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ANTICANCER ACTIVITY OF BEE VENOM AND ITS COMPONENTS AGAINST BREAST CANCER : A REVIEW

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ABSTRACT

Cancer is a disease in which some of the body's cells grow uncontrolled and spread to other parts of the body. Cancer is among the leading cause of death worldwide. Breast cancer is most common and life-threatening cancer in females characterized by abnormal proliferation of tumor cells in lobules or ducts. Various treatments and anti-cancer drugs are discovered for the treatment of breast cancer including radiation therapy, endocrine therapy, stem cell transplant and targeted therapy. Because patients have to face many challenges after undergoing these treatments, researchers are looking for nature based therapies. Recently, bee venom therapy has shown positive impact in the treatment of breast cancer. Venom present in the solitary bag of honey bee. Bee venom is composed 40 active ingredients approximately which posses anti-inflammatory and analgesic properties and also used to treat various disorders related to cancer. The mechanism of anticancer effect of bee venom includes cell lysis, cytotoxic activity, apoptosis and regulation of gene expression. Melittin is the major component of honey bee venom that attacks to the cell surface, disturb phosphorylation at receptors and make pores in the cell membrane to destabilize it. A proper carrier is required to deliver melittin at the site of action to prevent hemolytic side-effect and non-specific toxicity of melittin. Melittin also inhibits the cell signaling pathways that allow cancer cells to communicate and replicate. In combination with chemotherapy drugs, melittin is found very affective at killing tumors.

Key words : Anticancer activity, Bee venom, Breast cancer, Melittin.

Introduction

Large number of countries have high mortality rate in women and breast cancer is one of the reason (Fitzmaurice *et al*, 2015). In America, Africa and Asia breast cancer is strengthening its roots, as per report cases, which is a serious situation (Rahimzadeh *et al.*, 2014). In 1990s, breast cancer is on fourth rank on the list of the most prevalent cancer in India but nowadays it is at the top (Mehrotra and Yadav, 2022). If patient get regular checkups of visible symptoms, it is possible to diagnose breast cancer at early stage which may reduce number of death of females because of breast cancer. Survival rate of the patient decreases by progression in stage of cancer (Wang, 2017). Age increases the likelihood of developing cancer (Mc Guire *et al.*, 2015).

Breast cancer can originates in different parts of breast, such as epithelial cell lining of lobules, ducts of glandular tissues or tissues in between. In situ cancerous cells do not show any symptoms and growth is also confined to duct or lobule only. Gradually, these cancerous cells grow and invade the neighboring tissues and then spread to lymph nodes or body organs by metastasis (Feng *et al.*, 2018).

On the basis of presence of molecular markers, breast cancer can be categorized into three subtypes, which are as follow: hormone receptor positive/human epidermal growth factor receptor-2 gene (ERBB2) negative, human epidermal growth factor receptor-2 gene positive and triple-negative breast cancer. The rate of recurrence and treatment strategies are developed on the basis of these sub-types (Kwon *et al.*, 2022). Estrogen

receptors (ER), Progesterone Receptor (PR), Human Epidermal Growth Factor Receptor 2 (HER2) are the prominent biomarkers present in breast cancer. Triple Negative Breast Cancer does not have any receptor but it show same signs and symptoms as other types of breast cancer (Yadav *et al.*, 2015). About 20% of breast cancer patients are suffering from TNBC. It majorly diagnosed in women of age less than 40 years (Feng *et al*., 2018).

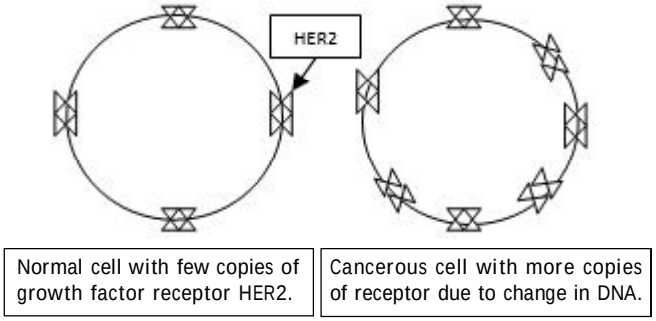

Fig. 1 : HER 2 receptors on normal cell *vs* cancerous cell.

