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BEE VENOM THERAPY: A PROMISING APPROACH AGAINST BREAST CANCER

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ABSTRACT

Breast cancer is the most common cancer in women, which emphasizes the need for novel and efficient treatments. Melittin, the main component of bee venom (BV), which is generated by Apis mellifera, has drawn attention for its potent anticancer activities. In a number of breast cancer cell lines, including MCF-7, MDA-MB-231, and 4T1, melittin has strong cytotoxic, pro-apoptotic, and anti-metastatic activities. It causes controlled cell death by rupturing cancer cell membranes, causing mitochondrial malfunction, triggering caspases, and producing reactive oxygen species. Phospholipase A_2 and other BV components work in concert to amplify these effects. Recent developments in melittin-loaded nanocarriers, including liposomes, PLGA nanoparticles, and magnetic nanoparticles, have enhanced therapeutic efficacy, reduced systemic toxicity, and enhanced drug targeting. Furthermore, mixing melittin or bee venom with chemotherapy drugs like doxorubicin or tamoxifen increases apoptosis and decreases treatment resistance. Despite encouraging preclinical findings, issues like cytotoxicity to healthy cells, allergenicity, and a lack of human clinical trials need to be resolved. According to available data, bee venom, especially melittin, has a great deal of promise as a novel or supplemental treatment approach for breast cancer. This calls for more research through sophisticated preclinical and clinical trials.

KEYWORDS: Breast cancer, Bee venom, Apis mellifera, Mellitin, Apoptosis.

INTRODUCTION

Breast cancer is one of the most prevalent tumors in women, about Thirty percent of all newly diagnosed malignancies are breast cancers. In 2020, breast cancer was the fifth biggest cause of cancer mortality globally, with an estimated 2.3 million new cases diagnosed and 685,000 deaths from the disease, according to the American Cancer Society. In the United States, female breast cancer has the third-highest 5-year relative survival rate among major malignancies, with a 5-year survival rate of 90% for all stages combined. But the survival rate likewise drops off quickly as the level goes on.[1]

For thousands of years, the European honeybee (Apis mellifera) has produced a variety of goods that people have used medicinally, including venom, propolis, and honey. But little is known about the molecular factors that contribute to bee venom's anticancer properties, especially when it comes to breast cancer, which is the most prevalent cancer in women globally. In order to create and optimize novel effective therapies from a naturally occurring product that is widely accessible and affordable to generate in many communities worldwide, it is essential to comprehend the molecular basis and selectivity of bee venom against cancer cells.[2]

Numerous anti-breast cancer medications have been studied throughout the years, and some of them have shown serious side effects and drug resistance. Bee venom's various biological and pharmacological properties have recently been shown to have antibacterial, antiviral, and anti-inflammatory properties against a variety of malignancies, including breast cancer.[3]

BREAST CANCER AND ITS TYPES

1. Non-Invasive Breast Cancer

According to the site, non-invasive breast cancer cells are limited to the ducts and do not spread to the breast's surrounding connective and fatty tissues. Ninety percent of non-invasive breast cancers are ductal carcinoma in situ (DCIS). Less frequently occurring, lobular carcinoma in situ (LCIS) is thought to be a sign of an elevated risk for breast cancer.[4]

2. Invasive Breast Cancer

Cells of invasive breast cancer penetrate the surrounding fatty and connective tissues of the breast after penetrating the duct and lobular wall. It is possible for cancer to be invasive without spreading to other organs or lymph nodes.[4]

TYPES OF INVASIVE BREAST CANCER

Invasive Lobular Carcinoma

With up to 15% of cases, invasive lobular carcinoma (ILC) is the second most prevalent subtype of breast cancer.[5]

Invasive Ductal Carcinoma

With 70–80% of cases, invasive ductal carcinoma (IDC) is the most prevalent form of breast cancer.[6]

INFLAMMATORY BREAST CANCER

One to five percent of cases and eight to ten percent of breast cancer fatalities are caused by inflammatory breast cancer (IBC), an uncommon but aggressive type of the disease.[7] It frequently mimics benign illnesses with its quick onset of symptoms, which include erythema, skin anomalies, and breast warmth.[8]

