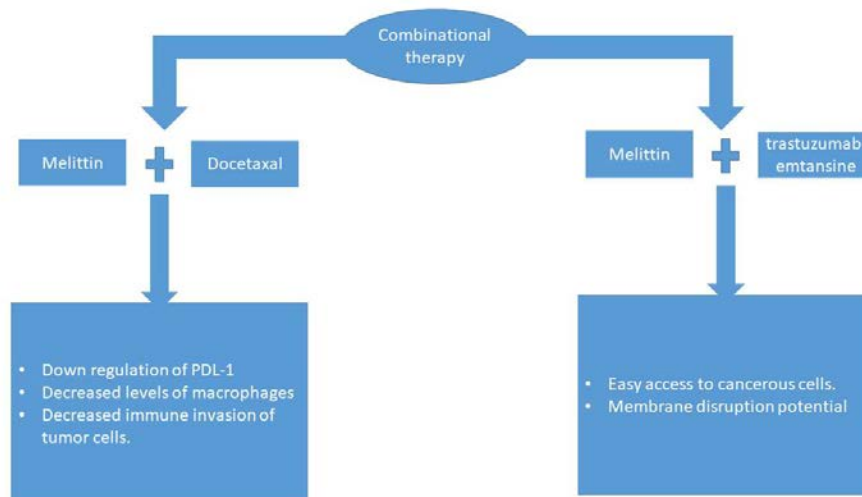


Figure 3. The enhanced activity of melittin in combination with several anti-tumor drugs can be seen. Docetaxal and trastuzumab-emtansine in combination with melittin result in anti-cancerous activities such as decreased immune invasion, easy access as well as membrane disruption of cancer cells.

Melittin has a very selective action against the HER-2 related tumors and so a combinational therapy of melittin and HER-2 targeted agents could be a very potent strategy. Melittin along with monoclonal antibodies, trastuzumab-emtansine and antibody-drug conjugates can have desirable effects as melittin can enhance the efficacy by assisting in easy access of drugs to cancerous cells through membrane disruption. Melittin could also be delivered through targeted nanoparticle approaches such as those previously reported with “nanobees”.⁷⁷

CONCLUSION

In conclusion, this review article focused on the role of Honey Bee Venom and its component melittin in rapidly inactivating two types of breast cancer cells which are otherwise difficult to treat. Breast cancer is the most prevailing cancer amongst women all over the world. Although different treatment options are available it is crucial to come up with an alternative therapy which carries no side effects. For hundreds of years, humans have been utilizing honey and venom from the *Apis mellifera* honeybee as medicine. Quite recently, scientists have exhibited the targeted effect of melittin and honeybee venom in suppressing the growth factor receptor activation in HER2-enriched

and triple-negative breast cancer. It is also lethal to a variety of tumors such as melanoma, pancreatic, ovarian and lung cancers in lab tests. This treatment has a surprising effect on the reduction of the chemical messages of cancer cells essential for the cell growth and division which other therapeutics are unable to carry out. Honeybee venom is accessible worldwide and offer economical and easily available treatment solutions for developing countries. As melittin holds the potential to treat the breast cancer in future, it is important to carry out further research to find out whether venom of some genotypes of bees are more effective. Moreover, studies should be conducted in future to evaluate the ideal method of provision of melittin, level of toxicity and average accepted dose. It will not only open avenues for study of advanced treatment strategies for breast cancer but also make it possible to explore the miraculous properties of natural remedies found in the world.

ACKNOWLEDGEMENTS

We acknowledge “Pixabay”, an open source of non-copyrighted images, for providing free of cost and free to use images for research purposes.

CONFLICT OF INTEREST

Authors declare no conflict of interest.



REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2015;136(5):E359-86.
2. Clegg LX, Reichman ME, Miller BA, Hankey BF, Singh GK, et al. Impact of socioeconomic status on cancer incidence and stage at diagnosis: selected findings from the surveillance, epidemiology, and end results: National Longitudinal Mortality Study. *Cancer causes & control*. 2009;20(4):417-35.
3. American cancer society. What is breast cancer? 2009
4. MA. K. Breast cancer: Merck Manual Consumer Version 2020 [Available from: <https://www.merckmanuals.com/home/women-s-health-issues/breast-disorders/breast-cancer>]
5. Breast Cancer Stages. 2020 [Available from: Breastcancer.org.]
6. Rahimzadeh M, Baghestani AR, Gohari MR, Pourhoseingholi MA. Estimation of the cure rate in Iranian breast cancer patients. *Asian Pac J Cancer Prev*. 2014;15(12):4839-42.
7. Fitzmaurice C, Dicker D, Pain A, Hamavid H, Moradi-Lakeh M, et al. The global burden of cancer 2013. *JAMA Oncol*. 2015;1(4):505-27.
8. Eberl MM, Sunga AY, Farrell CD, Mahoney MC. Patients with a family history of cancer: identification and management. *The Journal of the American Board of Family Practice*. 2005;18(3):211-7.
9. Hartmann LC, Sellers TA, Frost MH, Lingle WL, Degnim AC, et al. Benign breast disease and the risk of breast cancer. *N Engl J Med*. 2005;353(3):229-37.
10. Stoppler MC. Breast Cancer. *emedicinehealth*. 2020.
11. Wehbe R, Frangieh J, Rima M, El Obeid D, Sabatier JM, et al. Bee Venom: Overview of Main Compounds and Bioactivities for Therapeutic Interests. *Molecules*. 2019;24(16).
12. Global Burden of Disease Cancer C, Fitzmaurice C, Akinyemiju TF, Al Lami FH, Alam T, et al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-Years for 29 Cancer Groups, 1990 to 2016: A Systematic Analysis for the Global Burden of Disease Study. *JAMA Oncol*. 2018;4(11):1553-68.
13. Orsolich N. Possible molecular targets of bee venom in the treatment of cancer: application and perspectives. *Onco Therapeutics*. 2013;4(3-4).
14. Fidelio GD, Maggio B, Cumar FA. Interaction of myelin basic protein, melittin and bovine serum albumin with gangliosides, sulphatide and neutral glycosphingolipids in mixed monolayers. *Chem Phys Lipids*. 1984;35(3):231-45.
15. Jamasbi E, Mularski A, Separovic F. Model Membrane and Cell Studies of Antimicrobial Activity of Melittin Analogues. *Curr Top Med Chem*. 2016;16(1):40-5.
16. Polyak K. Breast cancer: origins and evolution. *J Clin Invest*. 2007;117(11):3155-63.
17. A. F. What to know about breast cancer. *Medical News Today*. 2017.
18. B. B. Rewari, SUDHIR. Gupta. Radiation Therapy in the Management of Cancer. 50 Years of Cancer Control in India. Ministry of Health and Family Welfare. 2019.
19. Do N, Weindl G, Grohmann L, Salwiczek M, Kokschi B, et al. Cationic membrane-active peptides - anticancer and antifungal activity as well as penetration into human skin. *Exp Dermatol*. 2014;23(5):326-31.
20. Forman D, Ferlay J, Stewart B, Wild C. The global and regional burden of cancer. *World cancer report*. 2014;2014:16-53.
21. Deng Y, Sriwiriyan S, Tedasen A, Hiransai P, Graidist P. Anti-cancer effects of Piper nigrum via inducing multiple molecular signaling in vivo and in vitro. *J Ethnopharmacol*. 2016;188:87-95.
22. Chaisakul J, Hodgson WC, Kuruppu S, Prasongsook N. Effects of Animal Venoms and Toxins on Hallmarks of Cancer. *J Cancer*. 2016;7(11):1571-8.
23. Kim YW, Chaturvedi PK, Chun SN, Lee YG, Ahn WS. Honeybee venom possesses anticancer and antiviral effects by differential inhibition of HPV E6 and E7 expression on cervical cancer cell line. *Oncol Rep*. 2015;33(4):1675-82.
24. Liu CC, Hao DJ, Zhang Q, An J, Zhao JJ, et al. Application of bee venom and its main constituent melittin for cancer treatment. *Cancer Chemother Pharmacol*. 2016;78(6):1113-30.
25. Liu CC, Yang H, Zhang LL, Zhang Q, Chen B, et al. Biotoxins for cancer therapy. *Asian Pac J Cancer Prev*. 2014;15(12):4753-8.
26. Diaz-Garcia A, Morier-Diaz L, Frion-Herrera Y, Rodriguez-Sanchez H, Caballero-Lorenzo Y, et al. In vitro anticancer effect of venom from Cuban scorpion *Rhopalurus junceus* against a panel of human cancer cell lines. *J Venom Res*. 2013;4:5-12.
27. Premratanachai P, Chanchao C. Review of the anticancer activities of bee products. *Asian Pac J Trop Biomed*. 2014;4(5):337-44.
28. Soletti RC, de Faria GP, Vernal J, Terenzi H, Anderluh G, et al. Potentiation of anticancer-drug cytotoxicity by sea anemone pore-forming proteins in human glioblastoma cells. *Anticancer Drugs*. 2008;19(5):517-25.
29. Al-Sadoon MK, Rabah DM, Badr G. Enhanced anticancer efficacy of snake venom combined with silica nanoparticles in a murine model of human multiple myeloma: molecular targets for cell cycle