A single technique or combination of techniques can be used for the treatment of specific type of cancer. Treatment methods involve endocrine therapy, chemotherapy, surgery, radiation therapy, or any other method depending upon the type of cancer (Ridner, 2013). Eventhough, there is improvement and development in technology on the diagnosis and treatment of cancer in past few years, but it is still one of the diseases which have highest mortality rates worldwide (Wang *et al.*, 2018).

Natural products derived from plants and animals are used to treat various disorders with the help of their therapeutic properties (Kwon *et al*., 2022). Toxins that can damage other living creatures are evaluated clinically for the treatment of cancer (Shapira and Benhar, 2010). These toxins or components derived from nature have shown positive results in number of disorders, including various types of cancer.

Honeybee is widely used to derive products for the human welfare. Disease therapy is the main application of honeybee derived components and products. Honeybee venom is also used as a therapeutic agent in the treatments of various disorders. “Apitherapy” is the term used for the cure of many diseases with the help of bee derived compounds. Honeybee derived compounds are used to treat different disorders like Alzheimer, Parkinson, viral infections, bacterial infections, and different type of cancers (Wehbe *et al*., 2019). Honeybee venom comprises of following active components- Melittin, Apamin, peptides, Adolapin, Phospholipase A2, hyaluronidase and aminoacids (El Sharkawi, 2015).

Melittin is the main element of honey bee venom that is used for the treatment of various types of cancer especially breast cancer in humans. Melittin, the chief component, comprises 40-60% of the total composition of bee venom. Honeybee venom and its main compound melittin are proved to be good agents for cancer treatment as they initiate apoptosis, inhibit cell proliferation, cell growth and control metastasis (Orsolic, 2014). Bee venom and its components are also confirmed to be efficacious in the treatment of ovarian cancer, postrate cancer and human malignant hepatocellular carcinoma (Moga *et al.*, 2018; Badawi, 2021; Mohamad Reza Kamran, 2020).

Melittin is extracted and purified from venom of honey bee with the help of various laboratory techniques like HPLC (High performance liquid chromatography), gel filtration and capillary electrophoresis. After extraction, melittin is analyzed by reverse phase HPLC, ultraviolet assay and amino acid sequence (Wang *et al*., 2022).

Melittin show anti-tumor activity by disrupting the cell membrane of cancer cell in a non-selective manner. Melittin is also known to cause hemolysis and nonspecific cytotoxicity. Therefore, a suitable delivery vehicle such as a nanocarrier is required to deliver bee venom to the site of action. To prevent side effects, it is also necessary to reduce the dose of melittin.

In this review, we analyzed the existing methods that are in use in the treatment of breast cancer as well as the studies conducted on the use of bee venom in inducing cell death, mainly in human epidermal growth factor receptor 2-enriched and triple-negative breast cancer and the mechanism underlying the treatment of breast cancer with the help of bee venom and melittin.

Therapies in use for breast cancer

Various therapies are developed to conduct a successful treatment of breast cancer. Two important steps in the successful elimination of breast cancer include selection of efficacious treatment therapy and management of breast cancer (Roha Tariq, 2021). Selection of effective therapy eases the process of treatment for doctors by selecting a single treatment method or combination of methods with which they have to proceed further. In making the treatment plan of a cancer patient, specialized doctors in different fields of cancer treatment such as surgery, medical oncology, pathology and radiology work together. Alternate measures are used to combat after therapy side effects. Treatment therapies used for breast cancer depends upon the sub-type of breast cancer, patient is suffering from.

Some of these therapies are listed below:

