Journal of Nursing and Patient Safety

Review Article Open Access

Melittin and Breast Cancer: A Brief Review of the Evidence

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Received: 17 October 2020; **Accepted:** 10 November 2020; **Published:**17 November 2020

Abstract

Bee venom is commonly used for treating ailment including pain and tumor. There are various investigations concerning melittin in terms of tumors treatment or antitumor activity. Melittin consists of 26 amino acid residues, mostly with hydrophobic or at least uncharged side chains, except for the C-terminal region, and the principal function of melittin as a component of bee venom is to cause pain and destruction of the tissue of intruders that threaten a beehive. There are various shreds of evidence regarding the effect of melittin on cancer or tumor cells. The aim of this review study was to investigate the effects of melittin on breast cancer. Studies with inclusion criteria from 2016 were included in this study. The second reason for death in women is breast cancer. The development of breast cancer is a multi-step process involving multiple cell types, and its prevention remains challenging in the world. By various biochemical and molecular mechanisms, Melittin could lead to a reduction of tumor size, prevention of metastasis, and in some cases cancer treatment. It was particularly significant cytotoxicity on damaging breast cancer cells. Some pieces of evidence also suggested that for diminishing the hemolytic and allergic reactions and fulfilling the efficacy of treatment outcome combine melittin with nanoparticles or chemotherapeutic agents. Melittin has positive effects on several types of cancer, such as renal, lung, liver, prostate, bladder, breast, thyroid, and melanoma. However, it should not be underestimated that most studies are in vitro and in vivo; therefore, more randomized control trials are required.

Keywords: Melittin, Breast cancer, Chemotherapy, Cancer, Tumor

Background

In Korean medicine to treat wide range of diseases like pain or tumor bee venom is commonly used [1]. It is composed of a complex mixture of biologically active peptides, including melittin(mostly), apamin, adolapin, mast-cell-degranulating (MCD) peptide; enzymes (phospholipase A2, and hyaluronidase), and non-peptide components (histamine, dopamine, and norepinephrine), which have a variety of pharmaceutical properties. Selective cytotoxicity of melittin alongside is the anti-cancer peptide cause the main synergistic effect of bee venom [2].

Melittin (C131H229N39O31) is the major component of honey bee venom, representing approximately 50% of the total honey bee venom. It consists of 26 amino acid residues, mostly with hydrophobic or at least uncharged side chains, except for the C-terminal region [3]. Melittin primary activity as an ingredients of bee venom are to cause pain and demolition of fiber of troublemaker that threaten a beehive. The two venom molecules, melittin and secapin, that are over-expressed in honey bees infected with various pathogens, possibly indicate a role for melittin in the immune response of bees to infectious diseases [4].

There are various investigations concerning melittin in terms of tumors treatment or antitumor activity. However, nonspecific cytotoxicity and the resulting hemolytic activity disrupt the clinical program. Therefore, it can be said that melittin has several effects on the cellular functions of cancer cells such as proliferation, apoptosis, metastasis, angiogenesis and cell cycle [5]. Accordingly, the main peptide of bee sting (melittin) can play a useful role in the treatment of cancer and has the properties of inducing apoptosis, cancer cell necrosis, disrupting mitochondrial cells and disrupting angiogenesis, stopping the growth cycle and cell division and preventing its metastasis. Due to the possible side effects, research is ongoing on the widespread use of this substance in the treatment of cancer [6]. Melittin, a pore-forming peptide from Apis mellifera venom exerts

neoplastic activity on many types of cancer cell lines. Anti-proliferative effects of melittin proportionally involve the inhibition of calmodulin binding activity [7], which appears to be a major intracellular target. Many in vivo studies have demonstrated that administration of melittin is capable of minimizing tumor size suggesting the presence of antitumor activity in this peptide [8, 9]. Melittin is anticipated to prevent adaptive resistance caused by specific inhibition of targeted therapy, potentially involving mutation or remodeling of cancer growth [10].

Second reason of death in women is breast cancer. The breast cancer progress is based on various factors involving multiple cell types, yet prevention remains demanding in the world [11]. In 2012, roughly two million women worldwide were diagnosed with breast cancer (BC), and 521,900 women died from it [12]. Currently chemotherapy (individual or in combination with radiotherapy), radiotherapy, immunotherapy, and targeted therapy are the available breast cancer treatment around the world. However, treatments with a novel approach in the treatment of breast cancer are emerging.

