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A Brief Review on Anti-Cancer Property of Bee Venom

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Abstract: *Cancer immunotherapies, including immune checkpoint inhibitors, elicit long-term clinical responses but many cancer patients do not respond. Intensive efforts are therefore underway to identify additional immune pathways that may be modulated to enhance the efficacy of existing immunotherapies. Bee venom strongly stimulates the immune system, and is used as a complementary therapy to treat cancer pain in patients with advanced tumors in China. Bee venom contains several allergenic protease inhibitors and peptides. It triggers hypersensitivity reactions; that is, it is an immune system agonist. The generation of a spontaneous T cell response against tumor-associated antigens requires innate immune activation; this drives type I interferon production. We report a patient with a relapsed and refractory liposarcoma who had undergone several operations, chemotherapies, and radiotherapies. The tumor was large. The patient had attained the maximum radiation exposure dose. The tumor was resistant to chemotherapy and was infiltrating the pericardium, lungs, and diaphragm. The patient was a poor candidate for resection. He thus received apitherapy (a combination of bee venom and acupuncture) to control pain; then apatinib (an anti-angiogenic drug) was given to inhibit tumor growth but was terminated early because the patient could not tolerate the side effects. Subsequently, a programmed death 1 inhibitor was combined with apitherapy. Bee venom served as an innate immune system agonist promoting immune cell priming and recruitment in the tumor microenvironment. The patient was finally able to undergo radical liposarcoma resection, and no evidence of recurrence was found at re-examination 16 months after surgery.[4][5] [6] [7] [8].*

Keywords: Cancer immunotherapies.

I. INTRODUCTION

Honeybee venom kills aggressive breast cancer cellsBy James Kingsland on September 7, 2020 — Fact checked by Zia Sherrell, MPH.

Honey bee venom in its composition contains many biologically active peptides and enzymes that are effective in the fight against diseases of various etiologies.

The history of the use of bee venom for medicinal purposes dates back thousands of years.

There are many reports in the literature on the pharmacological properties of bee venom and/or its main components, e.g., anti-arthritic, anti-inflammatory, anti-microbial or neuroprotective properties.

In addition, both crude venom and melittin exhibit cytotoxic activity against a wide range of tumor cells, with significant anti-metastatic activity in pre-clinical studies.

BV is a secretion from the venom gland of worker bees that is supposed to have a defensive function against predators.

In laboratory studies, the active component of honeybee venom rapidly killed two types of breast cancer cells that are particularly difficult to treat. Crucially, the toxin left healthy cells unharmed.

Carefully targeted melittin from honeybee venom may kill aggressive breast cancer cells.For thousands of years, humans have used honey, propolis, and venom from the European honeybee Apis mellifera as medicines.

More recently, scientists have discovered that honeybee venom and its active component, melittin, are toxic to a wide range of tumors — including melanoma, lung, ovarian, and pancreatic cancers — in laboratory tests.Melittin is the molecule that creates the painful sensation of a bee's sting. Scientists do not fully understand how it kills cancer cells, however.

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For the first time, researchers have investigated the effect of melittin and honeybee venom on a range of breast cancers, including two of the most aggressive and hard-to-treat types.

Breast cancer is the most common cancer in women. The two aggressive types, known as triple-negative breast cancer and HER2-enriched breast cancer, are associated with the poorest outcomes. They tend to develop resistance to existing treatments.

Scientists at the Harry Perkins Institute of Medical Research in Perth, Australia, and the University of Western Australia, also in Perth, found that melittin and honeybee venom rapidly kill these cancer types, with negligible effects on normal cells.

"The venom was extremely potent," says Dr. Ciara Duffy, who led the research. "We found that melittin can completely destroy cancer cell membranes within 60 minutes."

