EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 10
Issue: 8
213-236
Year: 2023

CHEMISTRY OF MELITTIN, THE MAIN PAIN-PRODUCING COMPONENT OF BEE VENOM AND ITS TREATMENT PROCEDURES. (CHEMISTRY, PAIN AND PAIN PSYCHOLOGY)

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Article Received on 26/05/2023 **Article Revised on 16/06/2023** **Article Accepted on 06/07/2023**

ABSTRACT
The innate and adaptive immune systems cause widespread inflammation in order to preserve homeostasis. Inflammation often promotes healing and infection recovery, but if not managed appropriately, it can result in immune system diseases. Bees employ the toxin bee venom to defend themselves against predators. Melittin, the main component of bee venom, has the ability to overreactive immune responses and cause inflammatory illnesses. Recent experimental research have demonstrated that melittin's biological properties could be used both *in vitro* and *in vivo* for medicinal purposes. Thus, the chemical studies of melittin and its action in body is very important or significant to derivatise its easy breakdown or develop a pharmaceutical solution that can be helpful in human healing when a bees or bee stung has occurred or impacted a human of any either of the gender. (Despite the tolerance to the pain).

KEYWORDS: Melittin-bio organic compound, *Apis mellifera toxins*, Apitoxin, pain psychology, development of medicine.

I. INTRODUCTION

II. Background

III. Case/history of bee sting: The potential for the sting of a wild bees to be poisonous and impair a person's psychomotor activity or paralyse their ability to bear pain, however, raises serious safety concerns. The worry, however, is with how toxic the wild bees is able to be in producing the sting effect and stifling the person's psychomotor activity or paralysing the person's capacity to tolerate pain, resulting to difficulties and crying for a long time. A person with a wild bees sting bite is not eligible for rapid medical attention.

IV. I. Study conduct and/or observations: An investigational study report or scientific investigative report conducts: In recent understanding and finding, it could be documented that the rate of bee stings has been vast in places where wild species of the bees/bees are in large numbers or with high populations of wild bees and bee species, like in the forests places of hilly and mountainous ranges of Anjaneri and Trambakeshwar in Nashik. A recent case of the rise of honey bee bites has raised psychological concern about the threshold capacity of pain in men, women, and children. Both women and children are more prone to pain than men. However, the concern is how toxic the capacity of the wild bees is to produce the sting effect and jam the psychomotor activity of the person or paralyse the person's capacity to tolerate pain, leading to trouble and crying for a long time. An immediate treatment is not available to the person with a wild bee sting bite. However, this wild bee sting bite causes a stinging sensation that lasts for hours together, raises the heartbeat, makes the person sweat, and leads to day-blind sight in the affected person or causes day blindness in the victim.

To the immediate remedy over the wild bees sting bite is applying the mud pack that is commonly collected from the earthen pots growing holy basil. It is traditionally believed that this mud pack cures immediately the sting bites of bees.

In people often the _think of pain‘ or thought is as a purely physical sensation. However, pain has biological, psychological and emotional factors. Furthermore, chronic pain can cause feelings such as: anger, hopelessness, sadness and anxiety. To treat pain effectively, you must address the physical, emotional and psychological aspects.[25]

Psychologists are the experts in helping people cope with the thoughts, feelings and behaviours that accompany chronic pain. They may work with individuals and families through an independent private practice or as part of a health care team in a clinical setting. Patients with chronic pain may be referred to psychologists by other health care providers. Psychologists may collaborate with other health care professionals to address both the physical and emotional aspects of the patient‘s pain.[25]

An essential component of pain management is psychological therapy. Understanding and controlling the thoughts, feelings, and behaviours that go along with the discomfort can help deal with it more successfully and even lessen its severity.[25]

Bee stings can cause varying degrees of pain and discomfort in individuals, and the psychological response to the pain can vary from person to person. It's important to note that pain and its psychological impact are highly individual and can vary significantly. If a person experiences severe pain or has an allergic reaction to a bee sting, seeking immediate medical attention is crucial. Additionally, for individuals with a significant fear or anxiety related to bee stings, seeking support from healthcare professionals or therapists specialising in anxiety or phobias may be beneficial.

1. Perception of pain: pain perception is a complex experience influenced by various factors, including biological, psychological, and sociocultural factors. When a bee sting occurs, nociceptors in the skin are activated, sending pain signals to the brain. The brain then processes and interprets these signals, resulting in the experience of pain.
2. Subjective experience: The subjective experience of pain can vary greatly among individuals. Factors such as: pain tolerance, past experiences with pain, and psychological state can influence how a person perceives and responds to a bee sting. Some individuals may experience the pain as more intense or distressing, while others may find it less bothersome.
3. Fear and anxiety: Bee stings can trigger fear and anxiety, especially in individuals who have had previous negative experiences with bee stings or who have a fear of insects (entomophobia). The anticipation of pain and the fear of being stung again can heighten the emotional and psychological response to a bee sting.
4. Context and expectations: The context in which a bee sting occurs and a person's expectations about the pain can also influence the psychological response. For example, if a person believes that bee stings are extremely painful or dangerous, their anticipation of pain may intensify, leading to increased anxiety and distress.
5. Coping mechanisms: Individuals employ various coping mechanisms to manage the pain and psychological distress associated with a bee sting. These can include cognitive strategies (e.g., distraction, positive self-talk), relaxation techniques, seeking social support, or engaging in activities that help take their mind off the pain.
6. Post-traumatic stress: In some cases, individuals who have had a severe allergic reaction or a particularly traumatic experience with a bee sting may develop post-traumatic stress symptoms. This can include intrusive thoughts, flashbacks, avoidance behaviours, and heightened anxiety related to bee stings or similar situations.

A number of recent research on the positive functions of bee venom suggest that it has radioprotective, anti-mutagenic, anti-nociceptive, anti-cancer, and anti-inflammatory effects. Bees use bee venom, a poison, to protect themselves from predators. The main component of bee (*Apis mellifera*) venom, melittin, makes up around 50% of the weight of dried bee venom.

Bee venom, produced by honeybees (*Apis mellifera*), is a complex substance that is primarily used as a defence mechanism by bees. It is a clear, colourless liquid that is produced and stored in the bee's venom sac.

Melittin is a bioorganic molecule, specifically a peptide, produced from honeybee venom (*Apis mellifera*). It is a tiny, cationic peptide with a molecular weight of about 2.8 kilodaltons and 26 amino acid residues.

Melittin has a distinct structure and a wide spectrum of biological functions, which are mostly related to its amphipathic character. It has both hydrophilic and hydrophobic areas, allowing it to interact with many different biological membranes.

V. Melittin's primary features and activities include

Melittin is a powerful bio-toxin discovered in honeybee (*Apis mellifera*) venom. It is the primary active component of honeybee venom and acts as a defence mechanism for honeybees against potential dangers or predators. Because of its cytolytic and inflammatory qualities, melittin can have considerable consequences when injected into an organism.

VI. Highlighted are some of the most important properties of melittin as a biotoxin

1. Membrane disruption: Melittin has the ability to interact with and disrupt lipid membranes. Its amphipathic structure enables it to insert into the lipid bilayer, causing membrane destabilisation and pore formation. This disruption can lead to cell lysis and death.
2. Antimicrobial activity: Melittin exhibits potent antimicrobial activity against a broad spectrum of microorganisms, including bacteria, fungi, and viruses. It disrupts the integrity of microbial membranes, leading to cell death. Its activity against drug-resistant pathogens has made it a subject of interest for antimicrobial research.
3. Anti-inflammatory effects: Melittin has been found to possess anti-inflammatory properties. It can modulate

immune responses by inhibiting the release of pro-inflammatory cytokines and chemokines. These effects may be beneficial in conditions associated with excessive inflammation.

4. Anticancer potential: Melittin has shown promising anticancer activity in preclinical studies. It can induce cell death in cancer cells through various mechanisms, including membrane disruption, mitochondrial dysfunction, and modulation of signaling pathways. It has demonstrated selective cytotoxicity towards cancer cells while sparing normal cells.

5. Drug delivery: Melittin has been explored as a potential component in drug delivery systems. Its ability to disrupt cell membranes can be utilised to enhance the delivery of therapeutic agents across biological barriers. Various melittin-based drug delivery strategies, including liposomes and nanoparticles, have been investigated.

While melittin has various potential medicinal applications, its usage in humans requires additional research and development. The cytotoxicity and potential adverse effects of the peptide must be thoroughly investigated, and delivery mechanisms must be designed to provide targeted and regulated administration.

Overall, melittin is a fascinating bioorganic chemical with a wide range of biological actions, making it an important study topic in disciplines such as: antibacterial therapy, inflammation, cancer treatment, and drug delivery.

VII. Other potential highlights on Melittin

1. **Cytolytic activity:** Melittin acts on cell membranes by disrupting their integrity. It forms pores or channels in lipid bilayers, leading to increased permeability and leakage of cellular contents. This disruption can cause cell lysis and cell death.

Melittin has high cytolytic activity, which means it can cause cell lysis or destruction. The interaction with the lipid components of cell membranes is principally responsible for its cytolytic activity.

1. a. Study of how melittin works to destroy cells

1. Interaction with cell membranes: Melittin is a small peptide with an amphipathic structure, meaning it has both hydrophobic and hydrophilic regions. This structure allows melittin to interact with the lipid components of cell membranes.

2. Membrane insertion: Melittin can insert itself into the lipid bilayer of cell membranes due to its amphipathic nature. It has a preference for interacting with negatively charged lipids, such as: phosphatidylserine, which are often found on the inner leaflet of cell membranes.

3. Disruption of lipid bilayer: Once melittin inserts into the lipid bilayer, it causes local perturbations in the membrane structure. It induces a widening of the lipid bilayer and disturbs the organisation of lipids. These effects lead to increased membrane fluidity and permeability.

4. Pore formation: As melittin inserts deeper into the membrane, it can aggregate and form transmembrane pores or channels. These pores are created by the alignment and clustering of melittin molecules within the lipid bilayer. The formation of pores results in the disruption of the membrane's barrier function.

5. Increased permeability: The pores formed by melittin allow the passage of ions, small molecules, and cellular contents through the cell membrane. This leads to leakage of intracellular components, including ions, proteins, and metabolites. The loss of cellular contents compromises cell viability and ultimately leads to cell lysis.

Melittin's cytolytic activity is mostly related to its disruption of cell membranes. It can have an impact on a variety of cells, including red blood cells, immunological cells, and cancer cells. The degree of cytolytic activity is determined by factors such as: melittin concentration, exposure duration, and target cell sensitivity.

While melittin's cytolytic activity might be damaging, it also has potential applications. Researchers are investigating melittin's antibacterial qualities as well as its capacity to selectively target and kill cancer cells. Furthermore, melittin's membrane-disrupting ability has prompted research into its potential in drug delivery systems, where it can help medicinal molecules breach cellular barriers.

It is crucial to highlight that melittin's cytolytic activity can be harmful to human cells, especially at high quantities or in people who are sensitive to or allergic to bee venom. To avoid adverse reactions and minimise exposure to large doses of melittin, precautions should be followed.

2. **Hemolytic activity:** Melittin has the ability to cause the destruction of red blood cells (hemolysis). It interacts with the lipid components of the cell membrane, leading to membrane disruption and subsequent release of hemoglobin.

Melittin's hemolytic activity refers to its ability to destroy or lyse red blood cells (erythrocytes). Melittin, a peptide found in bee venom, has strong hemolytic effects.

2.a. Highlights of melittin's hemolytic action works[19]

1. Interaction with red blood cell membranes: Melittin interacts with the lipid bilayer of red blood cell membranes. Its amphipathic structure allows it to insert into the membrane, with its hydrophobic regions interacting with the hydrophobic core of the lipid bilayer.

2. Disruption of membrane integrity: Once melittin inserts into the red blood cell membrane, it causes perturbations in the membrane structure. It disrupts the

organisation of lipids, leading to increased membrane fluidity and permeability.

