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Bee Venom and Its Therapeutic Uses

Arı Zehri ve Terapötik Kullanımı

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Abstract

The use of honey and other bee products goes back thousands of years. In fact its therapeutic benefits are mentioned in sacred books such as (Veda, the holy book of India), (the Bible, of Christians) and the Noble Quran. Apitherapy is the use of bee products for medical purposes, which including honey, royal jelly, propolis, flower pollen, and especially bee venom, is known as apitoxin. Apitherapy involves the use of various bee products for medical purposes, such as honey, royal jelly, propolis, flower pollen, and primarily bee venom, also known as apitoxin. Bee venom contains of at least 18 pharmacologically active compounds including enzymes such as phospholipases, peptide and amino acid compounds such as melittin, which has anti-inflammatory properties. Other properties such as anti-apoptotic and anti-cancer properties have also been reported for bee venom. Since, as the lethal dose (LD_{50}) of the venom for humans is 2.8 mg/kg per kilogram of body weight, it is a safe combination for therapeutic purposes. Bee venom has a great potential in the treatment of inflammatory diseases and the central nervous system diseases such as Parkinson's, Alzheimer's, myotrophic sclerosis and various types of cancer. Also, due to its antiviral activity, it has been effective even against the human immunodeficiency virus (HIV). Due to the prevalence of diseases in today's societies, makes it essential to find new treatment solutions. On the other hand, the drugs used in traditional medicine play an important role in the treatment of diseases. Among these natural substances is bee venom¸ which should be taken into considered in the treatment of diseases because of its many therapeutic properties.

Keywords: Bee Venom, Historical Records, Therapeutic Uses, Structure

Özet

Bal ve diğer arı ürünlerinin kullanımı binlerce yıl öncesine dayanmaktadır. Aslında tedavi edici faydalarından Hindistan'ın kutsal kitabı Veda, Hıristiyanların İncil'i ve Kuran-ı Kerim gibi kutsal kitaplarda bahsedilmektedir. Apiterapi, bal, arı sütü, propolis, çiçek poleni ve özellikle arı zehirini içeren arı ürünlerinin tıbbi amaçlarla kullanılmasıdır ve apitoksin olarak bilinir. Apiterapi, bal, arı sütü, propolis, çiçek poleni ve özellikle apitoksin olarak da bilinen arı zehiri gibi çeşitli arı ürünlerinin tıbbi amaçlarla kullanılmasını içerir. Arı zehiri, fosfolipazlar gibi enzimler, peptid ve anti-enflamatuar özelliklere sahip melittin gibi amino asit bileşikleri de dahil olmak üzere farmakolojik olarak aktif en az 18 bileşik içerir. Arı zehiri için anti-apoptotik ve anti-kanser özellikleri gibi diğer özellikler de bildirilmiştir. Zehrin insanlar için öldürücü dozu (LD_{50}) vücut ağırlığının kilogramı başına 2,8 mg/kg olduğundan, tedavi amaçlı güvenli bir kombinasyondur. Arı zehiri, iltihaplı hastalıkların ve Parkinson, Alzheimer, miyotrofik skleroz ve çeşitli kanser türleri gibi merkezi sinir sistemi hastalıklarının tedavisinde büyük bir potansiyele sahiptir. Ayrıca, antiviral aktivitesi nedeniyle, insan immün yetmezlik virüsüne (HIV) karşı bile etkili olmuştur. Günümüz toplumlarında hastalıkların yaygınlığı, yeni tedavi çözümlerinin bulunmasını zorunlu kılmaktadır. Öte yandan, geleneksel tıpta kullanılan ilaçlar hastalıkların tedavisinde önemli bir rol oynamaktadır. Bu doğal maddeler arasında, birçok tedavi edici özelliği nedeniyle hastalıkların tedavisinde dikkate alınması gereken arı zehiri de yer almaktadır.