PAGET'S DISEASE OF THE BREAST

A rare cancer that affects the nipple-areola complex, Paget's disease of the breast is frequently linked to invasive or in situ carcinoma.[9] Itching, burning, and eczematoid alterations in the nipple-areola region are typical symptoms.[10]

ANGIOSARCOMA OF THE BREAST

A uncommon and severe cancer, angiosarcoma of the breast makes up less than 1% of all breast cancers. It may develop as a primary tumor or as a side effect of breast cancer radiation treatment.[11]

PHYLLODES TUMORS

Less than 1% of all breast cancers are phyllodes tumors (PTs), which are uncommon fibroepithelial neoplasms of the breast.[12] PTs are categorized as benign, borderline, or malignant by the World Health Organization.[13]

TYPES OF NON-INVASIVE BREAST CANCER

Ductal Carcinoma In-Situ [Dcis]

According to the American Cancer Society, DCIS accounts for about 20% of newly diagnosed breast malignancies. A lump that develops in a milk duct, which transports milk from the lobules, or glands, to the nipple, is the initial sign of DCIS. There is no spread of a DCIS to other bodily parts. The likelihood that the tumor will penetrate the ductal walls and

enter the breast's surrounding tissue and fat increases with time. However, the majority of people treated for DCIS, also known as stage 0 breast cancer, have favorable results thanks to advancements in detection and treatment.[14]

Lobular Carcinoma In-Situ [Lcis]

About 2.5 percent of breast biopsies result in lobular carcinoma in situ (LCIS), an incidental discovery that mostly affects women who are not yet menopausal.[15] The recurrence rate of lobular carcinoma in situ of the breast is 17%, and the risk of developing invasive cancer is elevated.[16]

ETIOLOGY AND RISK FACTOR

Breast cancer is the most common disease diagnosed in women globally, with 2.26 million new cases [95% UI, 2.24–2.79 million] in 2020. In the United States, 29% of all new malignancies in women are predicted to be breast cancer.[17] These occurs due to Western lifestyle, which is linked to poor nutrition, nicotine, high levels of stress, and insufficient exercise, is mostly to blame for this tendency. Mammography is now accepted as a screening method for breast cancer.[18] We introduce a human breast cancer etiological model and investigate its ability to account for the disease's incidence patterns and risk variables. The model consists of four parts: the number of cells at risk determines the likelihood of breast cancer occurrence; the number of target cells is partially determined early in life, possibly even in utero; pregnancy imparts long-term protection through terminal cellular differentiation, structural changes, and possibly other mechanisms; and in adulthood, mammotropic hormones and their receptors influence the number of target cells, the likelihood of retention of spontaneous somatic mutations, and the rate of expansion of initiated clones.[19]

RISK FACTORS

1. Age

Age is one of the most significant risk factors for breast cancer, aside from sex, as the disease's occurrence is closely linked to growing older. Women over 40 and 60 years old accounted for around 99.3% and 71.2%, respectively, of all breast cancer-related fatalities in America in 2016. For this reason, women who are 40 years of age or older must get a mammography screening beforehand.[20]

2. Family History

Breast cancer is more likely to strike women who have a family history of the disease. Women with 1, 2, and 3 or more affected first-degree relatives have a relative risk (RR) of 1.8 (99% confidence interval (CI) respectively, compared to women without affected relatives, according to a significant pooled analysis of 52 epidemiological studies that included 58,209 cases and 101,986 controls. An early diagnostic age and an excess of bilateral breast cancer are common characteristics of hereditary breast cancers.[21]

3. Endogenous Hormone

As levels of various sex hormones, including testosterone and total oestradiol, rose, so did the chance of breast cancer. In comparison to women in the lowest quintile, postmenopausal women in the highest quintile of oestradiol had an RR of 2.0 [95%]. Additional endogenous hormones, notably insulin-like growth factor (IGF), have also been suggested to have a favourable correlation. Even though some research indicated that elevated IGF-I concentrations, particularly in premenopausal women, increased the risk of breast cancer, the overall effect is negligible.[22]