3. Pore formation: Melittin can aggregate and form transmembrane pores or channels in the red blood cell membrane. These pores are created by the alignment and clustering of melittin molecules within the lipid bilayer. The formation of pores compromises the integrity of the membrane.

4. Leakage of cellular contents: The pores formed by melittin allow the passage of ions, water, and other small molecules across the red blood cell membrane. This results in the leakage of intracellular components, including hemoglobin, from the red blood cells.

5. Hemolysis: The disruption of red blood cell membranes by melittin leads to the lysis of red blood cells, a process known as hemolysis. Hemolysis results in the release of hemoglobin into the surrounding environment.

The capacity of melittin to bind with and destroy the lipid bilayer of red blood cell membranes is related to its hemolytic activity. It increases membrane permeability, resulting in the release of cellular contents and, eventually, the death of red blood cells.

It is vital to remember that melittin's hemolytic activity can have both negative and positive consequences. In the case of bee stings, melittin's hemolytic action contributes to the typical pain, swelling, and redness associated with venom injection.

This activity, however, can be used for therapeutic purposes. Melittin, for example, has been studied for its antibacterial qualities since it can damage the membranes of bacteria and other pathogens. Furthermore, melittin-based drug delivery systems have been created to improve therapeutic agent transport across cell membranes.

It should be emphasised that melittin's hemolytic activity can be hazardous to human red blood cells, especially at high doses or in people who are sensitive to or allergic to bee venom. To avoid adverse reactions, proper care should be followed to avoid excessive melittin exposure.

VIII. Pain and inflammation: When melittin is injected into the skin, it induces pain and inflammation. It activates nociceptors (pain receptors: The relatively unspecialised nerve cell endings that initiate the sensation of pain are called nociceptors (noci- is derived from the Latin for “hurt”).[24] Nociceptors are specialised sensory receptors that play a crucial role in the perception of pain. Nociception is a subcategory of somatosensation. Nociception is the neural processes of encoding and processing noxious stimuli.[24] They are nerve endings found throughout the body, particularly in the skin, muscles, joints, and internal organs. Nociceptors are responsible for detecting and transmitting signals related to potentially damaging or noxious stimuli. When tissues are injured or damaged, various chemical, mechanical, or thermal stimuli can activate nociceptors. These stimuli can include extremes of temperature, intense pressure, or the release of inflammatory molecules such as prostaglandins. Nociceptors are highly sensitive to these stimuli and can initiate the sensation of pain. Once nociceptors are activated, they generate electrical signals that travel through nerve fibers to the spinal cord and eventually reach the brain. In the spinal cord, the signals are relayed to higher brain regions where pain perception and interpretation occur. Nociceptors are part of the larger peripheral nervous system, which includes sensory neurons that transmit information from the body to the central nervous system. They are distinct from other sensory receptors responsible for touch, pressure, temperature, or vibration because they specifically respond to noxious stimuli. The activation of nociceptors and the subsequent transmission of pain signals serve as an important protective mechanism for the body. They alert us to potential harm or injury and promote appropriate responses to avoid further damage. However, chronic activation of nociceptors or dysfunction in the pain signaling pathways can lead to persistent or chronic pain conditions. Understanding the function and signaling of nociceptors is essential for the development of treatments for pain management. Researchers and healthcare professionals aim to find ways to modulate or block nociceptor activity selectively to alleviate pain without interfering with other sensory functions) and triggers the release of inflammatory mediators, such as: histamine and prostaglandins. This response contributes to the characteristic pain, swelling, and redness associated with bee stings.

In general, the faster-conducting Aδ nociceptors respond either to dangerously intense mechanical or to mechanothermal stimuli, and have receptive fields that consist of clusters of sensitive spots. Other unmyelinated nociceptors tend to respond to thermal, mechanical, and chemical stimuli, and are therefore said to be polymodal. In short, there are three major classes of nociceptors in the skin: Aδ mechanosensitive nociceptors, Aδ mechanothermal nociceptors, and polymodal nociceptors, the latter being specifically associated with C fibers. The receptive fields of all pain-sensitive neurons are relatively large, particularly at the level of the thalamus and cortex, presumably because the detection of pain is more important than its precise localisation.[24]

IX. Allergic reactions: In some individuals, exposure to melittin can trigger an allergic response, leading to symptoms such as: hives, itching, swelling, difficulty breathing, and in severe cases, anaphylaxis. These allergic reactions can occur even with minimal exposure to bee venom.

X. **Defense mechanism:** Melittin plays a crucial role in the defense mechanisms of honeybees. When a honeybee stings, it injects venom into its target. The melittin present in the venom acts as a deterrent, causing pain and inflammation in the target organism. This response serves as a warning to potential threats and helps protect the bee colony.

It is crucial to highlight that, while melittin can be poisonous to some organisms, it may also have therapeutic benefits. Antimicrobial characteristics, anticancer potential, and drug delivery applications are being investigated. Melittin's capacity to rupture cell membranes has also prompted research into its application as a component in targeted medication delivery systems.

Overall, melittin is a bee venom biotoxin with cytolytic, hemolytic, and inflammatory characteristics. Its effects on organisms differ according to dosage, mode of exposure, and individual sensitivity. To reduce the danger of unpleasant reactions or allergic reactions, bee venom should be handled with caution.[17] [19]

XI. **Composition:** Bee venom contains a variety of components, including proteins, peptides, enzymes, and small organic molecules. The main components of bee venom include melittin, apamin, adolapin, and phospholipase A2. Melittin is the most abundant component and is responsible for the majority of the venom's biological effects.

XII. **Uses:** Bee venom has been used for various purposes throughout history. In traditional medicine, it has been employed to treat a range of conditions, including arthritis, rheumatism, and various inflammatory disorders. However, it's important to note that scientific evidence supporting the effectiveness of bee venom for these purposes is limited, and its use in modern medicine is still a subject of ongoing research.

XIII. **Potential Health Benefits:** Some studies have suggested that bee venom may have anti-inflammatory, analgesic (pain-relieving), and immunomodulatory properties. These properties have prompted research into its potential therapeutic applications. For example, bee venom therapy (BVT) involves the controlled administration of bee venom for the treatment of certain conditions, such as rheumatoid arthritis.

XIV. **Bee sting reactions:** When a bee stings a person, the venom is injected into the skin, resulting in an immediate localised reaction. Most people experience pain, redness, and swelling at the site of the sting, which typically subsides within a few hours. However, some individuals may have an allergic reaction to bee venom, which can lead to more severe symptoms, such as difficulty breathing, hives, or even anaphylaxis. In such cases, immediate medical attention is necessary.

It's important to note that if you have a known allergy to bee venom or if you suspect you may be allergic, it's best to avoid exposure to bee stings and consult with a healthcare professional for appropriate management and advice.

Melittin is a majour component of bee venom and is responsible for many of its biological effects. It is a peptide, specifically a linear polypeptide consisting of 26 amino acids. Melittin makes up approximately 50% of the dry weight of bee venom.

XV. Properties and mechanism of action

Melittin has unique properties that contribute to its biological activity. It is an amphipathic peptide, meaning it has both hydrophobic and hydrophilic regions. This characteristic allows melittin to interact with cell membranes.

When melittin comes into contact with a cell membrane, it disrupts its structure by forming pores or channels. These pores allow ions and other molecules to pass through the membrane, leading to cell membrane disruption and cell death. Melittin is known for its cytolytic activity, which means it can cause the lysis or destruction of cells.

XVI. Biological effects

Melittin has been shown to exhibit various biological effects, including anti-inflammatory, antimicrobial, and anticancer activities. It can modulate the immune response, acting as an immunostimulant and promoting the release of certain cytokines.

Additionally, melittin has been investigated for its potential anticancer properties. It has been found to inhibit the growth of cancer cells and induce apoptosis (programmed cell death) in tumour cells. However, more research is needed to fully understand its effectiveness and potential applications in cancer treatment.

XVII. Melittin as a therapeutic agent

Researchers have explored the potential use of melittin in various therapeutic applications. It has been studied as a topical agent for wound healing and as an antimicrobial agent to combat antibiotic-resistant bacteria. Melittin-loaded nanoparticles and liposomes have also been developed to improve drug delivery systems.

It's worth noting that while melittin shows promise in certain areas of research, its potential therapeutic use is still being explored, and more studies are needed to establish its safety and efficacy. As with any experimental treatment, it should be approached with caution, and medical advice should be sought from healthcare professionals.

Apitoxin, sometimes known as bee venom, is the venom produced by honey bees. It's a cytotoxic and hemotoxic bitter colourless liquid with proteins that might cause local inflammation. It may be related to sea bees toxin.[7]

Apitoxin refers to the venom produced by honeybees (*Apis mellifera*). It is commonly known as bee venom. Apitoxin is a complex mixture of substances, including peptides, enzymes, proteins, and small organic molecules.

XVIII.Composition

The main components of apitoxin include melittin, phospholipase A2, hyaluronidase, adolapin, apamin, mast cell degranulating peptide, histamine, dopamine, and various other peptides and enzymes. Melittin is the most abundant component and is responsible for many of the venom's effects.

XIX. Collection

Apitoxin is collected by stimulating bees to sting a collector surface, such as glass or a non-reactive material. When a bee stings, its stinger gets lodged in the collector, and the venom is released into the surface. The venom can then be collected, purified, and used for various purposes.

XX. Medical applications

Apitoxin has been used in traditional medicine for centuries and is still utilised today in certain therapies. Bee venom therapy (BVT) involves the controlled administration of apitoxin to treat conditions such as: rheumatoid arthritis, osteoarthritis, multiple sclerosis, and certain types of pain. However, the scientific evidence supporting the effectiveness of BVT is limited and controversial, and it is important to consult with healthcare professionals before considering such therapies.

Research is ongoing to explore the potential medical applications of apitoxin. Some studies suggest that certain components of bee venom, such as melittin, may have anti-inflammatory, analgesic, antimicrobial, and anticancer properties. However, further research is needed to determine the specific mechanisms of action and clinical effectiveness of these components.

XXI. Caution and allergic reactions

It's important to note that some individuals may have allergic reactions to apitoxin. For people who are allergic to bee stings, even a small amount of venom can cause severe allergic reactions, including anaphylaxis, a potentially life-threatening condition. If you have known allergies to bee venom or suspect that you might be allergic, it is crucial to avoid exposure to bee stings and seek appropriate medical advice.

Overall, while apitoxin and its components hold potential for various medical applications, it is essential to approach its use with caution and under the guidance of healthcare professionals.

XXII. Main text

Inflammation is a primary process of the immune response that is triggered by any stimulus such as infection, injury, and exposure to contaminants that poses a real or perceived threat to homeostasis.[5]

Inflammation is a natural process that occurs in the body in response to injury, infection, or irritation. It is part of the immune system's defense mechanism and is crucial for initiating the healing process.

