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Review Paper

Development Of Melittin- Based Nanocarriers for Targeted Cancer Therapy

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ABSTRACT

Peptides found in bee venom, particularly melittin, have shown promise as natural anticancer medicines. These peptides exert their anticancer effects by compromising cellular membranes, initiating programmed cell death, and influencing the function of the immune system. The clinical use of melittin is limited due to notable toxicity and insufficient molecular stability, even though it holds considerable therapeutic promise. By creating melittin-based nanocarriers including polymeric nanoparticles, liposomes, and nano emulsions, recent developments in nanotechnology have overcome these constraints and made it possible for precise tumour targeting, regulated drug release, and biocompatible delivery. These engineered platforms enhance the therapeutic efficacy of melittin while minimizing systemic toxicity and improving pharmacokinetic behaviour. Further functionalization with tumour-specific ligands and combination with other therapeutic modalities amplifies the effectiveness and overcomes drug resistance. Therefore, bee venom peptide is being transformed into promising tools for targeted cancer therapy through nanotechnology-driven delivery, bridging the gap between conventional methods and state-of-the-art nanomedicine..

INTRODUCTION

One in six deaths globally are caused by cancer, making it a significant global health concern. According to the WHO cancer was the second biggest cause of death globally in 2020, accounting for around 10 million deaths. Traditional treatments including immunotherapy, radiotherapy, and chemotherapy encounter challenge such non-selective cytotoxicity and drug resistance. Bee venom is one of the natural substances whose strong anti-inflammatory, anti-cancer, and immunomodulatory properties are becoming more well acknowledged [1].

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2.OVERVIEW OF BEE VENOM:

Certain animals have evolved to produce harmful substances that serves to protect them from threats as well as assist in capturing prey. [25] Peptides with a broad variety of structures and functions that have chemical and neuropharmacological effects make up these secretions.

Bee venom, also referred to as **"apitoxin,"** consists of a mixture of biologically active compounds produced by bees from their abdominal cavity and inject into victims using a stinger. These components may stimulate the immune system and induce inflammation at the site of contact. [2]

2.1 PHYSICAL PROPERTIES OF BEE VENOM: [3]

Bee venom appears as a clear fluid and typically has a PH between 4.5 and 5.5

Unpleasant taste and odour

The substance does not dissolve in Ammonium sulphate and Ethanol

It readily dissolves in water

3.BIOACTIVE COMPONENTS OF BEE VENOM:

Bees secrete venom from specialized glands located within the abdomen. The physiologically active compounds which are found in venom are Melittin, Apamin, Adolapin, PLA2, Hyaluronidase, α-D glucosidase. The composition also includes peptides that stimulate mast cells and additional non-peptide elements like Histamine, Dopamine, and Norepinephrine. [4] Further components such as Amino acid, sugars like glucose, Fructose and minerals like calcium, Magnesium. [5]

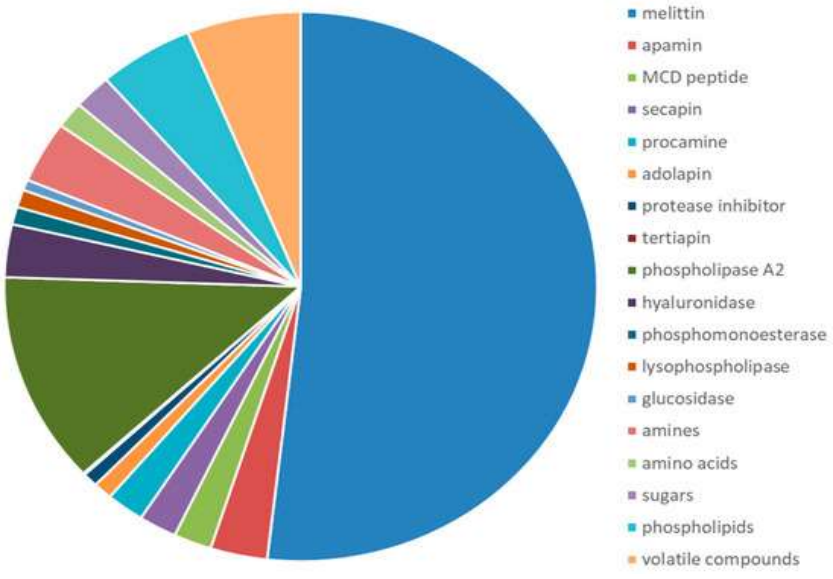

Figure 1. Bioactive components [24]