Anahtar Kelimeler: Arı Zehiri, Tarihsel Kayıtlar, Tedavi Amaçlı Kullanımları, Yapısı

1. INTRODUCTION

Among the many species of insects, only a-few insects have the ability to defend themselves by stinging and injecting venom when bitten. All insects that can sting belong to the order Hymenoptera, which includes ants and bees. The stinger is always at the end of the abdomen or near it. Each bee is a clear liquid that dries easily even at room temperature, odourless with a bitter taste. It forms greyish-white crystals when exposed to air. Dried venom takes on a pale yellow color, and some commercial products are brown, which is thought to be due to oxidation of some of proteins in the venom. Most venoms are sold as dry crystals (Ali et al., 2012). Bee venom is produced by female worker bees (Trumbeckaite et al., 2015). Bee venom is a natural poison produced by bees and plays an important defensive role for the bee colony. This material has an efficient and complex combination of ingredients designed to protect bees from predators (Lee et al., 2015). Bee venom contains at least 18 medically active compounds. Bee venom is safe for humans treatment, the median lethal dose (LD_{50}) for an adult human is 2.8 mg of venom per kilogram of body weight. Assuming that each bee injects all of its venom and that each sting contains 0.3 mg of venom, therefore 560 stings could be fatal for such a person. For a child weighing 10 kg, 93.33 stings can be fatal (Ali et al., 2012).

The idea of using BV in the field of medicine came from the belief that beekeepers hardly suffer from rheumatism or joints (Wehbe et al., 2019). This venom contains active peptides such as melittin, apamin, mast cell degranulation peptide, adolapin and enzymes such as phospholipase A2 and hyaluronidase (Trumbeckaite et al., 2015). As well as non-peptides such as histamine, dopamine and norepinephrine (Lee et al., 2015). Bee venom has been widely used in research to treat some diseases such as rheumatoid arthritis, and multiple sclerosis in traditional Eastern medicine. It is known as a natural anti-inflammatory agent (Ali et al., 2012).

One of the components of bee venom is melittin peptide.The cationic and amphipathic peptide melittin has 58 amino acids, the first 57 amino acids of this peptide are mainly hydrophobic, while the amino acids at the carboxyl end (amino acids 20 to 26) are hydrophilic with a positive electric charge. Treatment with bee products has been widely used in the past. In most countries, bee products are considered traditional medicines. Among complementary and alternative medicine methods, they have been shown to be effective in preventing some common diseases as relatively strong food supplements. Lithuania has very old beekeeping traditions and bee products have been used in folk medicine for centuries. They are used for cough, wound, tuberculosis and other diseases (Trumbeckaite et al., 2015). Interestingly, bee venom, similar to the venom from other animals, has shown a useful anti-viral and anti-cancer potential and has been effective against ovarian and prostate cancer as well as HIV (Wehbe et al., 2019). Studies have shown the ability of BV and its main component, melittin, to induce elevated levels of glucocorticoids, which may be responsible for its anti-inflammatory effects. High levels of GCs have been found after administration of BV (Racheda et al., 2010).

2. HISTORY

The roots of Apitherapy date: back to ancient Egypt 6000 years ago. In ancient Greece, bee products were used therapeutically. There is also evidence that honey was a part of traditional Chinese medicinal treatment. A famous ancient manuscript book with fifty-two copies from the 3rd century BC. Found in Changsha, Hunan Province, it contains two manuscripts about bees, one of which uses honey to treat diseases (Trumbeckaite et al., 2015). In the United States, the history of beekeeping (Figure 1) goes back about 100 years, which was described by several prominent physicians from So said Dr. Bodag Beck, who began treating people in his New York City office in the late 1920s. Dr. Beck's book "Bee Venom Treatment" has been used for 60 years. Dr. Beck's last surviving student is Middlebury, Vermont beekeeper Charles Marz, known by many as the "King of Bee Venom Therapy." He has been practicing apitherapy for

over 60 years with remarkable results, and most of his experience has been in the treatment of arthritis, but his success has been with multiple sclerosis (MS) (Ali et al., 2012).

Figure 1. *Apis mellifera*

3. MELITTIN

The main component of bee venom is bee venom. It is a fully cationic peptide of 26 amino acids (Figure 2). It is an amphoteric peptide whose terminal carboxyl region is hydrophilic and the terminal amino region is hydrophobic due to the presence of a group of positively charged amino acids. Melittin exhibits amphiphilic properties (hydrophilic and hydrophobic) when interacting with biological membranes or enzymes.