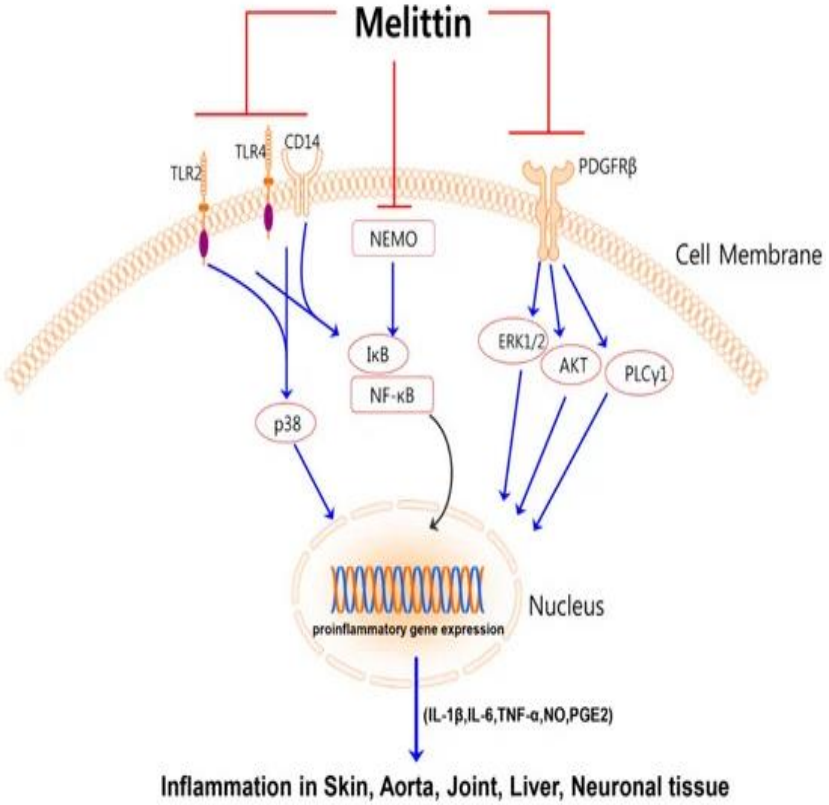
When tissue is damaged or infected, various immune cells, such as: white blood cells, release chemicals that trigger inflammation. These chemicals cause blood vessels to widen, leading to increased blood flow to the affected area. This results in redness, warmth, and swelling. There are two types of inflammation: acute and chronic.

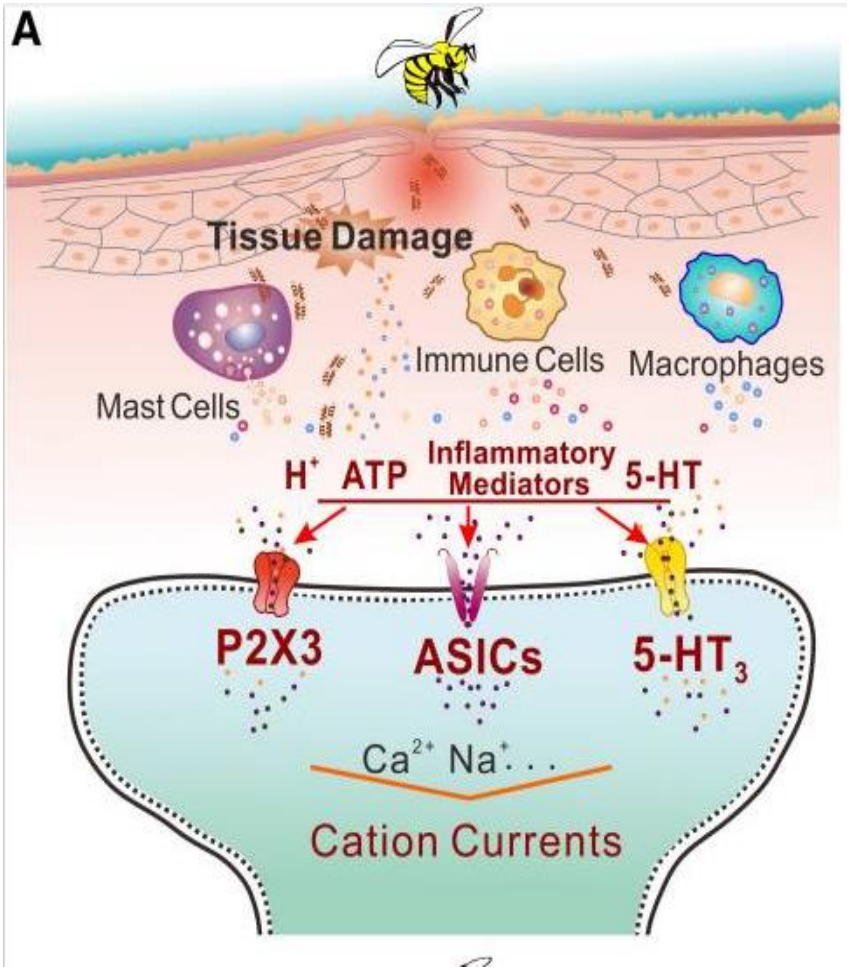
1. Acute inflammation: This type of inflammation occurs rapidly after an injury or infection. It is a short-term response that helps eliminate the cause of the injury or infection and promotes healing. Classic indications of acute inflammation include redness, swelling, heat, discomfort, and loss of function.

2. Chronic inflammation: When the inflammation persists for an extended period, usually weeks, months, or even years, it is considered chronic inflammation. Chronic inflammation can result from unresolved acute inflammation, autoimmune disorders, long-term exposure to irritants, or other underlying health conditions. Unlike acute inflammation, chronic inflammation may not produce obvious signs and symptoms, but it can cause damage to tissues and organs over time.

While inflammation is an essential process for healing, excessive or prolonged inflammation can have negative effects on the body. Chronic inflammation has been linked to various health conditions, including autoimmune diseases, cardiovascular diseases, diabetes, arthritis, certain cancers, and neurodegenerative disorders.

Inflammation treatment is determined by the underlying cause and severity. It may include medications like nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, immunosuppressants, or disease-modifying antirheumatic drugs (DMARDs). Lifestyle changes, such as a healthy diet, regular exercise, stress management, and avoiding known triggers or irritants, can also help reduce inflammation.


Melittin
TLR2
TLR4
CD14
PDGFRβ
NEMO
Cell Membrane
IκB
NF-κB
ERK1/2
AKT
PLCγ1
p38
Nucleus
proinflammatory gene expression
(IL-1β,IL-6,TNF-α,NO,PGE2)
Inflammation in Skin, Aorta, Joint, Liver, Neuronal tissue


A
Tissue Damage
Mast Cells
Immune Cells
Macrophages
H+ ATP
Inflammatory Mediators
5-HT
P2X3
ASICs
5-HT3
Ca2+ Na+ . . .
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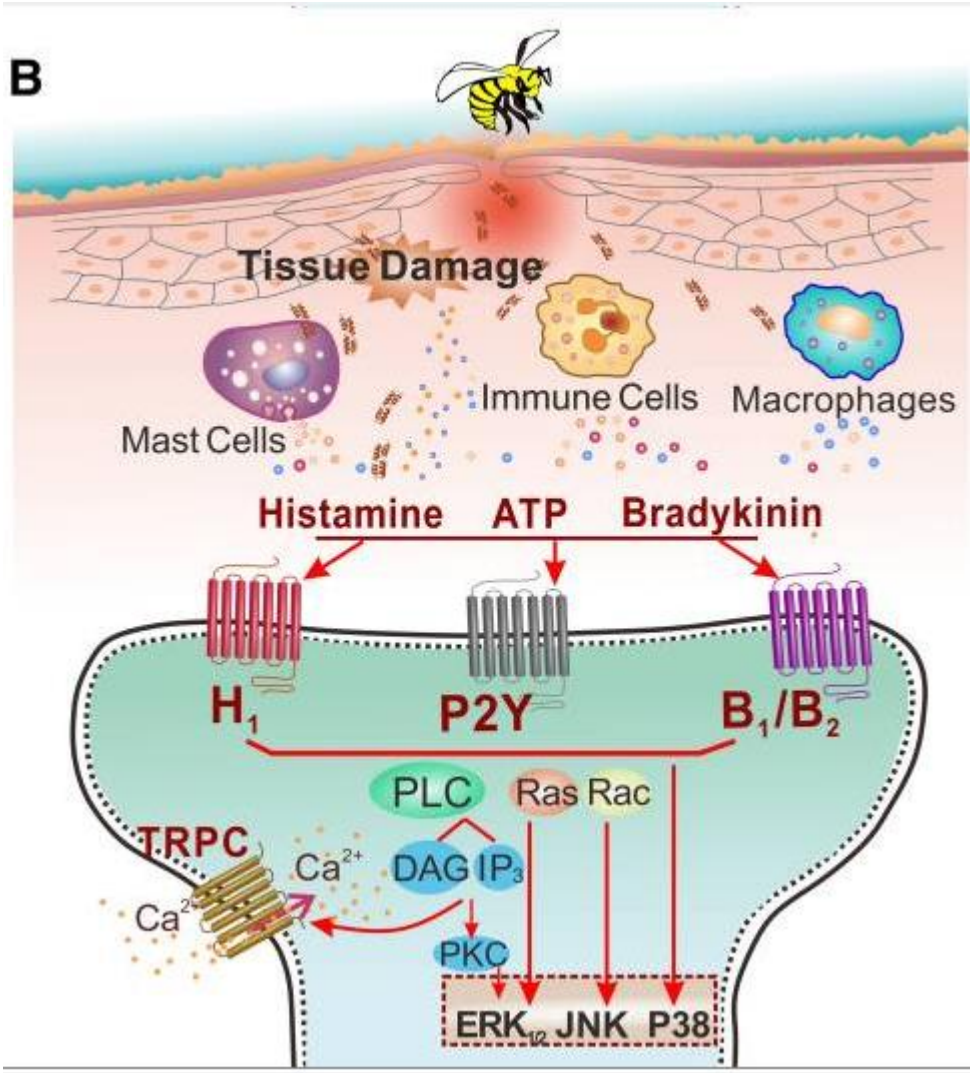


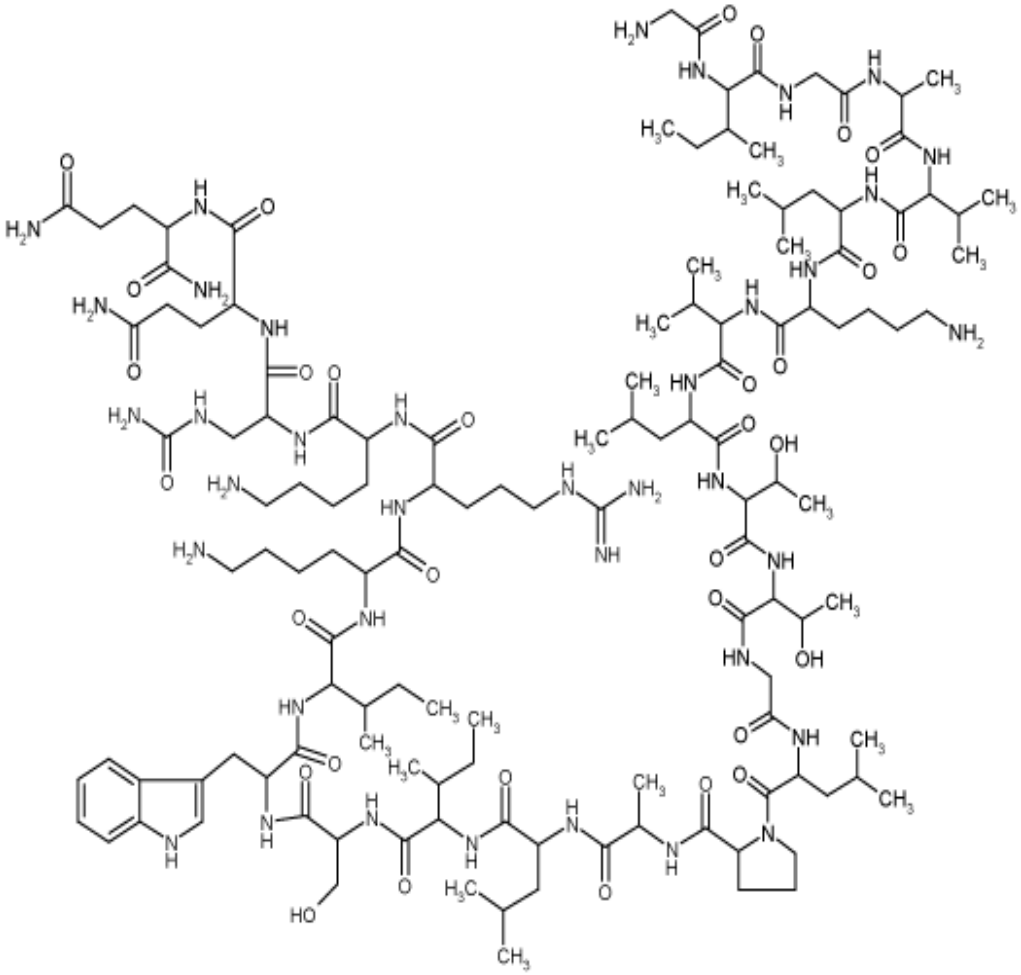
Figure 1: Important processes underlying melittin's anti-inflammatory effects.[9] [18]