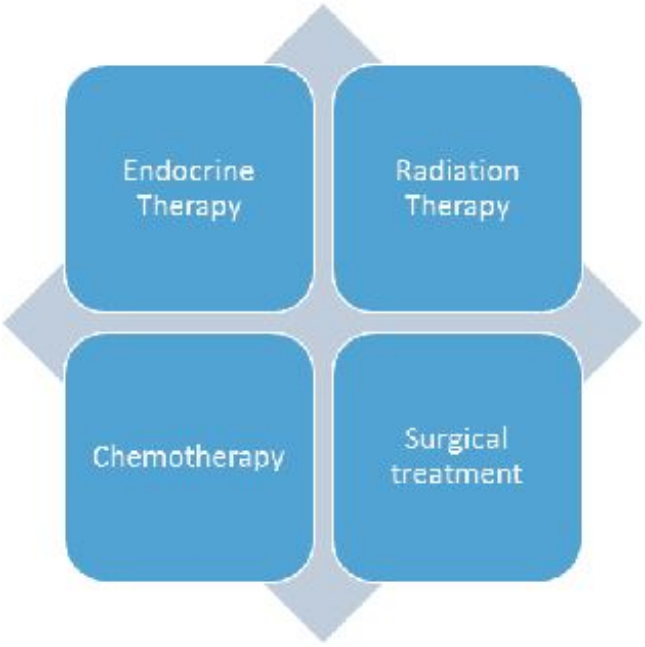

Fig. 2 : Different types of therapies.

Endocrine therapy

Hormone therapy interferes with the effect of hormones involved in breast and blocks the body's ability to produce hormone which further inhibits the growth of hormone sensitive tumors by selective aromatase enzyme inhibition which further leads to decrease in estrogen production in the body (Brodie and Njar, 1996).

Standard endocrine therapy involved in the treatment of breast cancer involves the use of medication that completely inhibits the binding of androgens to estrogen hormone. Side effects of hormone therapy depend upon the types of drugs used to treat breast cancer. In general, endocrine therapy can cause side effects such as menstrual irregularities, vaginal discharge, hot flashes, arthralgia and gynecological symptoms (Kwon *et al.*, 2022; Puhalla *et al.*, 2012).

Radiation therapy

To shrink or kill cancer cells, this therapy uses radiations, high energy x-rays or subatomic particles (Maani, 2022). There are several types of radiation therapies like external-beam radiation therapy, intra-operative radiation therapy, brachy therapy, three-dimensional conformal radiation therapy, image- guided radiation therapy, temporary internal radiation therapy, intensity modulated radiation therapy, permanent implants and proton beam therapy (Majeed and Gupta, 2023).

Radiation therapy lowers the risk of local recurrence and increases the survival benefits, but studies shows the recurrence and arm lymphedema in patients with radiation therapy.

Patient treated by the use of radiation therapy may face some side-effects such as swelling of breast, redness, burning and peeling of irradiated skin, discoloration of affected area, fatigue, etc. (Deng *et al.*, 2016).

Chemotherapy

Chemotherapy is a well known treatment of cancer. It is a significant process in early as well as advance stage of breast cancer (Amjad *et al.*, 2023). Chemotherapy treats cancer by preventing recurrence of cancer cells by disrupting mitosis or replication of DNA.

Use of a single type of drug may leads to serious side effects and resistance to that particular drug (Mohamad Reza Kamran, 2020). The major side effects that a patient undergoing chemotherapy face includes anemia, vomiting, neutropenia, mucotitis, edema, leukemia, asathenia and myalgia (Zraik and Heß-Busch, 2021).

Surgical treatment

Surgery involves the removal of cancer or tumor as well as some healthy tissues that surround the tumor. The degree of removal varies from some cells or some area of the breast to all breast tissues with axillary lymph nodes, depending upon the metastasis of cancer cells of breast.

Breast surgery may cause lymphedema as it interrupt the lymphatic drainage system or may cause nerve injury.

At present, in addition to endocrine therapy and chemotherapy, targeted therapy is also an effective treatment that attacks only cancerous cells without any harmful affect on normal breast cells. This therapy is generally used in combination with traditional chemotherapy. Stem cell transplant is also in use these days. In this technique, patient's stem cells that are degraded or destroyed by radiation therapy or chemotherapy are supplanted with healthy stem cells (Khan *et al.*, 2021).

About 80% of patients face side effects of drugs as well as develop resistance of tumor against taken anticancer drugs (Deng *et al.*, 2016). To reduce the side effects of treatment therapy, patients have to take complementary and alternative medicine.

Anticancer Properties of Bee venom and Melittin

Bee venom is produced by the venom gland of honey bee. Honey bee venom is consists of eighteen bioactive components approximately in *Apis mellifera* species (Hossen *et al.*, 2016). Melittin, apamin, peptides, Adolapin, Phospholipase A2, hyaluronidase and amino

acids (Wehbe *et al*., 2019). Bee venom is commonly used to treat various skin problems, chronic pain, swelling, Parkinson's disease and nerve pain.

