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

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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 specially 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.



## 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 ratio[2] 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

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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 $A_2$. 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 citated. 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.

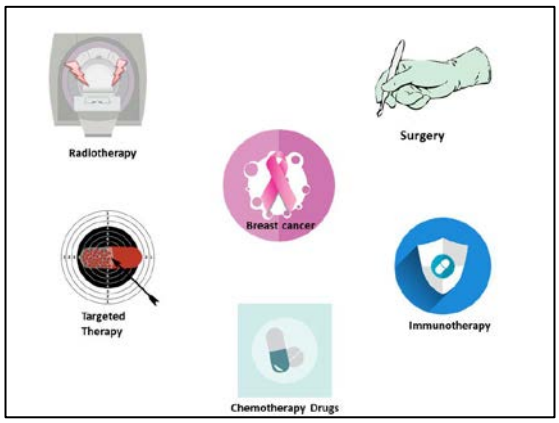


**Figure 1.** Main therapeutic approaches currently in practice for breast cancer treatment

*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 venom[26], Bee Venom (BV)[27], sea anemone toxin[28], snake venom[29], 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, rheumatism[35], arthritis[36], and chronic pain.[37] Many researchers have depicted amazing effects of BV on diverse range of human cancerous cells such as breast cancer[38], lung cancer[39], ovarian cancer[40], melanoma[41], bladder cancer[42], leukemia[43], 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 antibacterial[49], antifungal[19], antiviral[50], and anti-parasitic.[51, 52] Apart from that, a large number of research studies emphasize its antitumor effect in glioblastoma[53], leukemia[54], cervical cancer[55], non-small-cell lung cancer[56], 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 | 61 |
| | Leukemia | U937 cells | 0.5, 1, 2, 3 µg/mL | Initiating apoptosis with Bcl-2 and caspase-3 as key regulators 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 Ca2+ 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 | 65 |
| | Renal cancer | Caki-1 cells | 1, 2, 3 µg/mL | Suppressing PMA-induced invasion and migration by inhibiting MMP-9 expression | 66 |
| | Esophageal cancer | ECA109 cells, TE13 cells | 0.5, 1 µM 1.88, 1.64 µM (24 h) respectively | Radio-sensitizing 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].

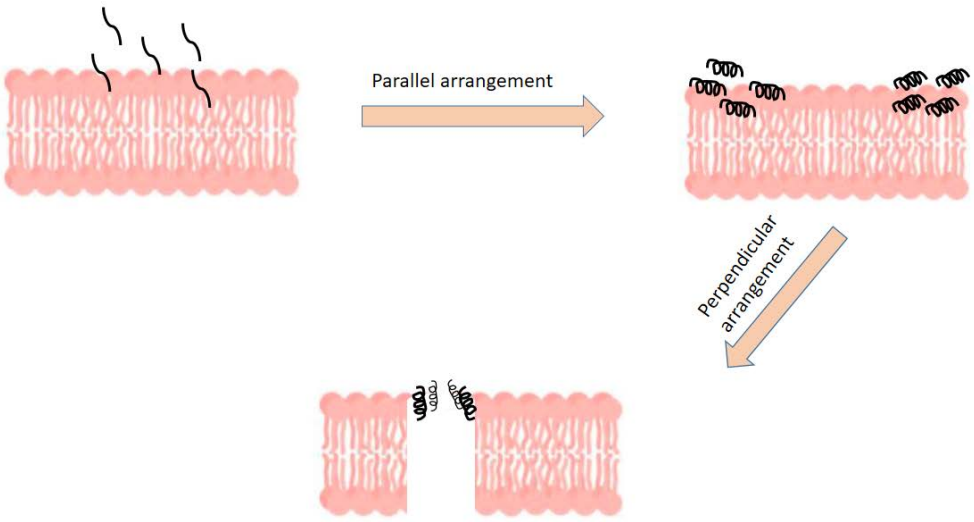


**Figure 2.** This model represents pore formation by melittin in membrane. Monomers of melittin accumulate on cell membrane and orient in parallel arrangement. Upon reaching a threshold concentration, it undergoes a shift from parallel to perpendicular arrangement. This perpendicular arrangement is 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 docetexal, showing favorable effects on breast cancer cell lines. Melittin in combination with docetexal 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.

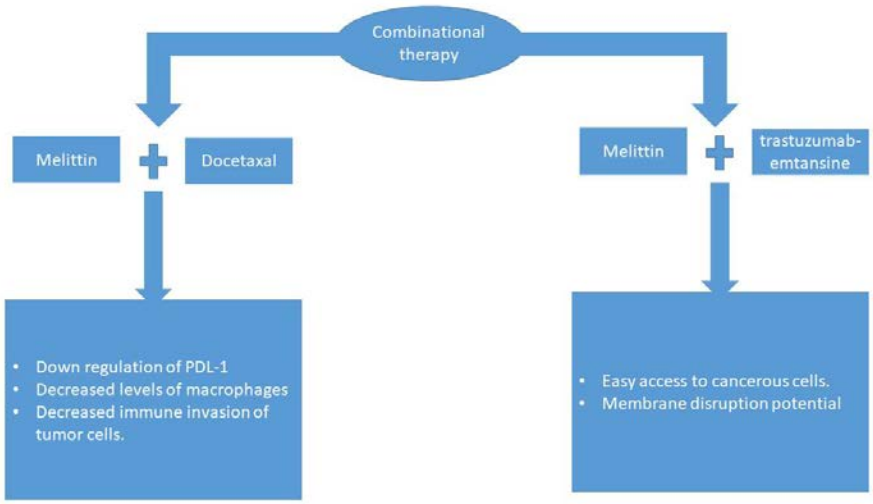


**Figure 3.** The enhanced activity of melittin in combination with several anti-tumor drugs can be seen. Docetaxal and trastuzumab-emtansine in combination with melittin result in anti-cancerous activities such as decreased immune invasion, easy access as well as membrane disruption of cancer cells.

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 mellitin 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.

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## CONFLICT OF INTEREST

Authors declare no conflict of interest.

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