4. Lifestyle

Breast cancer risk factors include modern lifestyle choices like binge drinking and eating too much fat. Drinking alcohol can increase blood levels of hormones linked to oestrogen and activate the oestrogen receptor pathways. According to a meta-analysis of 53 epidemiological studies, drinking 35–44 grammes of alcohol daily can raise the risk of breast cancer by 32%. The RR increases by 7.1% for every 10 grammes of alcohol consumed daily.[23]

BEE VENOM

A gland in the bee's (Apis mellifera L.) abdomen cavity secretes bee venom, also known as api-toxin. Bees frequently use this clear, odorless, acidic liquid as a protection mechanism against predators.[24] Bees employ honeybee venom, a translucent liquid that dries out fast even at room temperature, to defend themselves. It is a hydrolytic combination of proteins. It produces significant stinging and irritation when it comes into contact with the eyes or mucous membranes. Alcohol and ammonium sulfate do not dissolve bee venom, although it does dissolve in water. Grayish-white crystals are formed when it comes into contact with air.

The oxidation of some of the venom proteins is assumed to be the cause of the brown color of some commercial preparations and the light yellow coloration of dried venom. Bee venom

has a specific weight of 1.1331, is thought to be a rich source of enzymes, peptides, and biogenic amines, and contains a variety of highly volatile chemicals that are quickly lost during collection.[25]

Figure 1: [Honey bee]

COMPOSITION OF BEE VENOM

In order to defend their colonies, worker and queen bees' venom glands create venom, which is a complex mixture of biologically active substances.[26] Peptides (melittin, apamin, and MCD peptide), enzymes (phospholipase A2, hyaluronidase), amines, amino acids, and other bioactive substances are among its primary constituents.[27] The main ingredient, melittin, which makes up more than half of bee venom, has antibacterial, anticancer, and anti-inflammatory qualities. For ages, traditional medicine has utilized bee venom to treat a variety of ailments, including as rheumatism, arthritis, and inflammatory diseases.[28]

Table 1: [Composition Of Bee Venom].

COMPONENTS	% OF TOTAL
Melittin	50 – 55%
Phospholipase A	10 – 12%
Phospholipase B	1%
Hyaluronidase	1 – 2%
Apamine	2 – 3%
MCD	2 – 3%
Adolapin	1%
Protease – Inhibitors	3 – 4%
Secapin, Tertiapin, Cardiopep, Minimin, Procamine	3 – 5%
Histamine	0.7 – 1.5%
Dopamine, Noradrenaline	0.2 – 1.5%

MECHANISM OF BEE VENOM IN TARGETING BREAST CANCER

There isn't just one mechanism behind honey bee venom therapy; it explains a variety of therapeutic uses. A number of mechanisms have been put forth. The components that make

up bee venom explain how well it works to treat certain illnesses. By inducing a nonspecific reaction, bee venom activates important immune system centers. It seems to influence the generation of cytokines, improve the creation of antibodies, and increase the secretion of cortisone. Additionally, it is a potent inhibitor of the production of prostaglandins and antioxidant membranes. The components of bee venom determine its pharmacological effects. It has been discovered that melittin and phospholipase A2 work together to lyse erythrocytes. Phospholipase A2 (PLA2) has been linked to arthritis treatment. It is apitoxin's most harmful ingredient. The phospholipids that make up cellular membranes are broken down by this enzyme. The cyclooxynase cycle produces prostaglandins, which control the body's inflammatory response. The positive effects of apimin in the treatment of MS patients are due to its strong affinity for the central nervous system.[29]

Many studies are currently being carried out to investigate the antitumor effect of BV against various cancer types and the underlying mechanisms. About 50% of the dry BV is composed of MEL, a basic polypeptide that is primarily responsible for the anticancer action. Havas was among the first to document how BV affected cancer cells.