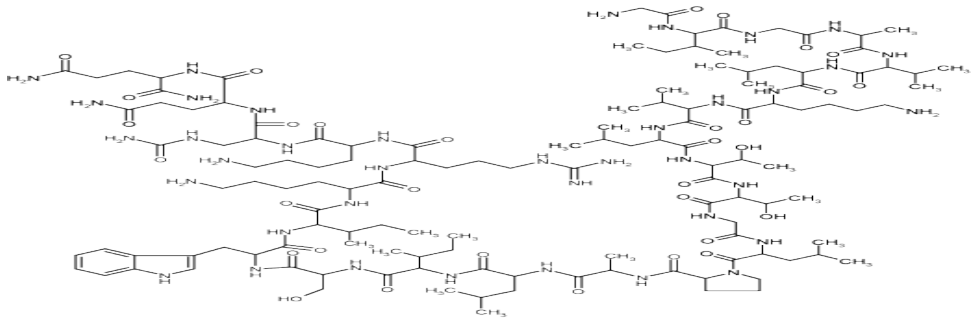

Figure 2. Structure of melittin

Melittin is the major component of bee venom, which makes accounting for approximately 40-50% of the dry powder weight of the venom. It is a small linear peptide with the chemical formula $C_{131}H_{228}N_{38}O_{32}$. Melittin forms a peptide that can penetrate the phospholipid bilayer as four polymers and is therefore able to study the interaction between the

bioactive membrane and the peptide through biological activity. Previous studies have shown that the mechanism of action of melittin to disrupt of membranes by creating pores that act non-specifically on both prokaryotic and eukaryotic cells. Melittin works with an activator called phospholipase A2, which has an increasing effect on PLA2 activity. Melittin can also act as a PLA2 activator. Interest in the medicinal properties of melittin has increased greatly in recent decades. Depending on its concentration, this biopeptide can induce both transient and persistent pores. When a transient pore is formed, only ions from the membrane can diffuse through it.When, if stable pores are formed, the membrane becomes permeable to relatively large molecules such as glucose. The formation of pores caused by melittin is responsible for its haemolytic, antimicrobial, antifungal and antitumour activities. Recently, melittin has been shown to cause smooth changes along pain signalling pathways by activating and sensitising nociceptive cells. It is also a major biologically active ingredient constituent of BV that producing analgesic, anti-inflammatory, and anti-arthritic effects after consumption (Wehbe et al., 2019).

Melittin is a compound that has been studied for a series of biological properties. The anti-inflammatory activity of melittin is mediated by several mechanisms. Basically, this mechanism involves blocking toll-like receptors (TLRs) receptors, CD14, 42) and platelet growth factor beta receptors. In addition, melittin has an inhibitory effect on a nuclear factor (kappa-B) (NF-kB). All these pathways lead to the release of molecules such as inflammatory cytokines, tumour necrosis factor (TNF), nitric oxide (NO) or prostaglandin (E2). (PGE) into the extracellular environment or blood vessels prior to inflammation. All of these molecules have inflammatory effects on tissues. Therefore, mellitin’s ability to prevent the production of these molecules, proves its anti-inflammatory properties (Klocek et al., 2009).

Melittin inhibits the pathways of TLR2, TLR4, CD4, NEMO and PDGFRβ thereby inhibiting the function of pro-inflammatory genes (Figure 3). This process leads to a reduction in the levels of pro-inflammatory molecules and a reduction in inflammation. Recently, a comprehensive review on the subject has been published, which summarising in vitro and in vivo studies and suggesting that one of the main mechanisms of melittin's antiviral activity is its interaction with enveloped viruses (or capsid proteins). Another mechanism by which shows this activity is the interaction demonstrated is that melittin, not only with the surface of the virus but also with the virus itself, which causing the host cells to avoid infection (Memariani et al., 2020). Melittin can inhibiting virus replication by stimulating type I interferon (I -IFN). Therefore, it can be an excellent method for pretreatment (Huang et al., 2012).