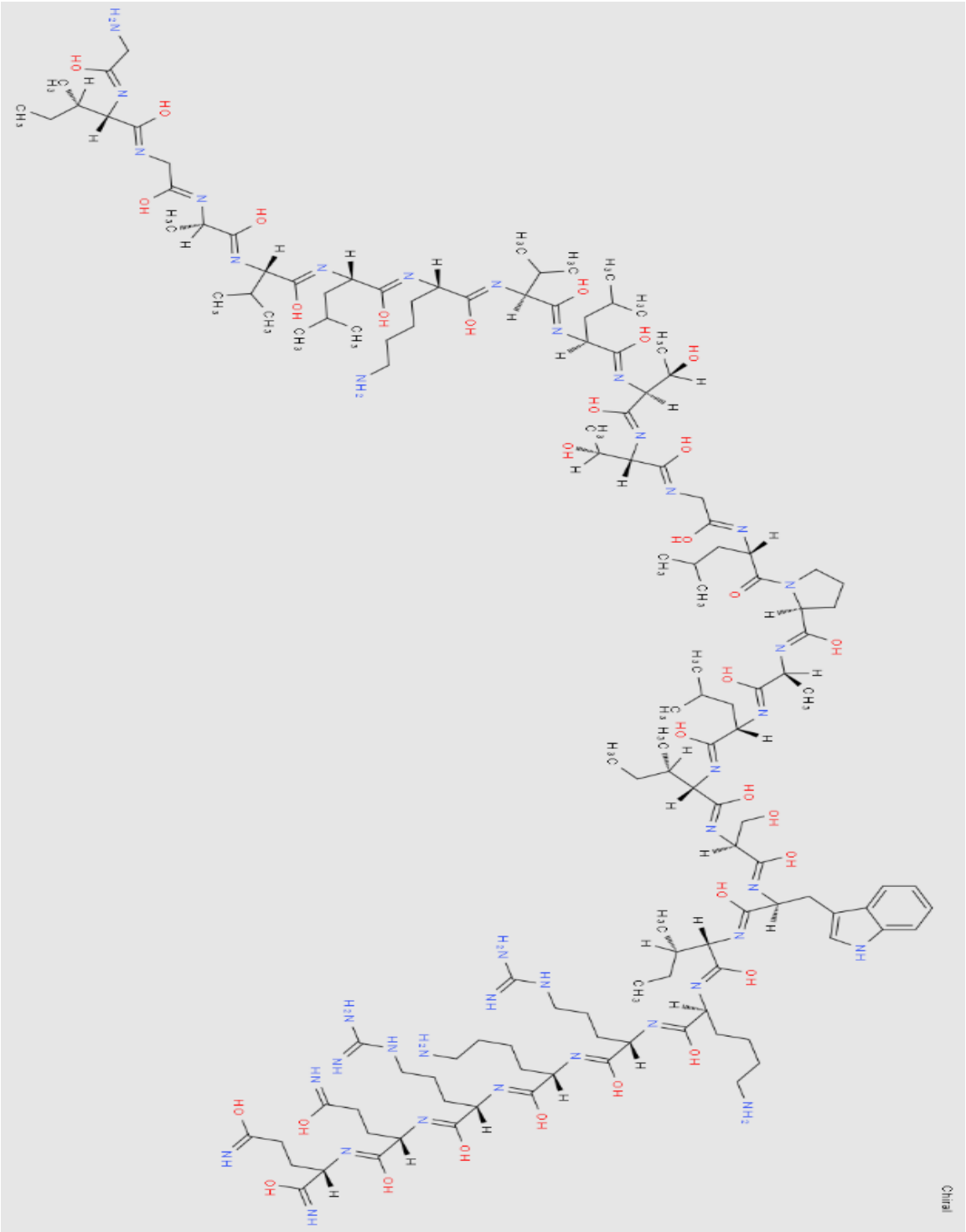
Melittin is the main component (40–60% of the dry weight) and the majour pain-producing substance of honeybee (*Apis mellifera*) venom. Melittin is a basic peptide consisting of 26 amino acids.[3]

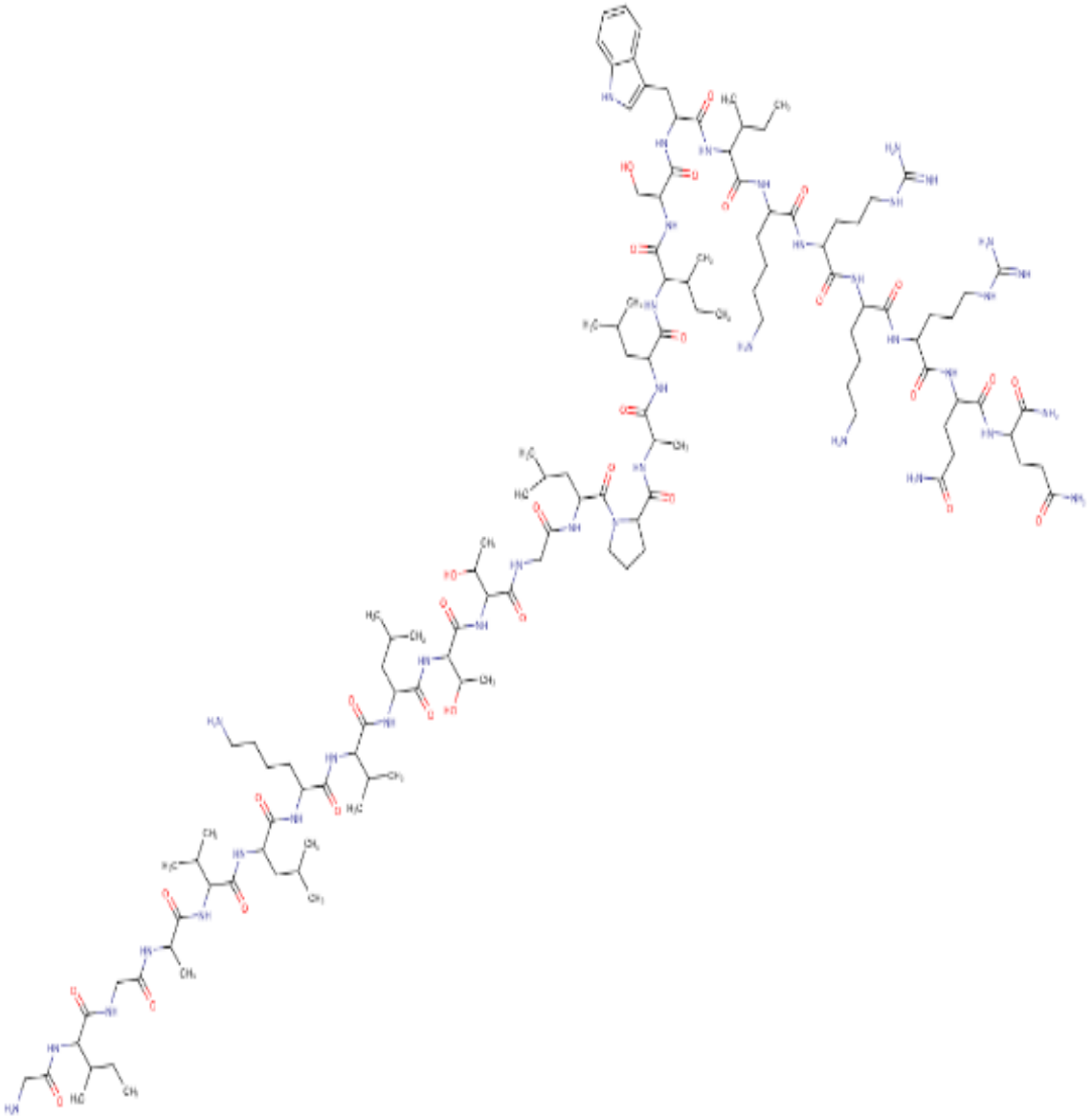
Melittin is a basic 26-amino-acid polypeptide that constitutes 40–60% of dry honeybee (*Apis mellifera*) venom.[1] Although much is known about its strong surface activity on lipid membranes, less is known about its pain-producing effects in the nervous system. melittin is the majour pain-producing substance of bee venom. At the psychophysical and behavioural levels, subcutaneous injection of melittin causes tonic pain sensation and pain-related behaviours in both humans and animals. At the cellular level, melittin activates primary nociceptor cells through direct and indirect effects. On one hand, melittin can selectively open thermal nociceptor transient receptor potential vanilloid receptor channels *via* phospholipase A2-lipoxygenase/cyclooxygenase metabolites, leading to depolarisation of primary nociceptor cells.[1] On the other hand, algogens and inflammatory/pro-inflammatory mediators released from the tissue matrix by melittin's pore-forming effects can activate primary nociceptor cells through both ligand-gated receptor channels and the G-protein-coupled receptor-mediated opening of transient receptor potential canonical channels. In both humans and rats, melittin has been demonstrated to be the unique pain-producing substance of honeybee venom. It activates primary nociceptor cells directly and indirectly due to its ability to activate plasma membrane PLA2 and its pore-forming activity. The melittin-triggered PLA2-LOX/COX down-stream metabolite pathways are involved in activating or enhancing TRPV1 receptor activity *via* HETEs or PGs, leading to the depolarisation of primary nociceptor cells.[1]

Melittin causes disruption of normal cellular activity and cell lysis. Binds calmodulin in a calcium-dependent manner. Activates phospholipase A_2 (PLA_2) and inhibits protein kinase C (PKC) by binding to the catalytic domain in a Mg-ATP sensitive manner. Antirheumatic.[2]

Formula:	$C_{131}H_{229}N_{39}O_{31}$
MW:	2846.5
Source:	Isolated from bee venom.
Appearance:	White to faint tan powder.
Solubility:	Soluble in PBS (5mg/ml) or water (5mg/ml).