Melittin might induced allergic reaction and result in hemolytic activity. In addition, accumulation in non-target tissues can also cause tissue damage. There are several nanoparticles [13] which could apply for delivery of melittin for reduction hemolytic activity and an increase in targeted accumulation in the tumor [14], including polyethylene perfluorocarbon, [15] poly (lactic-co-glycolic acid) nanoparticles, [16] glycol-stabilized lipid disks, [17] quantum dots [18] and core-shell lipid nanoparticles [19]. One review shows the interaction and treatment of melittin with several types of cancer, such as renal, lung, liver, prostate, bladder, breast. However, some side effects like hemolysis and injury of liver and kidney were detected in the treatment process of melittin. To minimize these body damage effects, a recombinant immunotoxin was obtained that is an antigen binding to melittin; showed significantly binding and killing tumor cell properties in vitro [20].

Melittin is explored here in a short systematic review as a promising therapeutic agent for breast cancer and other malignancies. Therefore, the aim of the present study was to determine if melittin has a direct action on processes of breast cancer cells.

Methods and Materials

The literature search using the following search strategy was conducted on Google scholar database on October1th, 2020 to identify eligible articles: (melittin*) and (breast cancer*). The publication time was limited to 2016 onward. A total of 1720 papers were identified by the initial search. Two reviewers independently reviewed the abstracts and full texts. Reports on the range of the effect of melittin on breast cancer or other cancers were included in this review.

Results

Overall, 37 studies regarding melittin and breast cancer were included in the final analysis.

Studies on melittin have shown that when injected intravenously, it can be toxic to lipid membranes. The anti-cancer effects of melittin have been found in breast, lung, prostate and liver [21].

Evidences of the effect of melittin on breast cancer

There were several papers regarding the anti-cancer and anti-neoplasm effects of melittin. A study conducted by C Liu et al. in 2016 examined bee venom and its major constituent extensively in the treatment of tumors. However, nonspecific cytotoxicity and the resulting hemolytic activity disrupt the clinical program. Melittin has several effects on the cellular functions of cancer cells such as proliferation, apoptosis, metastasis, angiogenesis as well as cell cycle [22].

In the study conducted by Ciara Duffy et al. in 2020 in Australia, they report that melittin induces potent and highly selective cell death in TNBC and HER2 -enriched breast carcinoma with negligible effects in normal cells. Melittin causes cell death by forming transmembrane toroidal pores that may enable the internalization of additional small molecules with cytotoxic activities. It also induced apoptosis in MCF7 cells and reduced cell viability and migration in MDA-MB-231 breast cancer cells. The C-terminus of melittin creates a positively charged -helix that has been suggested to intercede binding to the negatively charged plasma membrane, enforcing following pore formation and cell lysis. The C-terminal positive motif seems essential for anticancer activity. Melittin decreased the phosphorylation of EGFR and MAPK , downregulating leading oncogenic multiplication ways. With the combination of melittin and docetaxel in reducing TNBC growth, it is found that for the combination treatment, tumor control was superior compared to either melittin or docetaxel treatment alone, with the combination of achieving a significant reduction in tumor volume. The evidence proposed that docetaxel tumors-resistant could be rendered sensitive by the addition of melittin. Combination therapies would enhance the efficacy and diminish the cytotoxic dosage agents, providing more cost-effective remedies with potentially fewer adverse effects to be delivered. In addition, melittin can decrease the immune-suppressive effects of the tumor microenvironment, which are prevalent in TNBCs in the presence of chemotherapy. Melittin also can help attenuate the expression of immune-checkpoint proteins, therefore ameliorate antitumoral immune responses [23].

A 2016 study in China showed that treatment with melittin by increasing the dose (0.5 to 2.5 μg) by inhibiting MMP2 and inhibiting CD147 expression significantly reduced the risk of MCF-7 breast carcinoma attack. Trans well was used to determine the effects of melittin on MCF-7 cell invasion [24].

In the research conducted by Karolina Daniluk et al in 2019, the use of carbon nanoparticles as melittin carriers for breast cancer cells on in vitro stage was determined. Melittin causes the disintegration of cell membranes, and cell death analysis showed that it caused cell death mainly through necrosis. This peptide, after intravenous injection, causes severe toxic reactions, such as hemolysis, which is

a limitation of its widespread use in the treatment of cancer. However, the conjugation of melittin with the nanoparticles (carbon nanoparticles, graphene oxide, pristine graphene, and diamond) up taken by the cells will reduce the spread of melittin across the tissues.