- arrest and apoptosis induction. *Cell Immunol.* 2013;284(1-2):129-38.
30. Zhang Y. Why do we study animal toxins? *Dongwuxue Yanjiu.* 2015;36(4):183-222.
 31. Rady I, Siddiqui IA, Rady M, Mukhtar H. Melittin, a major peptide component of bee venom, and its conjugates in cancer therapy. *Cancer Lett.* 2017;402:16-31.
 32. Hossen MS, Shapla UM, Gan SH, Khalil MI. Impact of Bee Venom Enzymes on Diseases and Immune Responses. *Molecules.* 2016;22(1).
 33. Moreno M, Giralt E. Three valuable peptides from bee and wasp venoms for therapeutic and biotechnological use: melittin, apamin and mastoparan. *Toxins (Basel).* 2015;7(4):1126-50.
 34. Kim DH, Lee HW, Park HW, Lee HW, Chun KH. Bee venom inhibits the proliferation and migration of cervical-cancer cells in an HPV E6/E7-dependent manner. *BMB Rep.* 2020;53(8):419-24.
 35. Lee JA, Son MJ, Choi J, Jun JH, Kim JI, et al. Bee venom acupuncture for rheumatoid arthritis: a systematic review of randomised clinical trials. *BMJ Open.* 2014;4(11):e006140.
 36. Jeong YJ, Shin JM, Bae YS, Cho HJ, Park KK, et al. Melittin has a chondroprotective effect by inhibiting MMP-1 and MMP-8 expressions via blocking NF-kappaB and AP-1 signaling pathway in chondrocytes. *Int Immunopharmacol.* 2015;25(2):400-5.
 37. Son DJ, Lee JW, Lee YH, Song HS, Lee CK, et al. Therapeutic application of anti-arthritis, pain-releasing, and anti-cancer effects of bee venom and its constituent compounds. *Pharmacol Ther.* 2007; 115(2):246-70.
 38. Ip SW, Liao SS, Lin SY, Lin JP, Yang JS, et al. The role of mitochondria in bee venom-induced apoptosis in human breast cancer MCF7 cells. *In Vivo.* 2008;22(2):237-45.
 39. Jang MH, Shin MC, Lim S, Han SM, Park HJ, et al. Bee venom induces apoptosis and inhibits expression of cyclooxygenase-2 mRNA in human lung cancer cell line NCI-H1299. *J Pharmacol Sci.* 2003; 91(2):95-104.
 40. Jo M, Park MH, Kollipara PS, An BJ, Song HS, et al. Anti-cancer effect of bee venom toxin and melittin in ovarian cancer cells through induction of death receptors and inhibition of JAK2/STAT3 pathway. *Toxicol Appl Pharmacol.* 2012;258(1):72-81.
 41. Tu WC, Wu CC, Hsieh HL, Chen CY, Hsu SL. Honeybee venom induces calcium-dependent but caspase-independent apoptotic cell death in human melanoma A2058 cells. *Toxicol.* 2008;52(2):318-29.
 42. Ip SW, Chu YL, Yu CS, Chen PY, Ho HC, et al. Bee venom induces apoptosis through intracellular Ca²⁺-modulated intrinsic death pathway in human bladder cancer cells. *Int J Urol.* 2012;19(1):61-70.