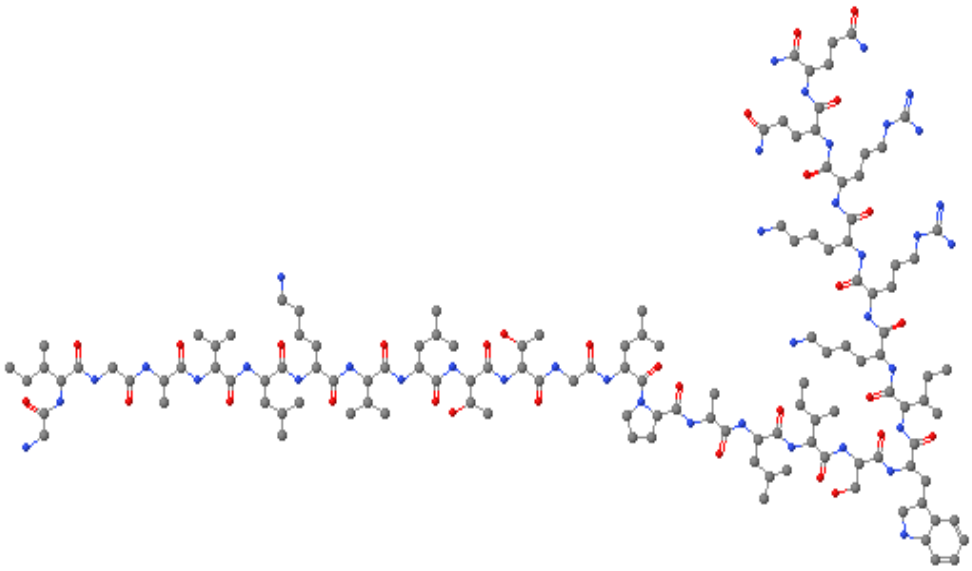


Figure 2: Structure of Melittin.[2] [11] [12]

a

Peptide	Amino Acid Sequence *												
Melittin	1	2	3	4	5	6	7	8	9	10	11	12	13
	G	I	G	A	V	L	K	V	L	T	T	G	L
	14	15	16	17	18	19	20	21	22	23	24	25	26
	P	A	L	I	S	W	I	K	R	K	R	Q	Q

* Blue: hydrophobic; Orange: hydrophilic; Red: charged

b

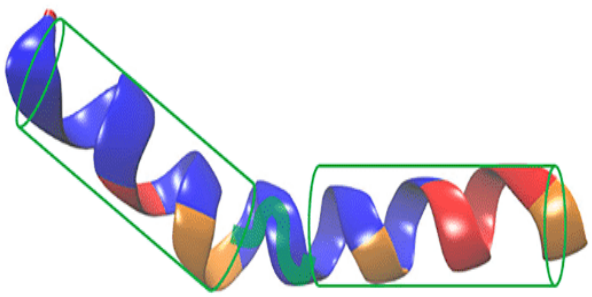


Figure 3: (Melittin's structural makeup. (A) Melittin's amino acid composition. Distinct types of residues have distinct colours: hydrophobic residues are blue, hydrophilic residues are orange, and charged residues are red.).[4] [6]

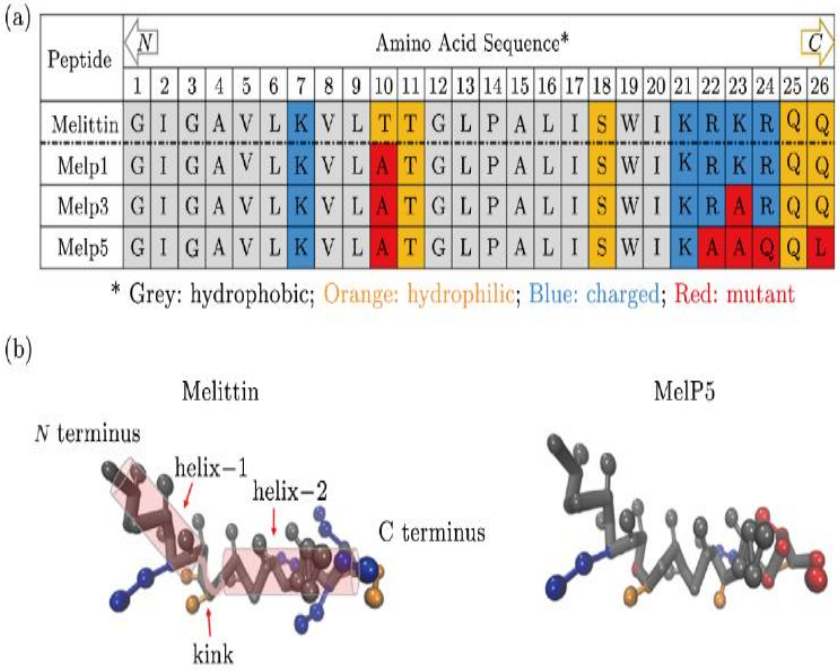


Figure 4: a. Structural demonstration of melittin and three representative gain-of-function variants, MelP1, MelP3 and MelP5. (a) Amino acid sequences of the peptides. Different types of residues are coloured differently: grey for hydrophobic residues, orange for hydrophilic ones, while blue for charged ones. Residues in red are the mutated ones from parent melittin. Arrow "N" or "C" indicates the N or C terminus of the peptide. (b) Conformational structure of melittin and MelP5 (when binding on a membrane). The two α-helixes of melittin are sketched with transparent cylinders, being connected with the kink part between them. Corresponding amino acid residues are highlighted with the same colour scheme as in (a).[8]

Melittin is a 26-residue poisonous peptide from honey bee venom that has been widely studied. Melittin has been the subject of numerous studies as a model peptide in protein folding studies as well as in studies involving binding to proteins, lipids, and polysaccharides because of its adaptability in adopting a variety of secondary (helix or coil) and quaternary (monomer or tetramer) structures in various environments.

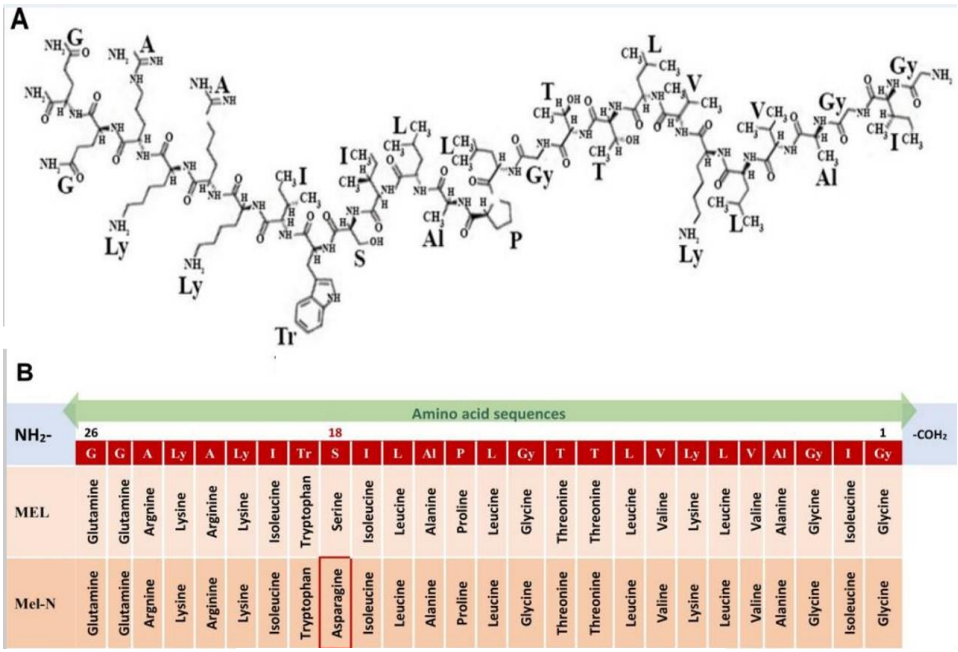


Figure 4: b. Mellitin chemical composition.

(A) Molecular structure, and (B) Amino acid sequences of two Mellitin isoforms, *Apis mellifera* and *Apis cerana*.[30] [31]

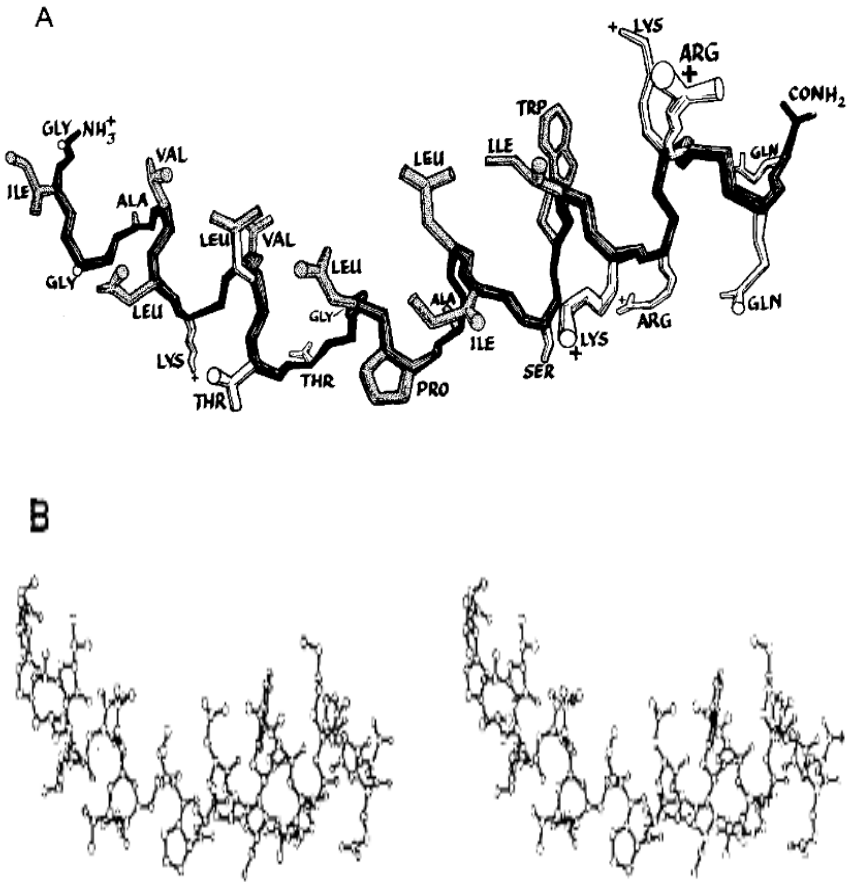


Figure 5: Conformation of one melittin chain from the tetramer. Mallory Pearce.) 6, stereo pair showing chain A in approximately the o der Waals radii.[13]