Melittin is the primary active component of bee venom. It is formed by 26 amino acids and contributes about 40-60% to the dry weight to bee venom (Oršoliæ, 2012). The chemical formula of melittin extracted from bee venom is C131H228O32 molecular weight of 2847.5Da. Amino acid sequence of melittin is as follow: Gly-Ile-Gly-Ala-Val-Leu-Lys-Val-Leu-Thr-Thr-Gly-Leu-Pro-Ala-Leu-Ile-Ser-Trp-Ile-Lys-Arg-Lys-Arg-Gln-GlnNH2. The C-terminal region of this amino acid sequence is hydrophilic in nature whereas the N terminal is hydrophobic in nature (Wang *et al*., 2022). It is a water soluble peptide that has ability to integrate into lipid membrane (Hematyar *et al*., 2018).

On the basis of preclinical studies on cell cultures, it is concluded that melittin posses anticancer activities. Melittin is inserted into membranes, by pore formation it disrupts the cell in a non-selective manner that results in antimicrobial and antitumor activities as well as hemolysis (Wehbe *et al*., 2019). Therefore, a suitable delivery vehicle is required to deliver bee venom at the site of action. Mainly two type delivery vehicles are available for the transportation of melittin: melittin nano-delivery vehicles and melittin modified nano-drug carriers. Melittin nano-delivery vehicles include inorganic carriers, carbon nanocarriers, polymer carriers, lipid-based carriers, lipid-coated polymeric nanoparticles and melittin modified nano-drug carriers include DNA condensates and enhanced endosomal escape for nucleic acid (Wang *et al*., 2022).

In brief:

In proportion to the dose and time, bee venom controls the spread of breast cancer cells to another site by metastasis and lowers the cell viability. Studies show that apart from breast cancer, melittin also shows anticancer activity against cervical cancer, liver cancer, esophageal cancer, gastric and colorectal cancer, pancreatic cancer, renal cancer, prostate cancer, ovarian cancer and skin cancer.

Mechanisms involved in Anticancer activity of Bee venom and its components

There are mainly four types of mechanism in anticancer activity of bee venom:

Cytotoxic activity

Combination of melittin with chemotherapeutic medication could be an effective harmonious treatment method because resistance to the membrane pore forming agents is less in cancerous cells (El Sharkawi, 2015).

Study of Kamran *et al.* concluded that on MCF-7 cells crude bee venom has cytotoxic effects as well as apoptoxic effect in dose dependent manner. In comparison of resistance of cytotoxic effect of bee venom between 2D and 3D culture, 3D culture proved to show high resistance (Mohamad Reza Kamran, 2020). Bee venom also reduces the cell viability and inhibits cell growth.

Various drug delivery systems have been developed, in which magnetic drug targeting (MDT) system is used in tumor to deliver drug effectively, rather than liposomes, polymers and micelles. Citric acid functionalized Fe_3O_4 magnetic particles are used to prevent oxidation and aggregation of nanoparticles. CA Fe_3O_4 NPs are used to

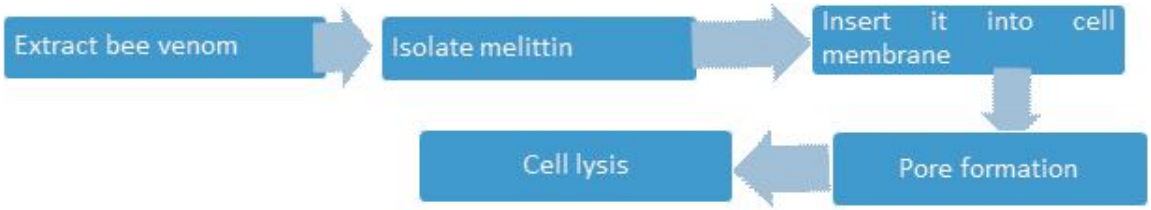

Fig. 3 : Mechanism of action of bee venom.

Table 1 : Types of mechanisms involved in anticancer activity of bee venom.

Author	Mechanism	Mechanism action
Kamran *et al.*	Cytotoxic activity	Action of bee venom results in decrease in cell viability and inhibition of cell growth.
Laure Perrin-Cocon *et al.*	Cell lysis	Phospholipase A2 matures the moDCs that activates immune reaction against cancer cells on re-injection.
Yeo *et al.*	Apoptosis activity	Bee venom subdues cancer cell proliferation that results in induction of apoptosis.
Duffy *et al.*	Regulation of gene expression	Downstream signaling pathway is regulated by bee venom.

deliver doxorubicin and melittin so that these components can perform their function effectively and efficiently (Hematyar *et al*., 2018).