3.1 MELITTIN:

Melittin is the predominant toxic component found in bee venom, representing approximately half of its dried content. [6] This peptide exhibits diverse effects on various physiological and biological processes. [7] Structurally, melittin is a peptide with 26 amino acids possessing both positive charge and amphipathic properties, and constitutes about 40–50% of the venom's dry weight (BV). [1]. Its amino acid chain is**: Glycine–Isoleucine–Glycine–Alanine–Valine–Leucine–Lysine–Valine–Leucine–Threonine–Threonine–Glycine–Leucine–Proline–Alanine–Leucine–Isoleucine–Serine–Tryptophan–Isoleucine–**

Lysine–Arginine–Lysine–Arginine–Glutamine–Glutamin. [6] Melittin regarded as the main biologically active element in bee venom, was initially separated and refined from the substance. Gel filtration, HPLC, and capillary electrophoresis were used to separate and isolate melittin from BV. UV testing, reverse phase HPLC, and amino acid analysis were used for analysis. Figure (1) depicts melittin's three-dimensional structure. [7]

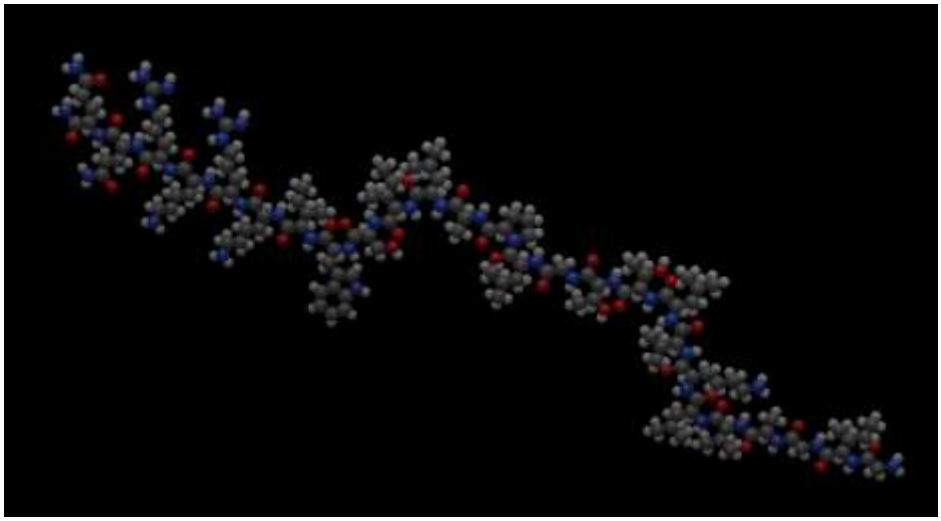

Figure 2. 3D structure of melittin.

4.MECHANISM OF ACTION:

Melittin's ability to insert itself into cell membranes allows it to form channels or compromise membrane structure, which can ultimately trigger cellular breakdown.

Melittin shows several anticancer mechanisms in cancer models. Through direct cytosis, it damages the membrane of cancer cells and rapidly induce cell death. [1].The peptide also initiates programmed cell death by increasing mitochondrial membrane permeability, subsequently producing Reactive oxygen species within the cell. Tumour growth is further suppressed by melittin through its influence on signal transduction pathways crucial for cell viability and replication, including those mediated by MAPK, PI3K/Akt, NF-κB pathways.In cervical malignancies, indirect effects include downregulating oncogenes such as HPV E6/E7 and immunogenic cell death, as well as reactivating tumour suppressor genes (P53, Rb). [8]