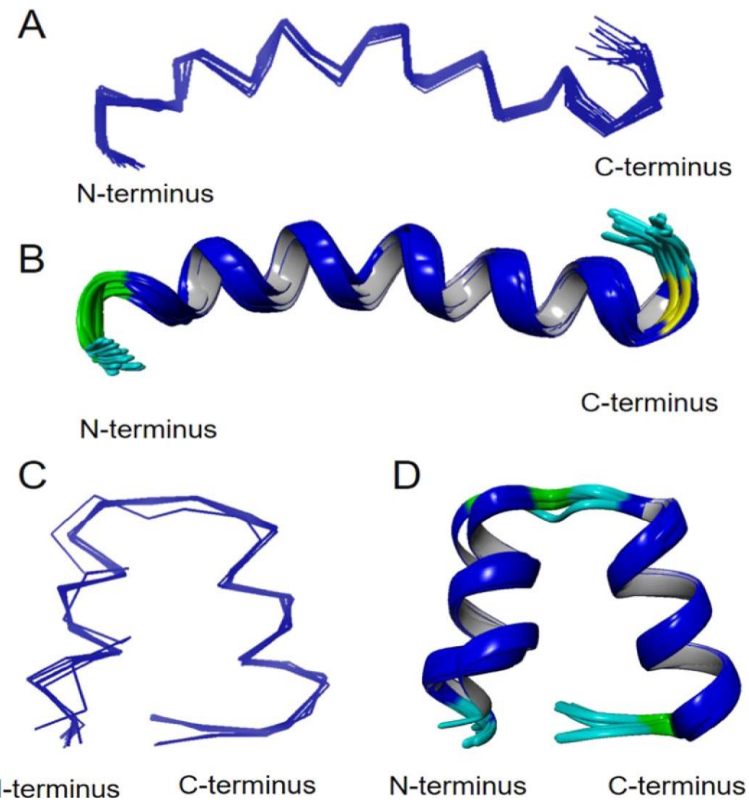
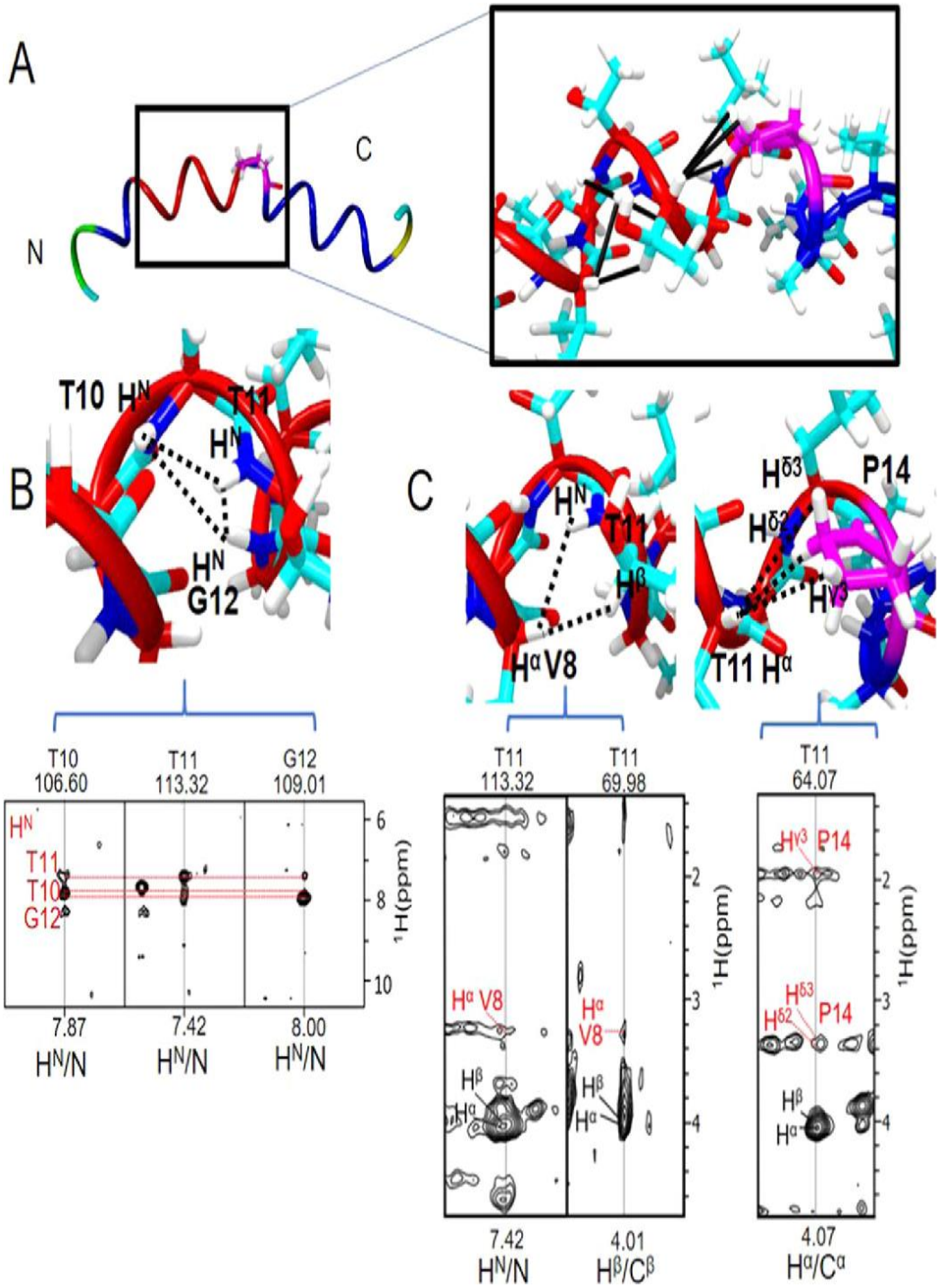


Figure 6: NMR solution structure of recombinant melittin in TFE/water/glycerol determined from NOE data (PDB ID: 6DST) differs from the structure predicted by CS-ROSETTA. For (A) and (B), structure calculation

was performed using CYANA45 version 3.98. For (C) and (D), structure prediction based on chemical shifts was performed using CS-ROSETTA.56 For (B) and (D), structured regions are rendered as thick ribbons.[14]



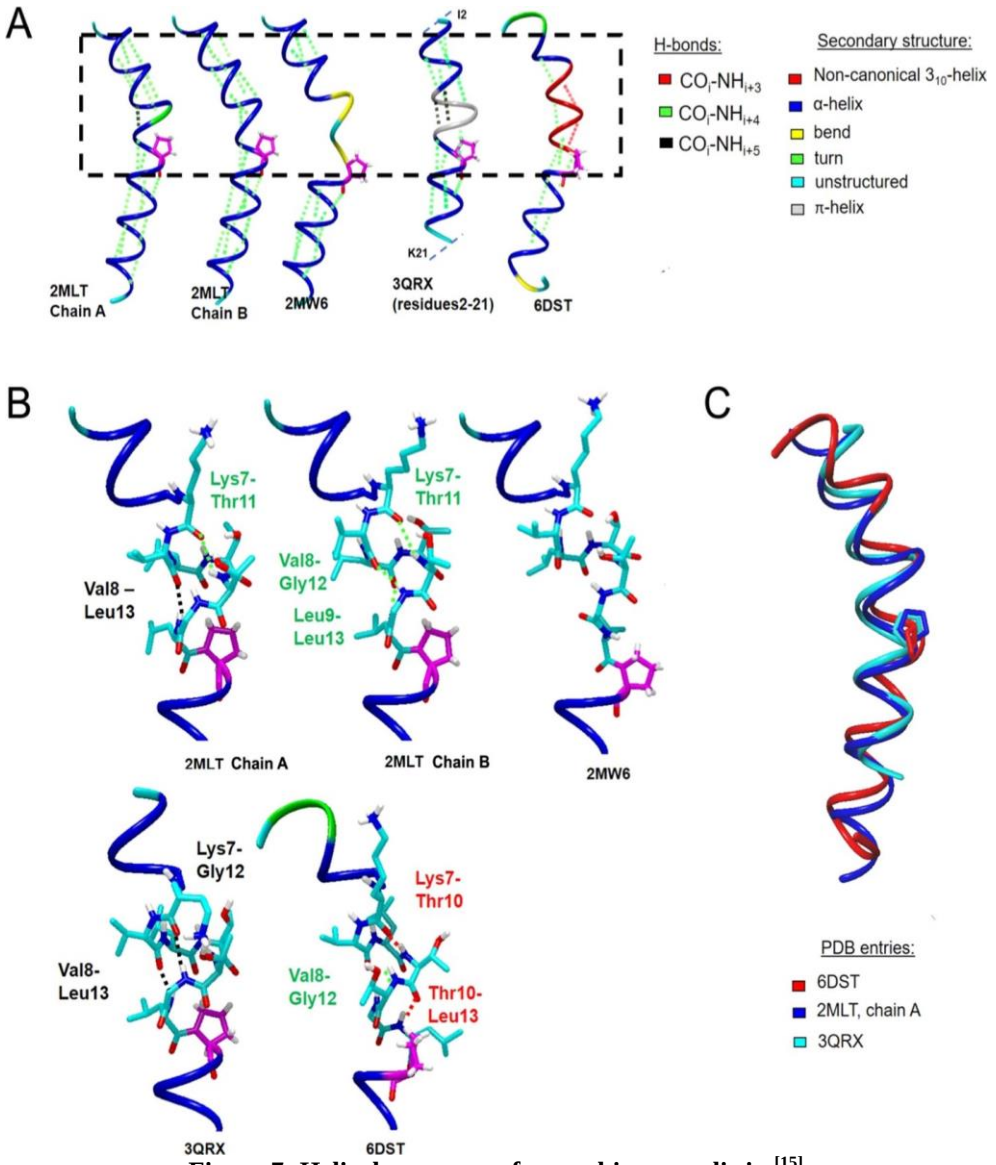


Figure 7: Helical structure of recombinant melittin.[15]

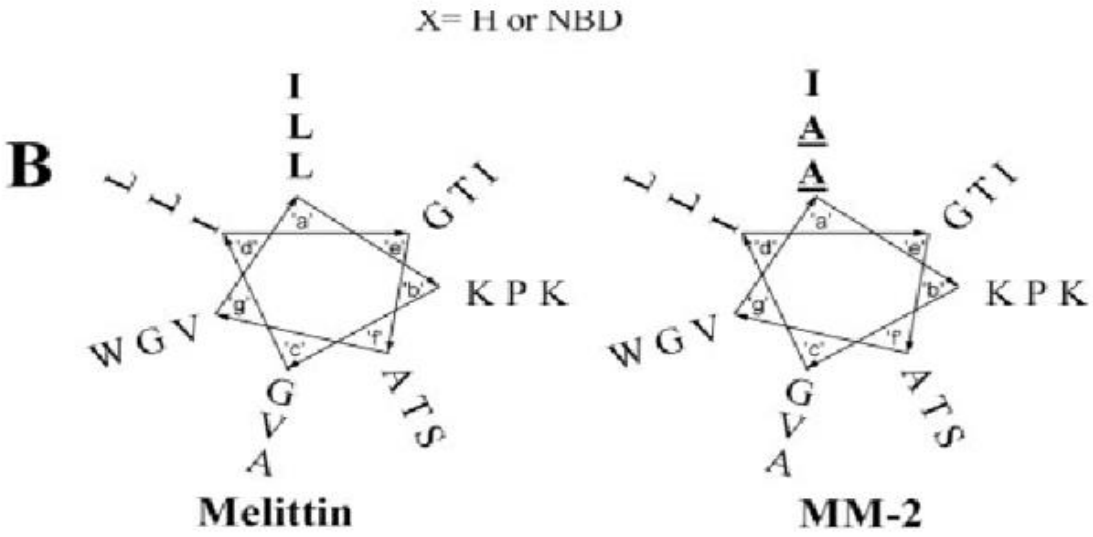


Figure 8: Designations and sequences of melittin and its analogues used.

A, designations and sequences of melittin and its analogs used in this study. Heptadic amino acids are marked in bold, whereas mutated amino acids are marked as bold and underlined. B, helical wheel projections of the first 21 amino acids of melittin, and MM-2 with the first amino acid glycine placed in the c position of the heptad.[10]

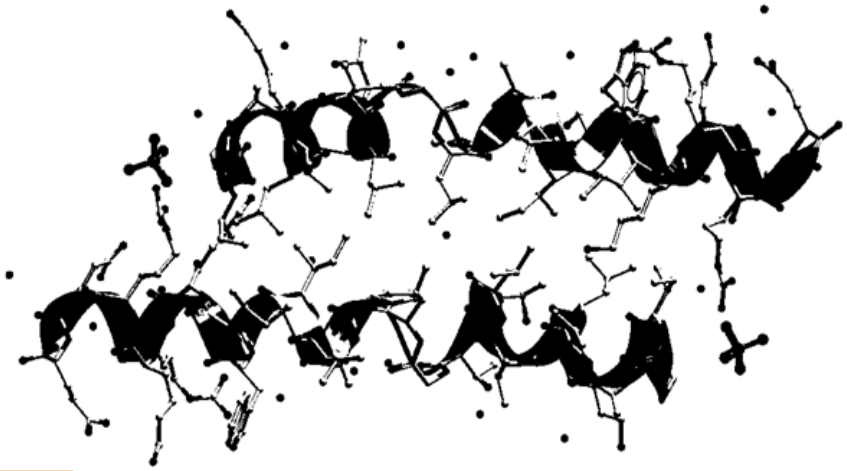


Figure 9: Apitoxin, the main active ingredient in bee venom, contains melittin. 3D construction.[10]

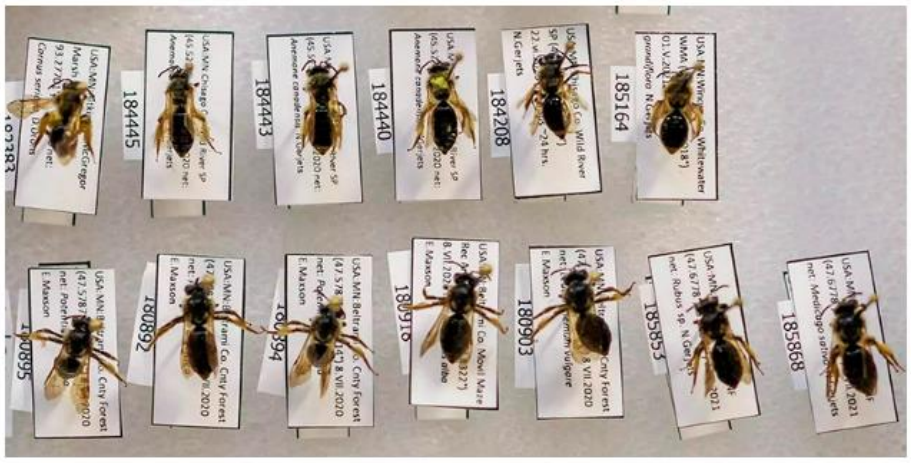


Figure 10: Types of bees. (Bees collected by researchers are stored at the Minnesota Department of Natural Resources in St. Paul on Jan. 19. Tags indicate where the bees were captured and their scientific name.)[26]

XXIII. Treatment[21]

Melittin is a peptide component found in bee venom, known for its potent antimicrobial and hemolytic (cell-destroying) properties. Antivenom, on the other hand, is a type of serum or medication used to counteract the effects of venom from snakebites or other venomous animal bites. It works by neutralising the toxic components present in the venom.