Later, Mufson and associates revealed that MEL can exhibit this capacity by piercing a phospholipid bilayer. MEL's interaction with cell membranes resulted in phospholipid acyl group impairment, increased susceptibility to phospholipase-induced phospholipid hydrolysis, and a rise in prostaglandin synthesis from arachidonic acid liberated from phospholipids. Furthermore, in a mortality research including 580 beekeepers, McDonald et al. investigated the anticancer properties of BV.[30] Melittin, the primary component of bee venom, has encouraging anti-cancer potential, notably against breast cancer.[31]

Melittin

Melittin has encouraging anti-cancer properties, some cancer cells may become resistant to the substance. The mechanisms of melittin resistance in cancer cells are covered here, and they may involve changes in the lipid content of the membrane, the overexpression of anti-apoptotic proteins, and the activation of survival signaling pathways.[32] Melittin is a well-studied cytolytic peptide derived from bee venom that is thought to serve as a model for cationic and other cytolytic peptides. Its effectiveness against a wide range of illnesses, including viruses, bacteria, fungus, parasites, and cancers, is fascinating. Melittin causes a number of cell death processes, including apoptosis, decreased angiogenesis or proliferation, cell cycle arrest, and inhibition of cancer motility, migration, metastasis, and invasion.

Phospholipid bilayer disruption, pore formation, and permeability induction during apoptosis all contribute to cell lysis. By causing necrosis and apoptosis in stomach cancer cells that is dependent on both time and dose, melittin has been shown to suppress the growth of AGS cells. These effects were demonstrated by cellular separation, membrane damage, cellular shrinkage, and abnormal cell shape. Melittin also caused apoptosis in gastric cancer cells by means of mitochondrial processes. There haven't been many studies on visualization, even though melittin is thought to kill cancer cells by inducing apoptosis.[33]

Melittin has been shown to have anticancer properties in preclinical research for a number of cancer types, including colorectal, pancreatic, prostate, and breast malignancies. Melittin has been demonstrated in these investigations to limit tumor growth, cause apoptosis, and inhibit cell proliferation. Melittin shown promising anticancer benefits in patients with advanced solid tumors and was well tolerated in a phase I clinical trial. More research through preclinical and clinical studies is necessary to determine melittin's potential as an effective anticancer drug. However, melittin may be a good option for cancer treatment based on the encouraging preclinical outcomes and the scant clinical data.[34]

Mechanisms

1. Induction Of Apoptosis In Breast Cancer Cells

Melittin, a key component of bee venom, has shown promise in treating breast cancer, according to recent studies. By causing apoptosis, preventing proliferation, and regulating metastasis in cancer cells, melittin demonstrates strong anticancer effects. It works by rupturing the membranes of cancer cells, causing mitochondrial malfunction, producing reactive oxygen species, and triggering caspases.[35] The cytotoxic effects of melittin on the breast cancer cell lines MCF-7 and 4T1 have been demonstrated; their respective IC50 values are 5.86 μg/mL and 32 μg/mL.[36]

2. Inhibition Of Tumor Growth And Metastatis

Through a variety of biological processes, metastasis suppressors prevent the spread of cancer without halting the growth of the underlying tumor.[37] The development of targeted medicines to prevent tumour growth and metastasis has been the main focus of recent research. A host defense-like peptide has showed promise in stopping development and preventing metastases in prostate and breast cancer xenografts by targeting phosphatidylserine and generating membrane depolarization.[38]

SYNERGISTIC EFFECT WITH OTHER THERAPIES

Recent research have shown that bee venom and its components, particularly melittin, can be used to treat breast cancer. Bee venom and natural substances like hesperidin and piperine enhance the efficiency of tamoxifen in vivo by upregulating apoptotic genes and downregulating antiapoptotic and angiogenesis genes.[39]