A non specific toxicity and hemolysis is observed in the action of melittin when used in high amount, that's why it is required to control the dosage of melittin. To cobat this, small dose of melittin that is sufficient to treat tumor is combined with plasma treated phosphate-buffered saline [PT-PBS]. This combination leads to synergistic effect on the breast cancer cells and lowers the non-specific toxicity of melittin in dose dependent manner (den Brok *et al.*, 2005).

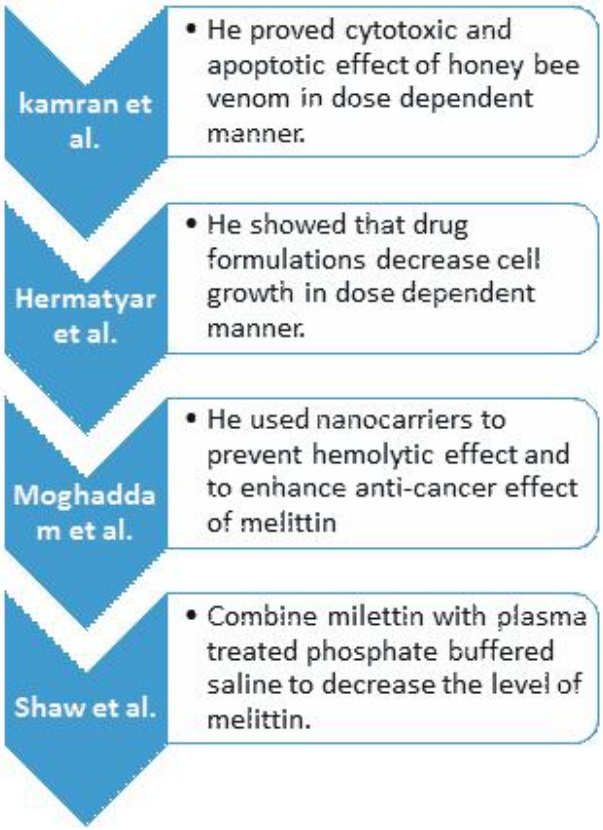

Fig. 4 : Work of researchers on cytotoxic activity of bee venom.

Cell Lysis

The process of cellular disruption refers to the process of degradation or lysis of cell membrane that causes the release of inner cellular organelles, fluid as well as genetic material outside the cell in the bloodstream either spontaneously or in response to therapy (Shehadul Islam *et al*., 2017; Howard *et al*., 2011).

Phospholypase A2 present in the bee venom leads to the maturation of monocyte-derived dendritic cells (moDCs) by enzyme activation. These cells are developed in peripheral blood precursor cells and are filled with tumor lysates. When these moDCs are re-injected in the patient they show immune reactions against tumors. Tumor lysate present in monocyte-derived dendritic cells leads to disruption of cell membrane (den Brok *et al*., 2005).

Phospholypase A2 → Maturation of moDCs

Re - inject moDCs → anti - tumor immune reaction

Apoptosis activity

The natural mechanism of cell death, either by extrinsic or intrinsic pathway is called apoptosis. In the patient of cancer, this pathway is inhibited (Pfeffer and Singh, 2018). Researchers reported the role of bee venom and melittin in the inhibition of cell growth and carrying out apoptosis in cancerous cells (Yu *et al*., 2022).

Jung *et al*. (2018), by doing multivariate analysis concluded the function of bee venom and its component