The use of complexes with GN and GO caused greater destruction of cell morphology compared to the action of melittin itself. MDA-MB-231 is more sensitive to nGO than the MCF-7 cell line, which caused 100%

1. Triple-negative breast cancer
2. Human Epidermal growth factor receptor2
3. Michigan cancer foundation-7 (primary tumor)
4. Human claudin-low breast cancer
5. Epidermal growth factor receptor
6. Mitogen-activated protein kinase
7. Matrix metallopeptidase 9
8. Cluster of differentiation 147
9. Graphene
10. Graphene oxide

membrane degradation. Melittin has a non-selective cytolytic effect, but it was proved that melittin selectively degrades cells' Ras oncogene expression which shows overexpressed in 20–50 percent of breast cancers. This study suggests that melittin in complexes could have a selective cytotoxic effect on cancer cells, but tests on healthy cells are needed. Changes in the potential of mitochondrial membranes are key for the induction of apoptosis. The results suggest that nGO maybe is an effective melittin carrier to the interior of cells and increases melittin lytic properties toward intrinsic membranes, including the mitochondrial membrane. Moreover, the complexes reduced the level of necrosis compared to melittin but did not completely eliminate it. The results indicate that the melittin complex with nGOs has a stronger toxic effect on breast cancer cells than melittin alone, especially for the estrogen-independent line MDA-MB-231 [21].

In the research conducted by Radhika Raveendram et al in 2020, the function of melittin, used in PIC micelles as a suitable nanocarrier, was observed. These nanocarrier systems are facile to prepare and can incorporate various biologically active molecules like proteins. PIC micelles posed the problem of neutralizing the toxicity of melittin. They were further cross-linked, which enforced stability and was effective in preventing the trypsin digestion at a higher melittin concentration in 2D cytotoxicity experiments. Melittin shielded in the core of the PIC micelles exhibited improved cytotoxicity in the spheroids compared to the free melittin in the 3D cytotoxicity studies [23].

In a study by Ali et al. it was experimentally shown that the release behavior of both DOX and MEL anticancer agents is strongly pH dependent and increases significantly at acidic pH. A laboratory method in a type of breast cancer cell line showed a synergistic effect between DOX and MEL, which resulted in a significantly greater antitumor effect than single administration of these anticancer agents in equivalent doses [22].

A study by Zhou et al. showed that promelittin effectively inhibits the progression of BCBM through AMD3100 conjugated nanoparticles [24].

In a study by Khamis et al. which conducted in Egypt in 2018, examining the combined anti-cancer effects of Hesperidin, piperine and bee venom with tamoxifen. This study showed that the combination of these three products enhances the effect of tamoxifen and because it reduces the required dose and duration of use, can reduce the side effects of tamoxifen. These natural products also potentiate the activity of tamoxifen by inducing apoptosis, stopping the cell cycle, and reducing ER and EGFR expression [26].

Evidences of the effect of melittin on other cancers

The findings of a study (Huh et al.) confirmed that melittin yielded more significant effects than NS398 (COX-2 inhibitor). In particular, subcutaneous injections of melittin at doses of 0.5 and 5 mg/kg significantly inhibited vascular endothelial growth factor (VEGF)-A-transfected highly metastatic Lewis lung cancer (VEGF-A-hm) tumor growth, with decreases in vessel numbers of 25% and 57%, respectively. Huh et al. suggested that the effect mechanism of melittin may be associated with anti-angiogenic activity inhibiting VEGF receptor-2 and inflammatory mediators [27].

11. Nano graphene oxide
12. Polyion complex
13. Doxorubicin
14. Melittin
15. Breast cancer brain metastases
16. A small molecule antagonist of CXCR4, highly expressed in BCBM
17. Estrogen receptor
18. Cyclooxygenase-2

The results of a study by Gao et al. indicate that melittin severely suppresses miR-183 expression by inhibiting it, activating caspase-2 enzymes and causing NSCLC apoptosis, as well as reducing the ability of these cells to invade, migrate and grow [28].