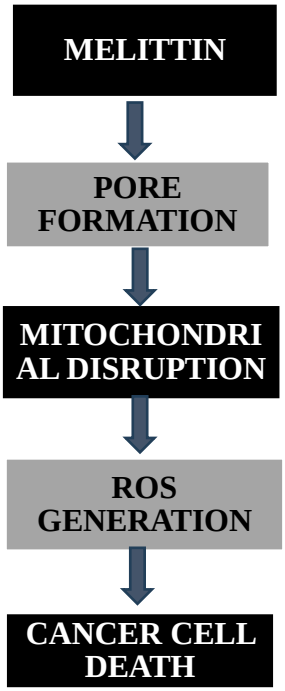

Figure 3. melittin mechanism of action

5.NANOTECHNOLOGY-BASED DELIVERY SYSTEMS:

5.1 RATIONALE FOR NANOFORMULATION:

Systemic usage of melittin is hindered by its haemolytic action and quick degradation. The peptide is protected, directed toward the tumour, and allowed for regulated, localized release when it is encapsulated in nanocarriers. Numerous platforms are made possible by nanotechnology to accomplish this objective. These systems improve tumour targeting, stability, and bioavailability while also aiding in the defeat of drug resistance mechanisms. One of the prospective substitutes for precise targeting and efficient treatment is nanotechnology. [1] [7] [10]

6.TYPES OF NANOCARRIERS FOR BEE VENOM PEPTIDE:

6.1 LIPOSOMES:

Liposomes are one of the most researched nanocarriers for drug administration, notably for peptides like melittin. They are composed of one or more layers of lipids that surround a central water-filled compartment. They consist of a core compartment filled with water surrounded by one or more layers of lipids. These carriers are especially prized for their capacity to interact with biological systems in a safe manner, their capacity to break down spontaneously, and their adaptability in carrying both fat-soluble and water-soluble substances. The addition of substances such as hyaluronic acid can further strengthen the structure of liposomes, minimize unintended release of melittin, and improve their precision in targeting tumours. [11] Melittin exhibits a lot of biological activity, but its use is restricted by the potential for serious adverse effects. Researchers tried to encapsulate melittin in nanoliposomes to make it more effective and harmless for therapeutic use in order to get over these

challenges. [12] When the nanocarrier gets to a malignant cell, it triggers a biological reaction that causes apitoxin to be released, which ultimately causes the cancerous cell to die. To improve the patient's prognostics, this new drug delivery concept is a targeted and effective cancer therapy method. [12]

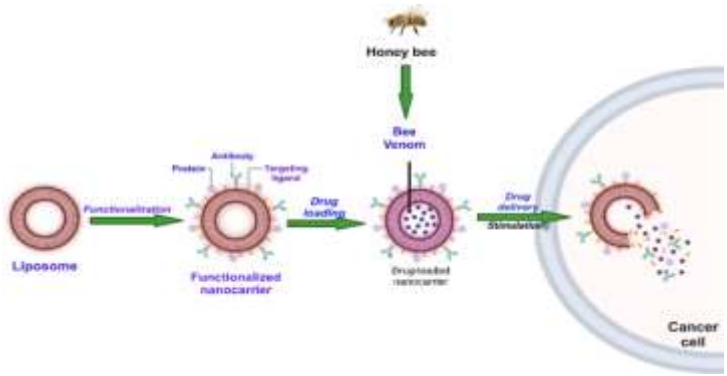

Figure 4. liposomes

6.2 POLYMERIC NANOPARTICLES:

The formulation of melittin-loaded lipid coated polymeric nanoparticles was created to be both biocompatible and stable. It consists of an exterior shell made of polyethylene glycol (PEG) and PEG targeting molecules, a middle layer of lipid membrane, and an inner core of melittin/poly-γ-glutamic acid nanoparticles. [13] Studies using PLGA carriers loaded with melittin have demonstrated that it offers variable release rates and improved penetration into tumour microenvironments.