However, there is no specific antivenom available for melittin, as it is a component of bee venom rather than being a venom itself. Antivenoms are typically developed for the specific toxins produced by venomous animals, and melittin is not targeted individually. Instead, treatment for a bee sting typically involves managing the symptoms, such as: pain, swelling, and allergic reactions.

If someone experiences an allergic reaction to a bee sting, immediate medical attention may be necessary, and an epinephrine auto-injector (such as: an EpiPen) may be used to treat severe allergic reactions. It is important to seek medical advice and follow the recommendations of healthcare professionals when dealing with venomous animal bites or stings.

While Ayurvedic remedies can be helpful for soothing the effects of a honey bee sting, it's important to note that immediate medical attention should be sought in the case of severe allergic reactions or if the symptoms worsen.

In Ayurveda, the traditional system of medicine from India, there are various remedies that can be used to soothe the effects of a honey bee sting. Please note that it's always important to consult with a qualified

Ayurvedic practitioner or healthcare professional for personalised advice and proper dosage.

XXIV. General Ayurvedic remedies that are sometimes recommended for honey bee stings

1. Triphala: Triphala is a well-known Ayurvedic formulation composed of three fruits—amalaki (*Emblica officinalis*), bibhitaki (*Terminalia bellirica*), and haritaki (*Terminalia chebula*). It is commonly used for its anti-inflammatory and wound-healing properties. Making a paste by mixing triphala powder with water and applying it topically on the affected area can heal and reduce the pain.

2. Aloe vera: Aloe vera gel is known for its soothing and cooling properties. Applying fresh aloe vera gel directly to the bee sting can help alleviate pain, reduce inflammation, and promote healing.

3. Turmeric: Turmeric (*Curcuma longa*) is a well-known Ayurvedic spice with anti-inflammatory and analgesic properties. Mixing turmeric powder with a small amount of water to make a paste and applying it to the bee sting can help relieve pain and reduce inflammation.

4. Neem: Neem (*Azadirachta indica*) is a powerful herb in Ayurveda known for its antimicrobial and anti-inflammatory properties. Applying neem paste or neem oil to the affected area can help soothe the sting and prevent infection.

5. Sandalwood: Sandalwood (*Santalum album*) has cooling and soothing properties. It can be made into a paste by mixing sandalwood powder from market or by with water and apply it to the bee sting for relief. Of the 15 different species of sandalwood that grow throughout the world, there are 2 main varieties that are traded internationally. These are ***Santalum spicatum*** **(Australian sandalwood) and *Santalum album* (Indian sandalwood)**.[29]

Remember, these remedies are general suggestions and may vary depending on individual circumstances. It is always recommended to consult with an Ayurvedic practitioner or healthcare professional for the most appropriate advice and guidance based on your specific situation.

Remember that these are general guidelines that may vary based on the circumstances. Based on your unique condition, it is always best to get the most appropriate advice and help from an Ayurvedic practitioner or healthcare professionals: like pharmacists or nurse in an emergency condition.

XXV. Seeking for a simple topical treatment for honey bee stings

XXV.I. Consider the following preparation

XXV.II. Ingredients

- 1 teaspoon baking soda
- 1 teaspoon water
- 1-2 drops of lavender essential oil (optional)

XXVI. Instructions

1. In a small bowl, mix the baking soda and water to form a paste. You may need to adjust the amount of water to achieve a thick, spreadable consistency.
2. If desired, add a few drops of lavender essential oil to the paste. Lavender oil has calming properties and may help reduce inflammation and itching.
3. Apply the paste directly to the bee sting area, covering it completely.
4. Leave the paste on for 15-20 minutes, then rinse it off with lukewarm water.
5. Repeat the application 2-3 times a day, as needed, until the symptoms subside.

Keep in mind/remember that this formulation is intended for mild cases of honey bee stings and may help alleviate pain, reduce inflammation, and provide temporary relief. However, it's essential to monitor the symptoms closely and seek medical attention if the condition worsens or if you experience severe allergic reactions.

Furthermore, if you have a known allergy to bee stings or have previously encountered severe responses, it is critical to have access to appropriate medical interventions, such as: an epinephrine auto-injector (EpiPen), and to seek quick medical attention in the event of an emergency.

Traditional or folk remedies for honey bee stings may vary across different cultures and regions.

XXVII. Few examples of traditional remedies that are sometimes suggested for honey bee stings

1. Onion: Cut a fresh onion in half and apply the cut side directly to the bee sting. Some believe that the enzymes in the onion can help neutralise the venom and reduce pain and swelling.

2. Plantain leaves: Crush fresh plantain leaves to release their juices, then apply the mashed leaves directly to the sting. Plantain is believed to have anti-inflammatory and soothing properties.

3. Mud or clay: Applying a poultice of mud or clay to the bee sting area is a folk remedy used in some cultures. The cooling effect of the mud or clay may help relieve pain and inflammation.

4. Vinegar: Soaking a cloth or cotton ball in vinegar and applying it to the bee sting can help neutralise the venom and reduce pain. However, vinegar may not be suitable for everyone, especially if you have sensitive skin.

5. Honey: While it may seem counterintuitive, some people believe that applying a small amount of honey to the bee sting can help soothe the area and reduce inflammation. However, this remedy should be used with caution, as some individuals may be allergic to honey.

It's crucial to note that the efficacy of these traditional cures varies, and there may be no scientific evidence to back up their claims. If you decide to attempt a traditional or folk cure, pay attention to your body's reaction and stop using if you see any negative

consequences. If you have serious symptoms or are unsure about the best course of action, it is always preferable to seek medical attention.

Using mud or clay as a remedy for a honey bee sting is a traditional folk practice in some cultures. The cooling effect of mud or clay is believed to help alleviate pain and reduce inflammation. If you decide to use mud or clay as a remedy, here are the steps you can follow:
1. Ensure the area around the sting is clean. Gently wash the area with mild soap and water, and pat it dry with a clean towel.
2. Collect clean mud or clay. You can find suitable mud or clay in areas with natural sources, such as: riverbanks or clay-rich soil. Make sure the mud or clay is free from contaminants or chemicals.
3. Take a small amount of mud or clay and apply it directly to the bee sting. Spread it evenly to cover the affected area.
4. Leave the mud or clay in place for about 15-20 minutes. During this time, it may start to dry and harden.
5. Once the mud or clay has dried, gently rinse it off with lukewarm water. Avoid rubbing the area vigorously, as it may cause further irritation.
6. After rinsing, pat the area dry with a clean towel.

Remember that applying mud or clay to a bee sting is an old cure whose effectiveness varies from person to person. If your symptoms increase or you have concerns, seek medical assistance and consult with a healthcare expert. Based on your specific situation, they can provide suitable counselling and treatment alternatives.

XXVIII. Taking care

When it comes to soothing a honey bee sting, using a gentle and soothing lotion can provide relief and help alleviate discomfort.

XXIX. A simple method for applying lotion to a honey bee sting

1. Clean the area: Start by washing the area around the honey bee sting with mild soap and water. Gently pat it dry with a clean towel.
2. Choose a soothing lotion: Look for a lotion that is mild, fragrance-free, and hypoallergenic. Aloe vera gel or calamine lotion are often recommended for their cooling and soothing properties. Make sure to check the label and choose a lotion that suits your needs and any specific allergies or sensitivities you may have.
3. Apply a thin layer: Take a small amount of the lotion on your clean fingertips or a cotton swab. Gently apply a thin layer of the lotion directly to the honey bee sting. Be careful not to rub or press too hard to avoid further irritation.
4. Allow it to absorb: Let the lotion absorb into the skin naturally. Avoid covering the area with clothing or bandages immediately to allow the skin to breathe.
5. Reapply as needed: If the discomfort persists, you can reapply the lotion 2-3 times a day or as directed by the lotion's instructions. Always follow the recommended usage guidelines on the lotion packaging.

While a soothing lotion can provide temporary comfort, severe allergic reactions or worsening symptoms necessitate rapid medical assistance. If you notice symptoms of an allergic reaction (such as: trouble breathing, swelling, dizziness, or a rapid heartbeat), seek emergency medical attention immediately.

Using a lotion can help relieve the pain associated with a honey bee sting. However, if you have any concerns or if your symptoms increase, it is best to seek the advice of a healthcare expert.

Calamine lotion can be beneficial in soothing the symptoms of a honey bee sting. Calamine lotion contains a mixture of zinc oxide and iron (III) oxide, which has been traditionally used to relieve itching and irritation associated with various skin conditions, including insect bites.

When applied topically to a honey bee bite, calamine lotion can help reduce itching, inflammation, and discomfort. It creates a soothing, protective barrier over the affected area and provides a cooling sensation that can help alleviate the symptoms.

XXX. To use calamine lotion for a honey bee bite

1. **Clean the area:** Wash the honey bee bite gently with mild soap and water. Pat it dry with a clean towel.
2. **Shake the calamine lotion bottle:** Shake the bottle well to ensure the lotion is mixed thoroughly.
3. **Apply the calamine lotion:** Pour a small amount of calamine lotion onto a cotton ball or your fingertips. Gently apply it to the honey bee bite, covering the affected area with a thin layer.
4. **Let it dry:** Allow the calamine lotion to air dry on the skin. Avoid rubbing or wiping it off.
5. **Reapply as needed:** If the symptoms persist, you can reapply calamine lotion 2-3 times a day or as directed by the instructions on the bottle. Follow the recommended usage guidelines.

Calamine lotion is generally considered safe for topical use, but it's always a good idea to perform a patch test on a small area of skin before applying it to the entire affected area. This helps to ensure that you don't have any allergic reactions or sensitivities to the lotion.

If you experience severe symptoms, such as: difficulty breathing, swelling, or signs of an allergic reaction, seek immediate medical attention.

While calamine lotion can provide temporary relief from the symptoms of a honey bee bite, it's important to note that it does not neutralise the venom or address potential allergic reactions. If you have concerns or if the symptoms worsen, it's best to consult with a healthcare professional for proper evaluation and guidance.

XXXI. Using a *Ocimum sanctum* Linn.[22] *(holy basil)* mud pack on a honey bee bite is a traditional folk remedy that is believed to help alleviate pain, reduce inflammation, and provide a soothing effect.

XXXII. A general guideline on how to create and apply a *Ocimum sanctum* Linn.[22] mud pack for a honey bee bite

1. Clean the area: Start by gently washing the honey bee bite area with mild soap and water. Pat it dry with a clean towel.

2. Prepare the *Ocimum sanctum* Linn mud pack: Take a handful of fresh *Ocimum sanctum* Linn leaves and thoroughly wash them. Crush the leaves or grind them to make a paste. You can add a small amount of water if needed to achieve a spreadable consistency.

3. Apply the mud pack: Take the *Ocimum sanctum* Linn paste and apply it directly to the honey bee bite, covering the affected area completely. Make sure the paste is evenly spread and in contact with the skin.