The study also showed that venom from bumblebees, which contains no melittin, did not kill the cancer cells — even at high concentrations.[1]

Australian scientists say the venom from honeybees has been found to destroy aggressive breast cancer cells in a lab setting.The venom - and a compound in it called melittin – were used against two cancer types which are hard to treat: triple-negative and HER2-enriched.The discovery has been described as "exciting", but scientists caution that further testing is needed.Breast cancer is the most common cancer affecting women around the world.[12]While there are thousands of chemical compounds which can fight cancer cells in a lab setting, scientists say there are few which can be produced as treatment for humans.Bee venom has previously been found to have anti-cancer properties for other types of cancer such as melanoma.The study by the Harry Perkins Institute of Medical Research in Western Australia was published in Nature Precision Oncology, a peer-reviewed journal.[12]

What did the researchers find?

It tested venom from over 300 honeybees and bumblebees. The honeybee extracts were found to be "extremely potent", said Ciara Duffy, a 25-year-old PhD researcher who led the study.One concentration of the venom was found to kill cancer cells within an hour, with minimal harm to the other cells. But the toxicity increased for other dosage levels.

Dr .Ciara Duffy ,IMAGE SOURCE,HARRY PERKINS INSTITUTE led the research. The researchers also found the melittin compound on its own was effective in "shutting down" or disrupting cancer cell growth. While melittin naturally occurs in honeybee venom, it can also be synthetically produced. Traditionally, triple-negative breast cancer – one of the most aggressive types – has been treated with surgery, radiotherapy and chemotherapy. It accounts for 10-15% of breast cancers.[12]

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Chemical composition of bee venom

BV is a rich source of secondary metabolites, such as: peptides, including melittin, apamin, mast cell degranulating peptide (MCD) or adolapin, enzymes such as phospholipase A2 (PLA2) and hyaluronidase, as well as amino acids and volatile compounds .

The main components of BV are melittin, which constitutes about 50% of the dry weight of the venom, and PLA2, whose content is about 12%.

Properties of bee venom

It is an odorless and colorless liquid with an acidic pH of 4.5-5.5. One drop of bee venom consists of 88% water and only 0.1 µg of dry matter .

Among the various types of products of natural origin, BV deserves special attention due to the complexity of its chemical composition and the potential inherent in its biological activity.

Melittin is a water-soluble, amphipathic linear polypeptide consisting of 26 amino acids, with a mass of 2840 Da and a chemical formula of C131H229N39O31. Its N-terminal region is hydrophobic, while the C-terminal region is hydrophilic

Melittin affects cell membranes and reduces their surface tension, stimulates smooth muscles, increases capillary permeability, reduces blood coagulability; in higher doses it has a pro-inflammatory and hemolytic effect

Effective Concentration

The cytotoxic effect of BV on tumor cells in in vitro studies is revealed at a concentration of >1 µg/mL in the medium (depending on the type of cell line). Theoretically, to obtain such a concentration of BV in the body fluids of a 75 kg human, approximately 75 mg of venom would have to be administrated. However, in animal studies, a venom dose from 0.5 mg/kg bw to 1.0 mg/kg bw was successfully used .The lethal dose of an adult is estimated about 2.8mg/kg of body weight.

Could it be used in the future?

On Wednesday, Western Australia's chief scientist described the research as "incredibly exciting".

"Significantly, this study demonstrates how melittin interferes with signalling pathways within breast cancer cells to reduce cell replication," said Prof Peter Klinken.

"It provides another wonderful example of where compounds in nature can be used to treat human diseases."

But the researchers warn more work is needed to see if the venom could actually work on scale as a cancer-fighting drug.

Other cancer researchers concur. "It's very early days," said Associate Prof Alex Swarbrick, from the Garvan Institute of Medical Research in Sydney.