To further address worries regarding melittin's non-specific toxicity, melittin in combination with plasma-treated phosphate buffered saline solution demonstrated encouraging results in lowering the necessary therapeutic dose for melanoma and breast cancer cells. These results imply that by increasing cytotoxic effects and possibly overcoming drug resistance, bee venom and its constituents, when combined with other medicines, may present new avenues for cancer treatment.[40]

MELITTIN - BASED NANOPARTICLE SYSTEM

MEL delivery has made extensive use of nanodrug delivery methods. Attempts like lipid carriers (like lipid disks, lipid nanoparticles, MEL–lipid conjugate nanoparticles, and liposomes), polymer carriers (like PLGA nanoparticles and β-cyclodextrin nanoparticles), and inorganic carriers (like quantum dots, Fe_3O_4 nanoparticles, and perfluorocarbon nanoparticles) significantly lessen the toxicity of MEL and offer the ability to target to the desired sites. The hemolytic action of melittin, a cytolytic peptide found in bee venom, limits its potential as an anticancer drug.[41]

The nanoparticles' size rose slightly from 223 to 550 nm after melittin complexed with them, while their charge increased from -40 to -2.97 mV (a minor rise). By evaluating the fluorescence density in the supernatants, the binding efficiency was found to be 83.45%, and the critical micelle concentration (CMC) was 17 μg/mL.[42]

One of the main cellular barriers for nonviral gene delivery vectors is the entry of exogenously applied nuclear acid into the cytoplasm and its subsequent transport into the nucleus. Numerous tactics, such as liposomes and polymer-or lipid-based nanoparticles, have been used to increase cellular absorption, endosome release, and targeted distribution to the target areas. MEL is a cell-penetrating peptide that can enhance therapeutic compound cellular uptake and nanoparticle endosomal escape. MEL can increase the bioavailability of nanoparticles by acting as a penetrating peptide that facilitates escape from endosomes due to

its great surface activity. Given that intracellular gene delivery has long been a technical challenge, these characteristics make MEL a popular oligonucleotide transfection agent.[43]

SAFETY, TOXICITY AND SIDE EFFECTS

Before giving bee venom to cancer patients, certain safety precautions must be taken to lessen the possibility of negative side effects and to guarantee the patients' well-being. When discussing a foreign agent as a therapeutic possibility for a condition, allergic responses are a significant concern. After being administered bee venom, the patient may have a mild local reaction or a severe systemic allergic reaction. Examining the patient for allergies to bug venoms and bee stings is essential. With the aid of comprehensive medical history collection and allergy testing procedures, these people can be identified.[44]

Local inflammatory reactions, allergic reactions, anaphylactic shock, and systemic toxicity are the four categories of clinical symptoms that might follow a sting. Severe sting reactions are more common in people with atopy and a family history of BV allergy. Although melittin and hyaluronidase are also involved, PLA2 is thought to be the primary substance that causes mast cells to become sensitized to IgE antibodies. The symptoms of local inflammatory reactions include sting site discomfort, edema, erythema, and itching. The majority of non-allergic people experience these symptoms, which often go away in a day. IgE-dependent allergic reactions to BV are categorized as type I hypersensitivity reactions. The symptoms can vary in intensity and manifest approximately ten minutes after the sting.[45]

Both the advantages and possible hazards of BV have been emphasized in toxicology reports. Hyperventilation, exhaustion, appetite loss, severe discomfort, elevated risk of bleeding, and vomiting are among the side effects of BV treatment that have been reported in studies. Additionally, studies have examined the evaluation of BV microspheres' cellular toxicity in the treatment of prostate cancer, highlighting the importance of having a comprehensive grasp of how it affects cellular health.[46]

CURRENT RESEARCH AND CLINICAL TRIALS

The potential of bee venom and its constituents, especially melittin, in the treatment of breast cancer has been highlighted by recent studies. According to studies, bee venom has the ability to reduce breast cancer cells, prevent cell migration and metastasis, and trigger apoptosis.[47] Clinical research has demonstrated encouraging outcomes in terms of enhancing tumor response, quality of life, and symptoms associated with cancer.[48] To determine the best

dosages, modes of administration, and safety profiles through carefully planned clinical trials, more investigation is necessary.[49]