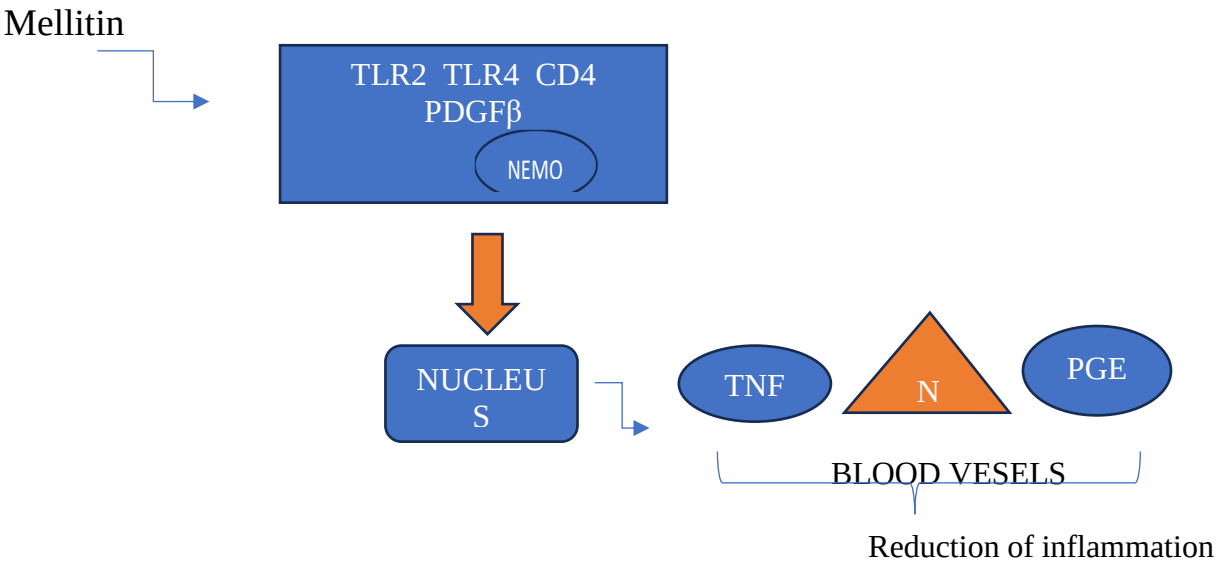

Figure 3. The mechanism of action of the anti-inflammatory effects of melittin

3.1. Physiological Properties of Melittin

Melittin is a polypeptide that is at a physiological pH of +6. One of the four positive charges is in the C-terminal region and the rest are two charges in the Lys-7 and N-terminal groups. Although non-polar amino acids cover a large part of the structure of the melittin, this peptide is partially soluble in methanol but very soluble in water. The three-dimensional structure of melittin tetramer by NMR method, with temperature change, shows that melittin has a structural transition between monomer and tetramer in aqueous solution, and this change has much to do with the remaining proline isomers in the melittin structure. Based on these studies, melittin is considered an important candidate for antibiotic-resistant bacteria, cancer and tumour treatment, and pathogenic viruses (Huang et al., 2016). For example, melittin can increase the cell growth of human ovarian cancer cells by increasing the expression of death receptors (DR3, DR4 and DR6) and inactivation of transcriptional signal transducers and activation of the pathway (STAT3) that ends in cell apoptosis (Carpena et al., 2020).

Recent studies have shown that melittin can induce cell cycle arrest, cell growth inhibition and apoptosis in various tumour cells. When multiple melittin peptides accumulate in the cell membrane, phospholipid packing is severely disrupted, leading to cell lysis. Melittin not only lyses a wide range of plasma membranes but also stimulates intracellular membranes such as those found in mitochondria. PLA2 and melittin act synergistically and break the membranes of sensitive cells and increase their cytotoxic effect. However, on article reported

that melittin does not disrupt the cell membrane of leukocytes at concentrations bellow 2 μM (Lee et al., 2005).

4. APAMIN

Apamin is an integral part of honey bee venom, accounting for approximately 2-3% of the dry weight (2111.4 daltons). It is a peptide neurotoxin consisting of 18 amino acids, which are tightly linked by the presence of two disulfide bonds (PubChem Apamin 2020). Although there are different models for the structure, studies show that the combination of an alpha helix has high stability at different pH. One of the interesting features of apamin is its permeability across the blood-brain barrier, indicating that apamin can access the central nervous system (CNS) (Palma 2013).

In addition, apamin can inhibit M2 muscarinic receptors in motor nerve endings and reduce muscle nerve transmission (Silva et al., 2010). In addition to its effects on the CNS, apamin is considered an anti-inflammatory agent that can inhibit cyclooxygenase-2 and reduce levels of TNF-, IL-1 (interleukin-1), IL-6 and NO (Shin et al., 2018; Lee et al., 2020). Apamin is known for its pharmacological properties in irreversibly blocking Ca2+-activated K+ channels (Lamy et al., 2010). These channels alter intracellular calcium by increasing K+ flux following an increase in intracellular calcium during an action potential associated membrane potential (Bond et al., 2004). Recent studies have investigated its biological and medicinal activities. However, little is known about the molecular mechanisms and levels of gene regulation involved in the anti-inflammatory process (Lee et al., 2015).