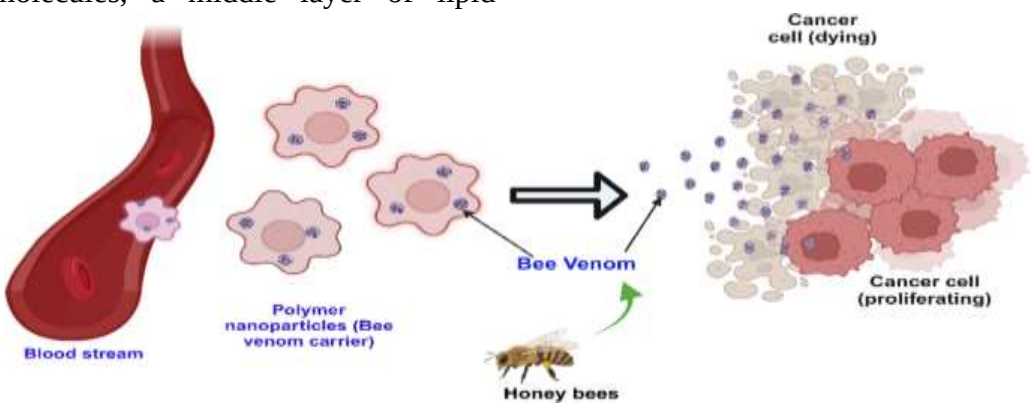

Figure 5. polymeric nanoparticles

6.3 NIOSOMES:

Niosomes are vesicles formed from non-ionic surfactants, capable of efficiently delivering therapeutic agents to cancer cells while reducing unwanted side effects.Challenges such as insufficient protection of active drugs, combined with the demands for stable formulations and extended shelf life, have contributed to slow progress in developing targeted delivery systems for clinical applications. [14]When used to carry melittin, niosomes are designed to maximize anticancer effectiveness and minimize harmful impacts, such as haemolysis, by circumventing previously observed drawbacks.Studies have shown that melittin encapsulated in niosomes leads to more potent tumour suppression in breast

cancer cell models, with fewer adverse reactions compared to other delivery forms. [15]

6.4 METAL NANOPARTICLES:

Bee venom-conjugated silver nanoparticles (AgNPs) are essential for combination therapy because they increase cytotoxicity and offer antibacterial advantages. By adding plant or biomolecule extract dropwise to a metallic salt solution while stirring until a colour shift indicated production, bee venom nanoparticles were created using green synthesis. Purified nanoparticles were obtained by centrifuging, washing, and drying the material at 45 to 50 degrees Celsius. UV-visible, TEM/SEM, and FTIR were used for characterization in order to verify size, form, stability, and crystallinity. [16]

7.ROUTE OF ADMINISTRATION:

BV ointment, creams, pills, drops, Apis homeopathic formulations, electrophoresis, phonophoresis, and bees physically stinging particular places are some of the methods that bee venom can be delivered. It has multiple disadvantage like pain and inflammation caused by sting, difficulty for maintaining its regular concentration in blood, the need for long-term administrator of a series of stings or injection because of short half-life of melittin and inconvenience to patients[17]. Because of BV's comparatively short plasma half-life and the difficulty in establishing a precise dosage, researchers and practitioners are promoting and developing alternate options, like combining it with polymers or nanoparticles. [5]

8.SAFETY AND TOXICITY PROFILE OF BEE VENOM:

Although bee venom contains toxic compounds, in individuals without allergies it can be administered as a relatively safe therapeutic agent.The amount of venom necessary to be lethal for an average adult is estimated at nearly 2.8 mg per kilogram, meaning that approximately 1300 bee stings would be required to reach a fatal dose since each bee produces only a small amount of venom.Using purified components from bee venom, such as melittin, offers improved safety and efficacy compared to treatments with whole, crude venom. [18] Strategies that lower the overall toxicity of bee venom, including modifications like incorporating specific amino acids, make it possible to administer higher doses of apitoxin for enhanced therapeutic results. Adjustments such as using dextrorotatory D-amino acids during peptide synthesis can help reduce toxicity

8.1 COUNTERINDICATIONS:

Bee Venom allergy remains the main contraindication for its therapeutic use; allergy testing is recommended before beginning of apitherapy. [19]

Acute and chronic infections
Post vaccination status
Tuberculosis and hepatitis
Malignancy
Young Children under 5 years old
Pregnancy
Diabetes
Renal failure
Hepatic failure
Impaired cardiac functions and respiratory problems.