Aptamers are small single-stranded DNA or RNA oligonucleotide ligands that can be used for targeted drug delivery. In a study conducted by Rajabnejad et al. in 2018, the construction of a melittin aptamer AS1411 for targeted delivery of melittin to cancer cells was investigated. AS1411 is a DNA aptamer that binds to the extracellular protein nuclein. Nuclein is overexpressed in the membranes of cancer cells, including breast cancer, kidney carcinoma, and lung cancer. Therefore, it seems that the growth of membrane nuclein can be used as a strategic target for the treatment of cancers. Melittin-aptamer conjugate can be more toxic to cancer cells than free melittin, and it can also be effectively placed between cancer cells and healthy cells, providing greater immunity for healthy cells than free melittin [29]. In a similar study conducted by Yazdian et al. in 2019, CCN were used as a delivery device to deliver epirubicin and melittin to target cancer cells. Aptamer was also used against Mucin 1 (MUC1), a cell surface glycoprotein that is highly expressed by early breast cancer

cells. The results indicate that, although epirubicin and melittin have different mechanisms in the treatment of cancer, but they have strong synergistic properties and also the combination of MUC1 Dimer and CCN aptamer can be used as a targeted delivery medium and this system as a targeted treatment and Use promising to treat cancer [30].

IL-2 is an efficient treatment for progressive malignancies. However, the therapeutic effect of IL-2 is limited by severe systemic toxicity, and melittin is an attractive anti-cancer candidate due to its wide range of lytic properties. In an experimental study by Liu et al. a melittin-MIL-2 synthetic protein consisting of melittin and an IL-2 mutant was generated and used to show that melittin-MIL-2-induced immune cells directly and indirectly kill cancer cells from their roots. Different tissues were in vitro and potent inhibition of tumor growth was performed in vivo. In addition, this synthetic protein inhibits breast cancer-related lung metastasis [31].

In study by Nermeen et al. the antitumor effect of melittin as a proapoptotic and antiangiogenic molecule in mice with ascites carcinoma (EAC) was investigated. Bee venom was found to reduce the growth of tumor cells and the inhibitory concentrations of this substance were calculated to be around 120 and 55 micrograms per milliliter [23]. If the use of bee venom is combined with radiation therapy, due to its synergistic properties and increased sensitivity of cancer cells to radiation therapy, tumor growth, angiogenesis, metastasis and tumor invasion are reduced and apoptosis is increased. Bee venom significantly inhibits lipid peroxidation and induces MDA-MB-231 breast cancer cells by inducing apoptosis and activating caspase and inactivating NF-κb breast cells. Two study results [23,32] showed that melittin is effective in cell proliferation and production of interferon B to kill cancer cells.

In the study conducted by Bin He et al. in 2018 in China, they designed the TCM-legM (a tumor microenvironment-activated cabazitaxel micelles functionalized with legumain-specific melittin) with specific responsiveness to the highly expressed legumain in tumor region and mildly acidic pH-stimuli in intracellular endosomes/lysosomes for programed targeting of breast cancer metastasis. The restored melittin in TCM-legM can promote the deep penetration in tumor and facilitate their internalization by cancer cells. In metastatic 4T1 (is a transplantable tumor cell line) breast cancer cells, TCM-legM could be largely internalized and showed considerable inhibition on the proliferation, migration, and invasion activities. In vivo, TCM-legM could be specifically delivered to the sites of primary and metastatic tumors with deep penetrating ability and efficiently internalized by cancer cells, thereby leading to a considerable reduction of primary tumor growth and producing a 93.4% prevention on the incidence of lung metastasis. Therefore, the rational design of TCM-legM can provide an intelligent drug delivery strategy for programed targeting of breast cancer metastasis [33].

19. micro RNA
20. Non-small-cell lung cancer
21. calcium carbonate nanoparticles
22. Interleukin-2
23. Nuclear factor κb

In an experimental study by Kong et al. melittin was incubated at different concentrations for a certain period of time and showed time-dependent inhibition of the growth of gastric cancer cells. Melittin induced apoptosis of the cell, which was confirmed by normal morphological changes. Supposedly, melittin can cause apoptosis of gastric cancer cells in humans through mitochondrial pathways and may be a factor in the treatment of human gastric cancer [34].

Ke et al. indicated that melittin is used to treat 5-fluorosil-resistant HCC by reducing the proliferation of HCC cells and increasing the effect of 5-fluorosil [35].

A 2019 study in Serbia by Nikodijević et al. [36] examined the effect of bee venom on colon cancer cells, which showed that bee venom significantly reduced the viability of HCT-116 and SW-480 cells . SW-480 is more sensitive to treatment than HCT-116. Also, in this study, it was shown that bee venom has a more efficient effect on colon cancer cells than melittin.