 43. Moon DO, Park SY, Heo MS, Kim KC, Park C, et al. Key regulators in bee venom-induced apoptosis are Bcl-2 and caspase-3 in human leukemic U937 cells through downregulation of ERK and Akt. *Int Immunopharmacol.* 2006;6(12):1796-807.
 44. Hussein AA, Nabil ZI, Zalat SM, Rakha MK. Comparative study of the venoms from three species of bees: effects on heart activity and blood. *J Nat Toxins.* 2001;10(4):343-57.
 45. Orlov B, Romanova E, Omarov S. Immunological properties of bee venom 28th Int. Congr. Apicult. Acapulco. Mexico, Apimondia Publishing House, Bucharest; 1981.
 46. Shaposhnikova VV, Egorova MV, Kudryavtsev AA, Levitman M, Korystov Yu N. The effect of melittin on proliferation and death of thymocytes. *FEBS Lett.* 1997;410(2-3):285-8.
 47. Dotimas E, Hider R. Honeybee venom. *Bee world.* 1987;68(2):51-70.
 48. Habermann E. Bee and wasp venoms. *Science.* 1972;177(4046):314-22.
 49. Shi W, Li C, Li M, Zong X, Han D, et al. Antimicrobial peptide melittin against *Xanthomonas oryzae* pv. *oryzae*, the bacterial leaf blight pathogen in rice. *Appl Microbiol Biotechnol.* 2016;100(11):5059-67.
 50. Skalickova S, Heger Z, Krejcová L, Pekarík V, Bastl K, et al. Perspective of Use of Antiviral Peptides against Influenza Virus. *Viruses.* 2015;7(10):5428-42.
 51. Adade CM, Oliveira IR, Pais JA, Souto-Pradon T. Melittin peptide kills *Trypanosoma cruzi* parasites by inducing different cell death pathways. *Toxicol.* 2013;69:227-39.
 52. Pereira AV, de Barros G, Pinto EG, Tempone AG, Orsi Rde O, et al. Melittin induces in vitro death of *Leishmania (Leishmania) infantum* by triggering the cellular innate immune response. *J Venom Anim Toxins Incl Trop Dis.* 2016;22:1.
 53. Sisakht M, Mashkani B, Bazi A, Ostadi H, Zare M, et al. Bee venom induces apoptosis and suppresses matrix metalloproteinase-2 expression in human glioblastoma cells. *Rev Bras Farmacogn.* 2017;27:324-8.
 54. Killion JJ, Dunn JD. Differential cytolysis of murine spleen, bone-marrow and leukemia cells by melittin reveals differences in membrane topography. *Biochem Biophys Res Commun.* 1986;139(1):222-7.
 55. Zarrinnahad H, Mahmoodzadeh A, Hamidi MP, Mahdavi M, Moradi A, et al. Apoptotic Effect of Melittin Purified from Iranian Honey Bee Venom on Human Cervical Cancer HeLa Cell Line. *Int J Pept Res Ther.* 2018;24(4):563-70.
 56. Gao D, Zhang J, Bai L, Li F, Dong Y, et al. Melittin induces NSCLC apoptosis via inhibition of miR-183. *Onco Targets Ther.* 2018;11:4511-23.