5. MAST CELL DEGRANULATING (MCD)

A polypeptide (401 peptide) containing 22 amino acids with a molecular weight of 2587.2 Da. and structurally similar to apamin, as both contain two disulfide bonds. It makes up 2-3% of the dry weight of BV. It also has two disulphide bridges linling aa 3, 15, 5, and 19. At physiological pH, it has a net charge of +8. (https://pubchem.ncbi.nlm.nih.gov 2020) (Ziai et al., 1990) At low concentrations, less than 0.1 mg/ml, MCD causes mast cell degranulation (Carpena et al., 2020). The name MCD reflects the biological action of histamine release from mast cells. an important inhibitor of K+ channels, and can cause a decrease in blood pressure in mice. (Hanson et al., 1974) Studies present MCD as a potent anti-inflammatory agent and may be a potential candidate for studying the mechanisms of inflammatory cells. act like mast

cells, basophils and leukocytes, which will lead to the design of compounds with therapeutic applications (https://pubchem.ncbi.nlm. nih.go, 2020)

6. ADOLAPIN

Adolapin is a polypeptide of 103 amino acids. This represent to 1% of the dry weight of BV. Researchers have shown that adolapin has anti-inflammatory, analgesic, and antipyretic effects by blocking prostaglandin synthesis and inhibiting cyclooxygenase activity (Park et al., 2011).

7. PHOSPHOLIPASE A2

PLA2, the most lethal enzyme and usually the major allergen in BV, consists of a single polypeptide chain of 128 amino acids containing four disulfide bridges. It is shown that 12-15% of the dry weight (Fenard et al., 2001) is BV (15-18 kDa). And to maintain structural stability, this enzyme has five disulfide bonds between amino acids 30-70, 31-9, 37-63, 61-95 and 113-105. There is a wide variety of PLA2 in nature, and these enzymes are classified into 16 groups. In particular, bee-derived PLA2 (bPLA2) belongs to group III (Jung et al., 2018).

This substance is very alkaline. It is interesting to note that its activity can be improved with melittin. A synergistic effect between bvPLA2 and melittin which occurs during the erythrocyte lysis process has been demonstrated and proves its existence. New experimental data have also shown that bvPLA2 elicits protective immune responses against a wide range of diseases such including asthma, Alzheimer's disease, and Parkinson's disease (Wehbe et al., 2019). It has also shown high cytotoxic activity against cancer cells with membrane disruption. Membrane disruption also confers antimicrobial activity to bPLA2 (Carpena et al., 2020) In addition, bPLA2 can act as a ligand for specific receptors. Thus, bPLA2 can bind to specific membrane receptors and generate cellular signals independent of their enzymatic activity. Two types of receptors have been identified for bPLA2: Type M and type N. (24) M Type receptors are found in skeletal muscle cells. N-type receptors are associated with the neurotoxic activity of bPLA2 (Hong et al., 2019)

8. HYLURONIDASE

Hyaluronidase makes up 1.5 to 2% of the dry weight of BV (Wehbe et al., 2019). It has 350 amino acids and one disulphide bridge (Carpena et al., 2020) It is known to break down

hyaluronic acid in tissues. Hyaluronidase allows the active components of BV to work in the victim's tissues by creating structural integrity and increasing blood flow to the effective area (Wehbe et al., 2019).

9. THERAPUTIC USES OF BEE VENOM

9.1. Anti-inflammatory

Inflammation is the body's protective response to harmful stimuli. Chronic inflammation can lead to the development of several diseases such as rheumatoid arthritis (RA), diabetes, cardiovascular diseases, obesity, asthma, skin disease and CNS-related diseases such as Parkinson's and Alzheimer's (Rim Wehbe et al., 2019). There are at least four major BV compounds that have anti-inflammatory properties (Lee et al., 2016).

Melittin, when administered in high doses, causes local pain, itching and inflammation. However, low doses of this BV compound can have broad anti-inflammatory effects. Many reports have investigated the anti-inflammatory mechanisms of melittin in various diseases such as rheumatoid arthritis (RA) and amyotrophic lateral sclerosis (ALS). In fact, it works by inhibiting inflammatory cytokines such as interleukin-6 (IL-6), IL-8, tumour necrosis factor- (TNF-) and interferon (IFN). The NF-κB pathway through a group of transcription factors plays a vital role in host immune and inflammatory response activities. In vitro, melittin can suppress nuclear NF-κB activation. Its anti-inflammatory effect is mediated by the reduction of IgE levels, and the release of cytokines and NF-kB (Carpena et al., 2020).