9.OVERCOMING RESISTANCE AND ENHANCING EFFICACY:

One major obstacle in the treatment of cancer is tumour resistance to conventional therapies. The lethal effects of nano formulated bee venom peptide on tumour cells can be improved by adjusting their release profiles from nanocarriers. Additionally, the peptide can be coupled with

other medicines to overcome resistance mechanisms. [12]

10.THERAPEUTIC APPLICATION:

Bee venom has therapeutic potential in managing and treating various conditions like Inflammatory, Autoimmune, Arthritis, Bursitis, Tendonitis, Cancer. Bee Venom has various therapeutic or pharmacological properties like [20]

Anti-cancer
Anti-microbial
Anti-inflammatory
Anti-diabetic
Anti-arthritis
Anti-fungal
Radioprotective

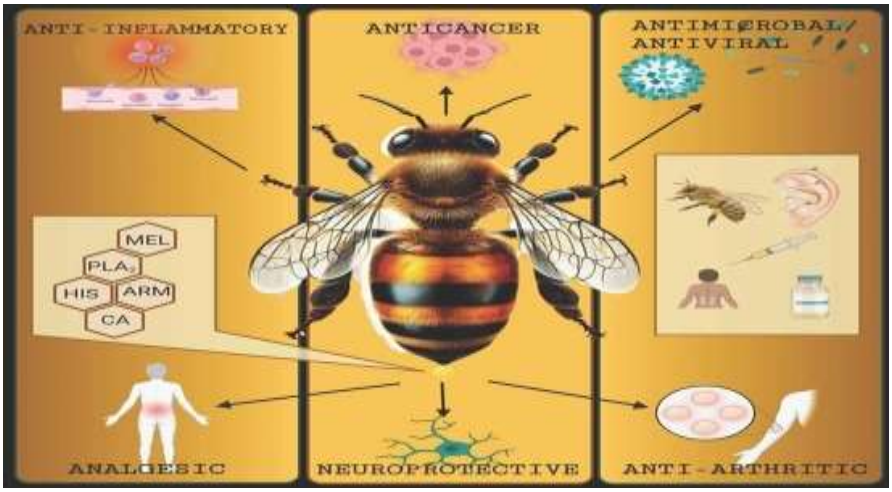

Figure 6. Applications [22]

FUTURE PERSPECTIVES:

AI based nanocarrier design:
Predictive modelling for personalized delivery system.
Combination Therapy:
Integration of BV nano formulation with chemotherapy, radiotherapy or photothermal techniques is expected to amplify anti-cancer efficacy while reducing drug resistance. [22]
Smart Nanoplatforms:
Stimuli-responsive particles releasing peptides under specific tumour triggers.
Synthetic melittin analogues and Recombinant peptides:
These with reduced toxicity and improved stability are being investigated for safer human application. [23]

CONCLUSION:

Bee venom peptides, especially melittin, are among the most promising biomolecules for innovative cancer therapy due to their strong cytolytic and immunomodulatory effects. However, their clinical utility remains limited by haemolytic toxicity, poor stability, and non-specificity toward healthy cells. The development of nanotechnology has made it possible to create advanced delivery methods with enhanced biocompatibility, controlled release, and precise tumour targeting, including polymeric nanoparticles, liposomes, and nano emulsions. Encapsulating melittin with these nanocarriers has notably enhanced its anticancer efficacy while reducing systemic toxicity and improving pharmacokinetic profile. Together, these developments establish melittin-based nanocarriers as effective and adaptable instruments in the battle against cancer, opening the door for next-generation targeted treatments

with fewer side effects and greater therapeutic potential.

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