In study of Jin et al. in china, it was stated that melittin can limit the expression of module-related DEGs in relation to the PI3K-Akt and TNF signaling pathways in bladder cancer cells, thereby limiting the ability of bladder cancer cells to proliferate and migrate [37].

Also, a 2016 study in Ukraine to investigate the susceptibility of myelin to ovarian cancer cells found that cisplatin-resistant cells (A2780CR) were more sensitive than cisplatin-sensitive cells (A2780), and melittin also had some effect on the lipid composition of the cells. Therefore, melittin might have some potential as an adjuvant therapy in cancer treatment [38].

The results of a study by Zarrinnahad et al. with the aim of investigating the anti-cancer effect of melittin on human cervical cancer cells showed that, flow cytometric analysis of melittin causes apoptosis at concentrations greater than 1 µg / ml. Accordingly, melittin may causes apoptotic death of cervical cancer cells [39].

The results of research by Lim et al. show that bee venom and melittin strongly suppress the growth and migration of melanoma cells (a type of malignant skin cancer). Melittin can be a promising chemical for the treatment of malignant melanoma. Treatment with bee venom and melittin leads to Significant inhibition of the ability of colony formation in melanoma cells [40].

Endothelial progenitor cells (EPCs) are pluripotent stem cells that have the ability to differentiate into mature endothelial cells. Endothelial progenitor cells are important in tumor angiogenesis. Angiogenesis is important in the development of malignant tumors, evolution, and metastasis. The results of Qin et al. study evident that melittin

reduces EPC adhesion and It may decrease the effect of osteosarcoma on EPC-mediated angiogenesis, possibly via inhibition of the SDF-1 / CXCR4 signaling pathway [41].

In research conducted by Shaw et al. in Belgium in 2019, It indicated that the ability of the RONS (e.g NO2-) present in PT-PBS to damage the lipids in the cell membrane increases the melittin permeation, therefore lowers the therapeutic dose of melittin required to exert a cytotoxic effect in cancer cells [42].

24. Hepatocellular carcinoma
25. 5-Fu
26. a human colon cancer cell line used in therapeutic research and drug screenings
27. Differentially expressed genes
28. Phosphoinositide-3 kinase-protein kinase B (PKB/Akt)
29. Tumor necrosis factor
30. Stromal cell-derived factor-1
31. C-X-C chemokine receptor type 4
32. reactive oxygen and nitrogen species
33. Plasma-treated phosphate buffered saline solution

The results of a 2020 study in Poland by Ceremuga et al. showed that melittin greatly reduced the survival of all leukemia cells, depending on the dose, but this effect did not affect the toxicity of melittin to peripheral blood mononuclear cells (PBMCs) [43].

There is evidence which shows that, melittin is genotoxic to HPBLs and provide evidence that oxidative stress is involved in its DNA damaging effects. Besides melittin cytotoxity for HPBLs , was a dose- and time-dependent manner and it induced morphological changes in the cell membrane and lysis of exposed cells. It also modulated the expression of selected genes involved in DNA damage response (TP53, CDKN1A, GADD45, MDM), oxidative stress (CAT, SOD1, GPX1, GSR and GCLC) and apoptosis (BAX, BCL-2, CAS-3 and CAS-7) [44]. In a similar study, it was found that Cat S may be a significant regulator of growth and angiogenesis in MHCC97-H cells, and that melittin is capable of inhibiting Cat S-induced invasion and angiogenesis via blocking of the VEGF-A /VEGFR-2/MEK1 /ERK1/2 signaling pathway, in a dose-dependent manner [45].

In the study conducted by Paulina Biniecka et al. in 2017 in Warsaw, the carbon nanoparticles were tested as components of drug delivery system for melittin, on glioma cells in vitro cell culture. Results prove the effectiveness of carbon nanoparticles as nanocarriers, especially UDD (nanodiamond), GN (graphene) and nGO (nanographene oxide). They effectively transport the targeted melittin and help with adhesion of it to the glioma cells, and cause the apoptotic way of cell death. Melittin has been tested as anticancer drug, on ovarian cancer cells, giving the promising results [46].

In the study conducted by Huang et al. in 2016, it was found out that the possible anti-cancer, anti-tumor mechanism of melittin is: inhibited cell growth by disturbed cell growth cycle, then induces cell apoptosis and necrosis. In vitro experiment, reveals a growth inhibition and lethality in human hepatoma and glioma cell [47].