"Many compounds can kill a breast cancer cell in a dish or in a mouse. But there's a long way to go from those discoveries to something that can change clinical practice," he told the BBC.[12]

Methods:

Firstly, the Cell Counting Kit-8 (CCK-8) assay was conducted to analyze the cytotoxicity of bee venom on PANC-1 and AsPC-1 cells. Then, we evaluated the cell cycle and apoptosis by flow cytometry and the terminal deoxynucleotidyl transferase (TdT) dUTP Nick-End Labeling (TUNEL) assay. In addition, cell migration was analyzed by the cell scratch test and Transwell assay. Western blot was performed to assess the expression of proteins involved in the regulation of cell cycle arrest and apoptosis.[2]

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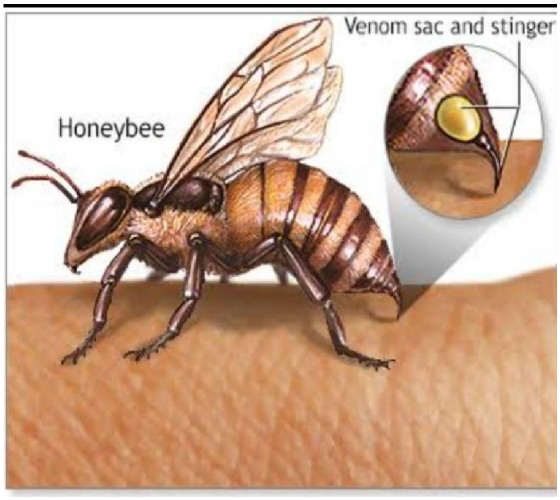

Bee Venom

There are around 20,000 species of bees: with the study looking at the European honeybee found in Australia, Ireland and England. The bee populations from each country produced almost identical effects in breast cancer cells.It also looked at the venom from bumblebees: but this did not have the same effect and was unable to induce cell death.

One of the first reports of the effects of bee venom was published in 1950, where venom reduced the growth of tumours in plants. Over the past two decades, interest in apitherapy has grown, as has interest in the effects on honeybee venom on different cancers.Despite this, the molecular mechanisms andSelectivity of biomolecular components ofHoneybee venom as anticancer agentsRemain largely unknown – prompting the newStudy.[3]

Medicinal uses

Apitherapy Halts Breast Cancer Growth

Using the venom from over 300 honeybees and bumblebees in England, Ireland, Perth, Western Australia, the researchers showed that even the most aggressive forms of breast cancer are susceptible to venom and melittin in its pure form. The high anti-cancer activity was observed in TNBC and HER2-enriched breast cancer cell lines bathed in venom within 1 hour of exposure. But, most importantly, there was a minimal cytotoxic effect of venom on normal cells, a quality that is desirable of any cancer therapy. Besides killing the cells, Venom and Mellitin also suppressed the cells' growth by suppressing phosphorylation of the growth factor receptors, EGFR, and HER2 within 20 minutes of exposure. Phosphorylation is required for the dimerization of the growth receptors essential for the relay of growth signals. This set of experiments demonstrated that, before killing the cells, melittin paralyzes the cell's growth by affecting growth signaling.

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Combination of Melittin With Chemotherapy is Effective

When combined with docetaxel, a chemotherapeutic agent, Melittin could further suppress the growth of breast cancer. In the in-vivo experiment, mice were administered breast cancer cells, giving rise to tumors in the body. Three days after the generation of tumors, mice were either treated with a combination of melittin and chemotherapy or melittin alone. The group found that "tumor control was superior compared to either treatment alone, particularly on days 7 and 9 post-inoculation of cancer cells."[9] [10]

While melittin showed synergy with a chemotherapeutic agent, it simultaneously reduced the levels of checkpoint protein, PD-L1 in tumors. PD-L1 protein is well known for its pro-tumor effect in the tumor microenvironment. The negative impact of melittin on checkpoint protein is quite desirable and could improve anti-tumoral immune responses for several chemotherapeutic agents. This effect also resembles melittin's response in the previous studies wherein the peptide was shown to reduce tumor-promoting macrophage population in the tumor microenvironment.[9] [10]