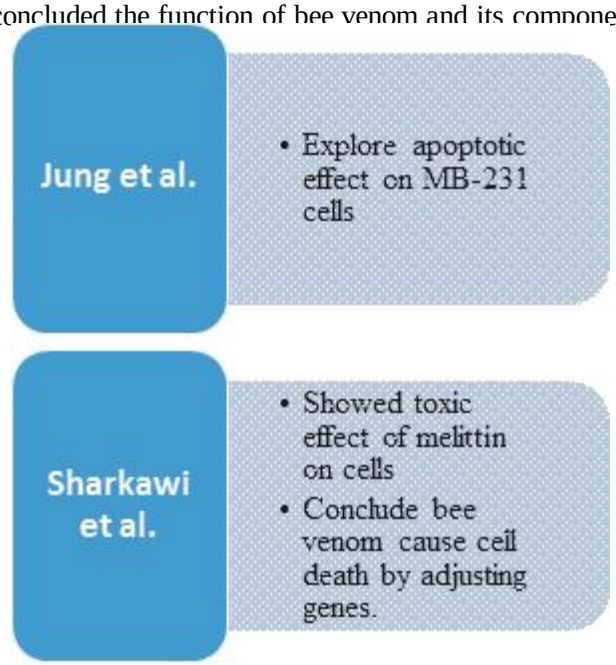

Fig. 5 : Work of researchers on apoptosis activity of bee venom.

in cells death. He worked on MDA-MB-231 cells. He proved that bee venom causes apoptosis in cancer cells of MDA-MB-231 by denaturation and deterioration of protein as well as fragmentation of DNA. Apoptosis activity of bee venom was affected of both time and concentration (Jung *et al*., 2018). Sharkawi *et al*. (2015), reported that melittin could be toxic for tumor cells as it caused cancer cell death by arranging the genes such as Bcl-2, p53 and Bax.

Regulation of Gene Expression

Researchers reported that melittin up regulates the genes of intrinsic and extrinsic pathways to stop the growth of breast cancer cells. Duffy *et al*. (2020) mentioned that bee venom and melittin inhibit the phosphorylation of ligands of EGRF and HER2 to regulate the downstream signaling pathway of breast tumor. Melittin show greater toxicity as compared to bee venom.

Melittin suppresses the gene expression for anaerobic

respiration that disrupts the microenvironment of tumor in breast (Mir Hassani *et al.*, 2021).

Effect of Melittin on TNBC and HER2 Cell Lines

Triple negative breast cancer and human epidermal growth factor 2 tumors are severe form of tumor as these types of cancer do not posses any receptor and are instable also (Roha Tariq, 2021). Melittin shows a positive effect in the treatment of TNBC and HER2 cancer cells by selective and targeted action by disturbing the process of phosphorylation. Melittin binds to the cell membrane by disturbing the phosphorylation at receptor site and also suppress the activation of HER2 (Duffy *et al.*, 2020). Melittin has ability to bind with negatively charged phospholipids found in the cell membrane, binding of melittin with cell membrane results in the formation of pores in the membrane.

Many mechanisms are developed on action of melittin on cancer cells, but the most accepted mechanism is "model of pore forming peptide" on the surface of cancer cells. This mechanism states that, monomers of melittin attach to the surface of cell membrane and collectively these monomers attack the membrane receptor present on cancer cells. This action of melittin results in the formation of pores (Lee *et al.*, 2008; van den Bogaart *et al.*, 2008).

Melittin is effective even in the lower concentration. Melittin binds to the cell membrane in fraction of seconds (Lee *et al.*, 2008). As soon as melittin binds to the phospholipid membrane of cell, conformation of melittin structure changes to alpha helical structure (Roha Tariq, 2021). The action of pore formation is a two step process:

In the first step, monomers of melittin bind to the cell membrane in parallel orientation, and remain in inactive state. In the second step, parallel attached melittin monomers shifted to perpendicular arrangement and convert into active form. Activation of melittin results in the formation of pores in the membrane of cancer cells. Mechanism of conversion is not clearly understood till now (Lee *et al.*, 2008).

Duffy *et al.* study on binding of melittin showed that melittin has a positively charged C terminus that binds with negatively charged cell membrane and then pore formation take place. The C terminus is helpful in the formation of alpha helix. Researcher designed a negatively charged C terminus to check the pore formation ability but no pore formation takes place (Van Den Bogaart *et al.*, 2008).