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FUTURE PERSPECTIVE AND LIMITATIONS

Further investigation is required to clarify the relationship between bee venom and immunotherapy for skin cancer. Bee venom's physiological response to human skin cancer should be evaluated in future clinical trials. This hasn't been tried consistently, methodically, or reproducibly yet. While research has demonstrated that phospholipase A2 can boost the immune system by promoting the production of tumor lysate and the maturation of DCs, the precise mechanisms by which it affects the tumor microenvironment are yet unknown.[51]

As was previously mentioned, there is still much to be done in this field even with the abundance of scientific publications and reviews on BV, its elements, and its uses. Despite the fact that BV components have been widely documented in the literature, little is known about their metabolic pathways and modes of action. Furthermore, as was previously addressed, additional research is necessary to establish precise administration procedures and ensure safety, even if BV (and particularly BV acupuncture) has the potential to be used in traditional medicine to treat musculoskeletal diseases. Three approaches could be pursued in light of this reality. For starters, some scientists looked into the idea of getting what they called "essential bee venom". This ingredient was pure venom that had been filtered for PLA2 and histamine to reduce allergic reactions and side effects while preserving its anti-inflammatory properties. Second, it has been reviewed that certain BV compounds by themselves have positive health impacts and are also safer and more effective, such as melittin.[52]

RESULT AND DISCUSSION

Bee venom (BV), especially its main active ingredient melittin, has been shown in recent preclinical research to have potent cytotoxic effects on a variety of breast cancer cell lines, such as MCF-7, MDA-MB-231, and SK-BR-3. Melittin causes apoptosis via the caspase-3/9 pathway, damages mitochondrial membrane potential, and creates holes in the cancer cell membrane to produce its anticancer effects. Numerous in vitro tests that demonstrated dose-dependent cell death and low IC_{50} values, indicating strong potency at low concentrations, corroborate these findings. Furthermore, research shows that melittin increases drug absorption and tumor cell death while decreasing drug resistance when combined with chemotherapeutic drugs like doxorubicin or paclitaxel. This combined effect points to a potential use of bee venom in combination cancer treatments.

There are still issues in spite of the encouraging outcomes. Because melittin is extremely cytotoxic and hemolytic to healthy cells in its free form, it cannot be used directly in therapeutic settings. Therefore, the creation of secure and efficient delivery methods is crucial to its therapeutic value. Additionally, the majority of the evidence now available is restricted to preclinical models, and human clinical trials confirming the safety and effectiveness of bee venom in patients with breast cancer are still lacking. Immune safety, formulation stability, and standardization of venom extraction continue to be key issues.

CONCLUSION

Melittin in particular, which has therapeutic promise in bee venom (BV), offers a novel and promising treatment option for breast cancer. A wide range of anticancer actions, including as membrane rupture, apoptosis induction, regulation of pro-survival signaling pathways, and metastasis inhibition, are demonstrated by melittin in numerous in vitro and in vivo investigations. These multi-targeted effects make it especially effective against HER2-positive tumors and triple-negative breast cancer (TNBC), two kinds of breast cancer that are challenging to treat.

Furthermore, by increasing bioavailability, reducing off-target toxicity, and permitting controlled release within the tumor microenvironment, the combination of bee venom with cutting-edge nanotechnology-based delivery systems—such as liposomes, polymeric nanoparticles, and hydrogels—has greatly increased its clinical promise. Furthermore, melittin's synergistic use with traditional chemotherapeutic drugs has demonstrated promise in overcoming drug resistance and enhancing treatment results overall.

In conclusion, bee venom shows great promise as a supplemental treatment for breast cancer, although still being in the preclinical stage. Its promise as a cutting-edge biotherapeutic tool is highlighted by its natural origin, strong anticancer mechanisms, and compatibility with contemporary drug delivery technologies. To fully grasp the clinical usefulness of bee venom in oncology, more multidisciplinary research integrating immunology, nanomedicine, and oncology is required.

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