In the study conducted by Lanlan Wan et al. in 2017 in china, a novel peptide TT-1, (taken from melittin, contained only 11 amino acids and glycine residues remodeled with lysine residues,) was designed, and its antitumor effect was investigated. TT-1 has an more hydrophobicity and a reduced net charge, which indicates a higher consistencyand lower toxicity compared with melittin.TT-1 suppressed the proliferation of TT (a human thyroid cancer cell line) cells by inducing apoptosis via upregulation of Bax (Bcl-2-associated X protein), downregulation of B-cell lymphoma-2 (Bcl-2) and the activation of caspase-3 and -9 at transcriptional and translational levels. Also, TT-1 demonstrated selective anti-tomur activity. These outcomes highlighted the therapeutic potential of TT-1 in thyroid cancer [48].

In the study conducted by Tipgomut et al. in 2018, the effects of melittin on bronchogenic carcinoma cell proliferation and tumor-associated macrophage differentiation were evaluated. Melittin was significantly more cytotoxic to human bronchogenic carcinoma cells (ChaGo-K1) than to the control human lung fibroblasts (Wi-38) cells. Melittin could suppress ChaGo-K1 cell proliferation and cause apoptosis and cell cycle arrest at the G1 phase. Melittin-induced apoptosis of ChaGo-K1 was supported by the observed morphological changes (cell shrinkage, round cell formation, nucleus and organelle condensation, cell floating, decrease in viable cell density and presence of cell debris) and the significantly higher and lower expression of Bcl-2 (B-cell lymphoma-2) and MADD (mitogen activating protein-kinase activating death domain) transcripts. Whether melittin induced apoptosis or necrosis depended on the dose. This suggests that melittin is a promising anti-lung cancer peptide [48]. According to the latest findings on the effects of chemotherapeutic agents such as chrysin in promoting antitumor activity when combined with polymer nanoparticles, it is recommended that researchers study the combination of these agents with melittin [49].

Conclusion

34. peripheral blood lymphocytes
35. cathepsin S
36. vascular endothelial growth factor
37. mitogen activated protein kinase kinase 1

It seems that despite the side effects of melittin (such as allergic reactions), it has positive effects on wide range of cancers, particularly breast cancer. However, it should not be underestimate that most of studies are in vitro and in vivo; therefore, there are long ways to be used in human.

Melittin contains the following properties in helping to treat cancer:

1. The effects of melittin are with phospholipase A2, caspase and metalloproteinase 2 and kill the cells that express oncoprotein.

2. Melittin is one of the most potent inhibitors of calmodulin, which is very important in the growth and division of cancer cells.

3. Induces apoptosis in cancer cells by changing the potential of mitochondrial membranes. Induction of apoptosis by melittin has been confirmed in gastric, lung, liver, ovarian, breast and cervical malignancies.

4. It has anti-metastatic properties and inhibits rac1 35expression.

5. The substance disintegrin linker melittin (DLM) is made of melittin and disintegrin and activator of plasminogen urokinase-type (uPA). uPA breaks down in tumor cells and allows DLM to release melittin.

6. Combination of nationality with amino terminal fragment (ATF)

7. Combination of nationality with interleukin 2.

8. Combination of bee venom with Cisplatin, which together have synergistic properties and cause fewer side effects.

9. Bee-produced propyl contains Chrysin, which can be used to treat breast cancer and develop chemotherapy in the future.

10. Using a combination of melittin and dutaxel, dutaxel-resistant tumors can be sensitive.

11. Melittin can decrease the immune-suppressive effects of the chemotherapy.

12. Nanoparticles, PIC13 micelles and combination of melittin-aptamer can be used as safe carriers of melittin.

13. Hespiridine, piperine and bee venom can be used to enhance the effect of tamoxifen.

14. Melittin reduces EPC adhesion and Prevents angiogenesis.

15. Melittin greatly reduced the survival of all leukemia cells.

Acknowledgment

The authors are thankful to all the respondents for their voluntary participation and staff in research.

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Citation: Yavari M, Salesi Z, Derakhti A, Azimzadeh S, Varpaei HA, Esmaeili H and Jafari M. "Melittin and Breast Cancer: A Brief Review of the Evidence." J Nur Patient Saf (2020): 001 doi: 10.47755/J Nur Patient Saf.2020.1.001