Combination therapy

Melittin can be used in combination with chemotherapy drugs to get maximum benefits. Maximum

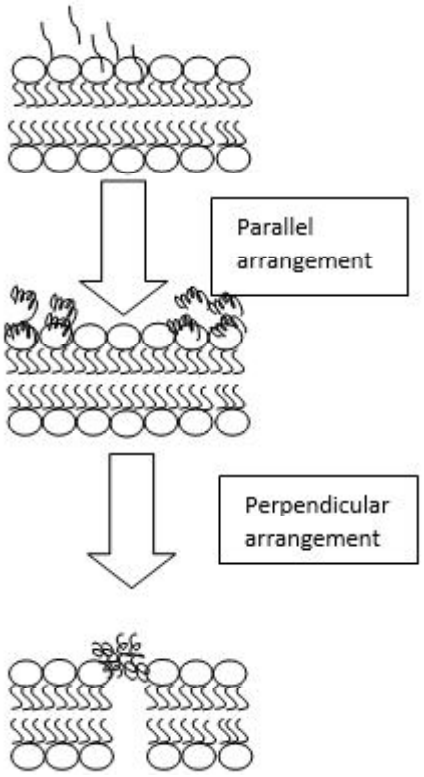

Fig. 6 : This figure shows the pore formation by melittin in membrane.

efficiency with the fewest side effects and tailored action are two aspects that determine how effective a treatment is. As the studies shows single melittin is powerful component against breast cancer, but patient can get the maximum desirable benefits from a precise and cautiously combined therapeutic plan without facing much toxicity and recurrence (Fisusi and Akala, 2019).

Melittin in combination with Trastuzumab-Emtansine

Trastuzumab-emtansine (T-DM1) is an antibody drug conjugate of a cytotoxic molecule known as DM1 and trastuzumab. (T-DM1) binds and forms a complex. T-DM1 release DM1 metabolite in the cytoplasm, DM1 degrade the cell by inhibiting microtubule assembly (Burguin *et al.*, 2021). Efficiency of trastuzumab-emtansine increases, when melittin is used with it. Melittin

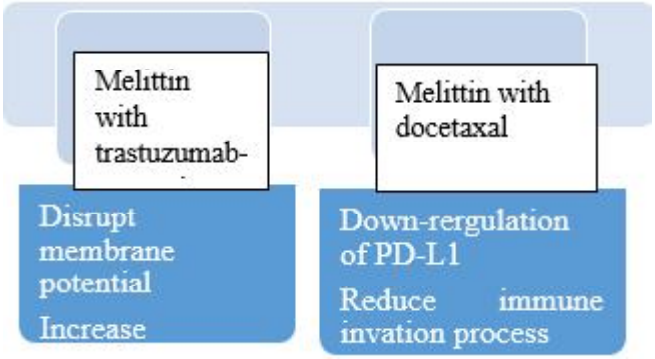

Fig. 7 : Combination of melittin with other drugs.

increases the availability of drug to cancerous cells by disruption of cell membrane. As the cell membrane disrupts, drug can easily enters the cell and perform its action.

Melittin in combination with Docetexal

On cancer cell lines, melittin along with docetexal show positive effects. Melittin inhibits the activity of PD-L1, when combined with docetexal, and decreases the ability of cancer cells to protect the immune system. This combination also reduces the level of macrophages related to tumor (Lee *et al*., 2017).

Melittin can also be used in combination with other drugs such as antibody-drug conjugates and monoclonal antibodies. Melittin can also be delivered to the malignant cells via nano-carriers (Pan *et al*., 2011).

Conclusion and Future Scope

Breast cancer is one of the reasons of high mortality rate in females all over the world. A number of treatments are available for the treatment of tumor but majority of them leads to side effects and decrease the quality of life. That's why, an alternate therapy is required with minimal to low side effects. Bee venom, present in honey bee's solitary bag is proved as an anticancer agent. Bee venom and its major component melittin show a positive result in the suppression of activation of growth factor receptor in triple negative breast cancer and HER2 cell lines.

Bee venom and its components inhibit the cancerous cell by cytotoxic activity, cell lysis, apoptosis activity and gene expression mechanism. Melittin disturbs the phosphorylation in cancerous cells by binding to cell membrane receptors and inhibits the activation of HER2. Even melittin alone is a powerful component but when melittin is used in combination with other chemotherapeutic drugs it provide maximum benefits to the patients.

In this review, we collected and analyzed the available data related to breast cancer and anti-cancer properties of honeybee venom and its components. However, a review article focusing on anticancer properties of bee venom and its component melittin in the treatment of breast cancer is not yet published.

Further studies are needed to find out which genotype of honeybee has more effective venom against the breast cancer. More study is required on efficiency and dosage of melittin for the effective treatment of breast cancer. Moreover, study on successful introduction of melittin in human body is needed to a great extent.

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