4. Let it dry: Allow the *Ocimum sanctum* Linn.[22] mud pack to dry naturally on the skin. This may take around 15-20 minutes.

5. Rinse off the mud pack: Once the mud pack is dry, gently rinse it off with lukewarm water. Avoid rubbing the area vigorously.

6. Pat the area dry: After rinsing, pat the honey bee bite area dry with a clean towel.

XXXIII. RESULT AND DISCUSSION

The effectiveness of holy basil mud pack treatment in case of honey bee or wild bee bite was found effective and soothing and calm the patient or affected person in observation and understanding from the affected.

XXXIV. CONCLUSION

Melittin, a majour component of bee venom, has been studied for its potential medicinal applications. However, it is important to note that melittin can also cause adverse effects, including the development of hives (urticaria) in some individuals. Here is a summary of the medicinal study on melittin and its association with hives:

XXXV. Systemic symptoms: In some cases, the body's response to a bee sting can go beyond the local reaction. Systemic symptoms may occur, especially in individuals who are allergic to bee venom. These symptoms can include hives **(urticaria),** itching or tingling[28] in other parts of the body, difficulty breathing, swelling of the face, throat, or tongue, dizziness, and even anaphylaxis, which is a severe, potentially life-threatening allergic reaction. Thus, the structural study of various toxins presents in the bee venom when bee bites have been studied. Its bio-chemical composition and action on the body with its scientific chemical structure studies have been the majour focus and have been studied thorough the carried-out synopsis study.

1. Medicinal study on melittin: Melittin has been investigated for its antimicrobial, anti-inflammatory, anticancer, and neuroprotective properties. Research has shown its potential in inhibiting the growth of bacteria, viruses, and fungi, as well as its ability to modulate immune responses and exert cytotoxic effects on certain cancer cells.

2. Adverse effect: One of the known adverse effects associated with melittin is the development of hives or urticaria. Hives are characterised by itchy, raised, and red welts on the skin. They can occur due to an allergic reaction or direct irritation from substances such as: melittin.

3. Mechanism of urticaria: The exact mechanism by which melittin induces hives is not fully understood. It is believed that the release of histamine and other inflammatory mediators plays a role in the development of this allergic reaction. Individual sensitivity and immune response can vary, resulting in varying degrees of hives in different individuals.

4. Importance of safety evaluation: When considering the potential medicinal applications of melittin or any bee venom-derived substance, it is crucial to conduct safety evaluations. These evaluations help identify potential adverse effects, such as: hives, and assess the overall risk-benefit profile of the substance.

5. Further research: Although melittin has shown promising medicinal properties, including antimicrobial and anticancer effects, more research is needed to fully understand its therapeutic potential and safety. This includes studying the mechanisms of adverse effects, such as: hives, and finding ways to mitigate or avoid them through development of proper formulation and study of the development proper formulation studies to develop creams, gels and lotions using herbal material such as: plants leaves, flowers, stems, rhizomes and also by using synthetic chemicals like aspirin, cetirizine or anti-histaminic agents to combat the severe symptoms of pain. Use of sterile preparation and formulation that effectively soothes and clams the victims or patients are a in great interest of development and formulation for same purpose. Use of fullers earth and other calming agents into proper formulation to reduce the pain at the site of action of bee sting is the majour purpose why this study was conducted and its purpose to prepare was no availability of an effective handy remedy. Through a survey conducted about 99% of the people reported to use of mud pack that is collect form the holy basil pots for the effective treatment and calming of patients in the case of honey or bumble bees[27] sting.

In conclusion, while melittin has demonstrated potential medicinal properties, it is important to be aware of its association with hives (urticaria) as an adverse effect. Further research is needed to explore the mechanisms underlying this reaction and to ensure the safe and effective use of melittin and bee venom-derived substances in therapeutic applications. It is always advisable to consult with healthcare professionals before using any bee venom-derived products or considering

them for medicinal purposes, especially if you have a history of allergic reactions or skin sensitivity.

In conclusion, melittin has both toxicity and potential medicinal properties. Its toxicity requires caution in its administration, especially in individuals with allergies or hypersensitivity to bee venom. However, its antimicrobial, anti-inflammatory, anticancer, and neuroprotective effects suggest its potential therapeutic value, although further research is needed to fully understand its mechanisms, optimise dosages, and evaluate its safety in clinical settings.

XXXVI. Summary: Melittin, a majour component of bee venom, has been studied for its potential medicinal applications. However, it is important to be aware of its toxicity and adverse effects. Here is a brief summary of melittin toxicity and its medicinal aspects:

1. Melittin toxicity: Melittin can be toxic, especially when administered in high concentrations or in individuals who are hypersensitive or allergic to bee venom. It can cause local pain, swelling, and redness at the site of injection. In severe cases, systemic reactions such as: anaphylaxis, cardiovascular effects, and renal damage can occur.

2. Medicinal potential: Despite its toxicity, melittin has shown potential as a therapeutic agent. It exhibits antimicrobial properties, including activity against bacteria, viruses, and fungi. It also has anti-inflammatory, anticancer, and neuroprotective effects.

3. Antimicrobial activity: Melittin disrupts microbial membranes, leading to cell lysis and death. It has shown activity against various pathogens, including drug-resistant strains. However, further research is needed to determine its optimal dosage and delivery methods for clinical use.

4. Anti-Inflammatory effects: Melittin can modulate immune responses and reduce inflammation. It inhibits the production of pro-inflammatory molecules and promotes the release of anti-inflammatory factors, which may have implications for conditions such as: arthritis, asthma, and autoimmune disorders.

5. Anticancer potential: Melittin has demonstrated cytotoxic effects against cancer cells by inducing apoptosis (cell death) and inhibiting tumour growth. It shows promise as a potential therapeutic agent for various types of cancer, although more research is needed to fully understand its mechanisms and optimise its application.

6. Neuroprotective properties: Melittin has been investigated for its potential neuroprotective effects in conditions such as: Alzheimer's disease and stroke. It has shown the ability to protect neurons, reduce neuroinflammation, and improve cognitive function in preclinical studies. However, clinical trials are needed to assess its efficacy and safety in humans.

XXXVII. Study outcome: After the sever sting of the bee the bee venom results the disruption in the skin and let the venom percolate through the blood and paralysis the human. It also causes anaphylaxis shock in many humans and thus leading to hives. Most of the bee sting pain giving and sever at its first. If many of the bees stung together it cause great discomfort to the patient.

Through this investigation, it was found that use of tradition mud pack usage can lead to comfort of therapy in many people. Through the survey it was found that 99% of the people use natural mud pack to bee stung as an effective remedy and 1% of the people suck the part with mouth or apply saliva at the sight of bite or stung.

The bee bite/sting person was investigated and observed for pain produced and found that in an opinion to use of traditional mud pack was a satisfactory treatment and sooth the pain at the time.

The wild bee stung is very sever and gets adverse inflammation at the time the bee has stung to the patient. The patient feels pain, sever burn and inflammation, blurred vison, dark sight view and also drowsy in some cases. The pain very discomfort given and lead the patient to sever mental and emotional disturbance. The swelling is very painful and has a psychological concern associated with it. Therefore, both the physical and psychological attention to the patient is must during the time of patient care giving and also developing the newer pain relief medicine that is quick at the sight of action is an essential part of this study investigation. Development of newer treatment procedures are very essential in such cases and also proper therapeutics are a must.

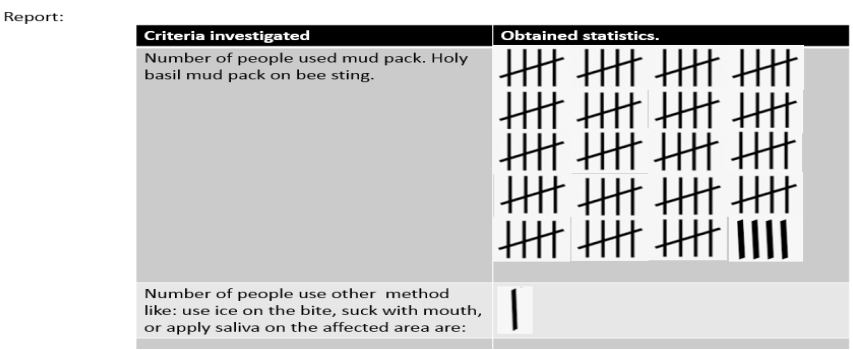


Figure 11: Statistical count of the implemented methodologies in treating of bee sting or the wasp sting.

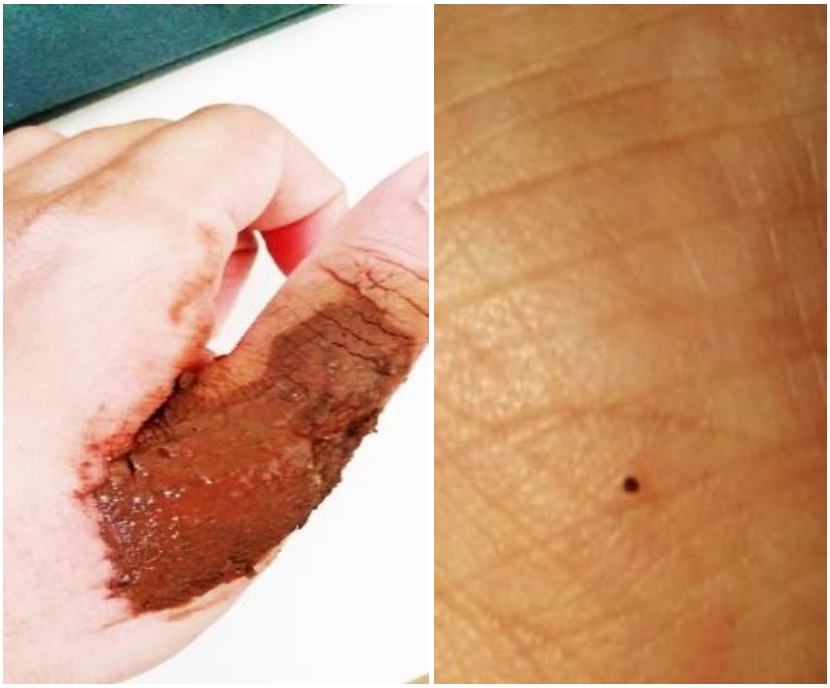


Figure 12: Image of the traditional treatment obtained form the incidence of bee sting.

Thus, it is clear from the above observation and statistics count that the maximum number of people are dependent on the usage of traditional methods in treating the bee sting due to the unavailability of particular medicines to treat it in the market. Therefore, through this study report, it can be understood that about 99% of people do not seek any medical attention for bee or wasp bites and treat them effectively with mud plaster or mud pack traditionally. However, an alternative therapeutic is much more essential for prescription purposes in the case of a requirement for medicinal treatment. In such cases, it is very important to have developed formulations for such uses. Either of the categories belonging to the OCT or, otherwise, a prescription category of drug product. An effective herbal remedy of scientific interest will also suffice to meet the requirements of such medical cases and their medicinal treatment. Media: Ingredient for medicinal treatment.

XXXVIII. Acknowledgement

XXXVIII. a. Special acknowledgements: I would like to present my special thanks to Dr. Valentina Petkova madam; editor in chief Vice Dean of Foreign students education and International Integration, Faculty of Pharmacy, Medical University-Sofia, 2-Dunav str., Sofia-1000, Bulgaria for providing some funding necessary to publish this article in this journal: The Society for Advance Healthcare Research's official publication is the EJBPS-European Journal of Biomedical and Pharmaceutical Sciences, registration number 01/01/01/31674/16-2349-8870. Thank you so much for your assistance in helping me publish this article and for contributing to the some of the cost of doing so.

XXXIX. Conflict of interest: None. Author expresses no conflict of interest in publishing this work.

XL. Funding sources: None/Nil. No funding has been provided to carry out this research work and is carried out of independent expenses.

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