Melittin Augments Existing Breast Cancer Therapies

Melittin treatment in combination with chemotherapy, makes a better case as breast cancer therapy as this type of cancer has a high expression of HER2 and EGFR along with checkpoint protein, PD-L1. Melittin could also augment treatments with antibody-drug conjugates such as Trastuzumab where melittin's membrane disrupting properties could enhance the cytotoxic payload's internalization. Linking melittin with toxins or prodrugs is another approach that could be exploited in the future. While all looks good for bee venom, its toxicity and tolerance in the human body have not been determined. Therefore, future studies are warranted before melittin could be potentially used to treat cancer in humans.[9][10]

The claim: Cancer patients should get a bee sting to kill cancer cells

An April 10 Facebook post (direct link, archive link) claims to describe an effective but unorthodox method for treating a potentially fatal disease. "If you have cancer, go get stung by a bee," the post reads. "The venom can slow down and kill cancerous cells. Look it up no cap!" [11]

General Medicinal uses

Bee venom (BV) (api-toxin) has been widely used in the treatment of some immune-related diseases, as well as in recent times in treatment of tumors. Several cancer cells, including renal, lung, liver, prostate, bladder, and mammary cancer cells as well as leukemia cells, can be targets of bee venom peptides such as melittin and phospholipase A2. The cell cytotoxic effects through the activation of PLA2 by melittin have been suggested to be the critical mechanism for the anti-cancer activity of BV. The induction of apoptotic cell death through several cancer cell death mechanisms, including the activation of caspase and matrix metalloproteinases, is important for the melittin-induced anti-cancer effects. The conjugation of cell lytic peptide (melittin) with hormone receptors and gene therapy carrying melittin can be useful as a novel targeted therapy for some types of cancer, such as prostate and breast cancer. This review summarizes the current knowledge regarding potential of bee venom and its compounds such as melittin to induce cytotoxic, antitumor, immunomodulatory, and apoptotic effects in different tumor cells in vivo or in vitro. The recent applications of melittin in various cancers and a molecular explanation for the antiproliferative properties of bee venom are discussed.[13]

Pharmacology

The researchers reproduced the melittin synthetically and found that it paralleled the majority of the anti-cancer effects of the honeybee venom. They found that melittin can destroy cancer cell membranes within 60 minutes.

Further, upon investigating, the team has found that in just 20 minutes, the melittin had another powerful effect – it interfered with the main messaging or cancer-signaling pathways, which are essential for the growth and replication of cancer cells.

"Honeybee venom and melittin suppress the activation of EGFR and HER2 by interfering with the phosphorylation of these receptors in the plasma membrane of breast carcinoma cells," the team concluded.

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"Our work unveils a molecular mechanism underpinning the anti-cancer selectivity of melittin, and outlines treatment strategies to target aggressive breast cancers," they added.

There are 20,000 species of bees, but the researchers wanted to compare the effects of Perth honeybee venom to other honeybee populations in England and Ireland. They also want to study the venom of bumblebees.

They found that the honeybees in Australia, Ireland, and England generated almost the same effects in breast cancer compared to normal cells. However, bumblebee venom was unable to trigger cell death even at very high concentrations.[15][16]

Strengths and limitations:

Strength

These studies were well-designed. The findings support the idea that honeybee venom and its main ingredient, melittin, could kill breast cancer cells in a dish or in mice.

Limitation

The major limitation is that these studies have only been done in laboratory models in cells and mice. It is not clear whether melittin would work the same way or be safe for people. The potential side effects of melittin in humans is unknown.[14]

II. CONCLUSION

In conclusion, we demonstrated that bee venom can induce autophagy in many types of cancer cells. Our data indicated that the mTOR signaling pathway is the critical regulator of bee venom-induced autophagy. Moreover, we found that HCQ- or si-ATG5-induced autophagy inhibition further demoted bee venom-induced apoptosis. These data indicate that bee venom-mediated autophagy could be important for bee venom-induced apoptosis, and the mTOR pathway may play a role in the underlying mechanism. [17]

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