57. Wang X, Li H, Lu X, Wen C, Huo Z, et al. Melittin-induced long non-coding RNA NONHSAT105177 inhibits proliferation and migration of pancreatic ductal adenocarcinoma. *Cell Death Dis.* 2018;9(10):940.
58. Duffy C, Sorolla A, Wang E, Golden E, Woodward E, et al. Honeybee venom and melittin suppress growth factor receptor activation in HER2-enriched and triple-negative breast cancer. *NPJ Precis Oncol.* 2020;4:24.
59. Park MH, Choi MS, Kwak DH, Oh KW, Yoon DY, et al. Anti-cancer effect of bee venom in prostate cancer cells through activation of caspase pathway via inactivation of NF-kappaB. *Prostate.* 2011;71(8):801-12.
60. Alizadehnohi M, Nabiuni M, Nazari Z, Safaeinejad Z, Irian S. The synergistic cytotoxic effect of cisplatin and honey bee venom on human ovarian cancer cell line A2780cp. *J Venom Res.* 2012;3:22-7.
61. Kondratskyi A, Kondratska K, Skryma R, Prevarskaya N. Ion channels in the regulation of apoptosis. *Biochim Biophys Acta.* 2015;1848(10 Pt B):2532-46.
62. Orsolich N. Potentiation of bleomycin lethality in HeLa and V79 cells by bee venom. *Arh Hig Rada Toksikol.* 2009;60(3):317-26.
63. Chu ST, Cheng HH, Huang CJ, Chang HC, Chi CC, et al. Phospholipase A2-independent Ca²⁺ entry and subsequent apoptosis induced by melittin in human MG63 osteosarcoma cells. *Life Sci.* 2007;80(4):364-9.
64. Liu S, Yu M, He Y, Xiao L, Wang F, et al. Melittin prevents liver cancer cell metastasis through inhibition of the Rac1-dependent pathway. *Hepatology.* 2008;47(6):1964-73.
65. Jeong YJ, Choi Y, Shin JM, Cho HJ, Kang JH, et al. Melittin suppresses EGF-induced cell motility and invasion by inhibiting PI3K/Akt/mTOR signaling pathway in breast cancer cells. *Food Chem Toxicol.* 2014;68:218-25.
66. Park JH, Jeong Y-J, Park K-K, Cho H-J, Chung I-K, et al. Melittin suppresses PMA-induced tumor cell invasion by inhibiting NF-κB and AP-1-dependent MMP-9 expression. *Mol Cells.* 2010;29(2):209-15.
67. Zhu H, Yang X, Liu J, Ge Y, Qin Q, et al. Melittin radiosensitizes esophageal squamous cell carcinoma with induction of apoptosis in vitro and in vivo. *Tumour Biol.* 2014;35(9):8699-705.
68. Vento R, D'Alessandro N, Giuliano M, Lauricella M, Carabillo M, et al. Induction of apoptosis by arachidonic acid in human retinoblastoma Y79 cells: involvement of oxidative stress. *Exp Eye Res.* 2000;70(4):503-17.
69. Anders C, Carey LA. Understanding and treating triple-negative breast cancer. *Oncology (Williston Park).* 2008;22(11):1233-9; discussion 9-40, 43.
70. Yao H, He G, Yan S, Chen C, Song L, et al. Triple-negative breast cancer: is there a treatment on the horizon? *Oncotarget.* 2017;8(1):1913-24.
71. Haffty BG, Yang Q, Reiss M, Kearney T, Higgins SA, et al. Locoregional relapse and distant metastasis in conservatively managed triple negative early-stage breast cancer. *J Clin Oncol.* 2006;24(36):5652-7.
72. Lee MT, Sun TL, Hung WC, Huang HW. Process of inducing pores in membranes by melittin. *Proc Natl Acad Sci U S A.* 2013;110(35):14243-8.
73. Lee MT, Hung WC, Chen FY, Huang HW. Mechanism and kinetics of pore formation in membranes by water-soluble amphipathic peptides. *Proc Natl Acad Sci U S A.* 2008;105(13):5087-92.
74. van den Bogaart G, Guzman JV, Mika JT, Poolman B. On the mechanism of pore formation by melittin. *J Biol Chem.* 2008;283(49):33854-7.
75. Fisusi FA, Akala EO. Drug Combinations in Breast Cancer Therapy. *Pharm Nanotechnol.* 2019;7(1):3-23.
76. Lee C, Bae SS, Joo H, Bae H. Melittin suppresses tumor progression by regulating tumor-associated macrophages in a Lewis lung carcinoma mouse model. *Oncotarget.* 2017;8(33):54951-65.
77. Pan H, Soman NR, Schlesinger PH, Lanza GM, Wickline SA. Cytolytic peptide nanoparticles ('NanoBees') for cancer therapy. *Wiley Interdiscip Rev Nanomed Nanobiotechnol.* 2011;3(3):318-27.

How to Cite This Article

Tariqa R, Liaqatb A, Ahmed Khalid U. An Insight into the Role of Bee Venom and Melittin Against Tumor Cells: A Review of Breast Cancer therapy. *Arch Breast Cancer.* 2021; 16(4):266-276.
Available from: <https://www.archbreastcancer.com/index.php/abc/article/view/374>