These studies showed that by blocking their primary signalling pathways, melittin inhibits inflammatory cytokines, which then leads to a reduction in inflammation in the skin, liver, joints and nervous tissue. In skin disease, a recent finding by Kim et al. showed that BV reduced atopic dermatitis, the most common chronic inflammatory allergic skin disease (Rim Wehbe et al., 2019)

9.2. Treatment of nervous disease

Parkinson's disease is a degenerative movement disorder that causes progressive disability in patients. The pathological hallmark of this disease is the progressive loss of dopaminergic neurons in the substantia nigra (the basal ganglia structure in the human brain) (Goldman et al., 2014; Aarsland et al., 2017). Abnormal microglial activation is also a pathological hallmark in several neurodegenerative diseases including PD (Iakovakis et al., 2018). Most clinical studies

show the effect of BV on leukocyte migration or microglial activation in animal and cellular models. Other studies have investigated the neuroprotective potential of BV acupuncture. Treatment with BV against rotenone-induced oxidative stress shows neuroinflammation and apoptosis in PD mouse models. Rotenone is a pesticide that may affect the pathophysiological mechanisms involved in PD (Aksoz et al., 2019). Interestingly, BV demonstrated its ability to prevent dopamine depletion after rotenone administration. Furthermore, locomotor activity was restored after treatment of PD with BV in a mouse model. The treatment effectively suppressed DNA damage and inhibited the expression of apoptotic genes Bax, Bcl-2 and caspase-3 in the brain of PD mice. These results show that BV normalises all markers of apoptosis and neuroinflammation after rotenone injury and restored brain neurochemistry (Khalil et al., 2015). BV has also been shown to protect against dopaminergic neuron degeneration in PD models (Wehbe et al., 2019).

Alzheimer's disease is the most common neurodegenerative disease and many pathological processes are involved in its development (Aksoz et al., 2019). Although the cause of AD remains unknown, evidence suggests that inflammatory responses may play an important role in its pathogenesis (Eldik et al., 2016; Kinney et al., 2018). Current treatments for cognitive decline in Alzheimer’s disease rely on the use of muscarinic or nicotinic receptor ligands and acetylcholinesterase (AChE) inhibitors (Terry et al., 2003). As an alternative strategy, Ye et al. (2016) showed that bvPLA2 could be used as a therapy to prevent the progression of AD in transgenic mice. The same study also shows that bvPLA2 can increase brain glucose metabolism and reduce neuroinflammatory responses in the hippocampus, thereby limiting the pathogenesis of AD (Ye et al., 2016). Amyotrophic Lateral Sclerosis (ALS) is a CNS disease that causes the death of motor neurons (Rajagopalan et al., 2019). Interestingly, BV has shown a special potential to deal with this disease (Jaarsma et al., 2000).

9.3. Use of bee venom in cancer

The use of apitoxin, especially its major component melittin, as a new strategy for cancer treatment has recently gained great importance (Junget al., 2018; Lim et al., 2019). Indeed, melittin is known to be a non-specific cytolytic peptide that can attack the lipid bilayer, thus resulting in significant toxicity when administered intravenously (Hong et al., 2019). However, many optimization approaches, including the use of melittin nonparticle-based delivery, have been exploited. It is noteworthy that raw BV as well as anti-tumour melittin have shown activity

against various types of cancer cells including breast, liver, leukaemia, lung, melanoma and prostate cancer cells (Liu et al., 2002; Jung et al., 2018; Hong et al., 2019). Park et al. (2011) also reported that BV and its major component, melittin, inhibited cancer cell growth both in vitro and in vivo through activation of caspase 3 and 9 pathways and inhibition of NF-κB signalling and anti-proliferative gene products. Apoptosis such as Bcl-2, cIAP-2, iNOS, COX-2 and cPLA2 (Park et al., 2011). Similarly, Zheng et al. (2019) showed that BV has an anti-proliferative effect and induces apoptosis through the activation of death receptors. Another interesting finding about melittin came from by highlighting its anti-growth and anti-metastatic properties (Figure 4). In cancer, metastasis and malignant cell attack are the main causes of disease progression (Wehbe et al., 2019). Therefore, cancer researchers have focused on understanding the molecular mechanisms that regulate malignant cell migration and possible ways to prevent it, as an important step in the fight against cancer (Rajabi et al., 2017; Zuazo-Gaztelu et al., 2018). In another study, results showed that bee venom can be used as a selective DNA(de)methylatorr in cancer. And suggest the use of bee venom or any component for epigenetic therapy in cancer cells (Uzuner et al., 2021).

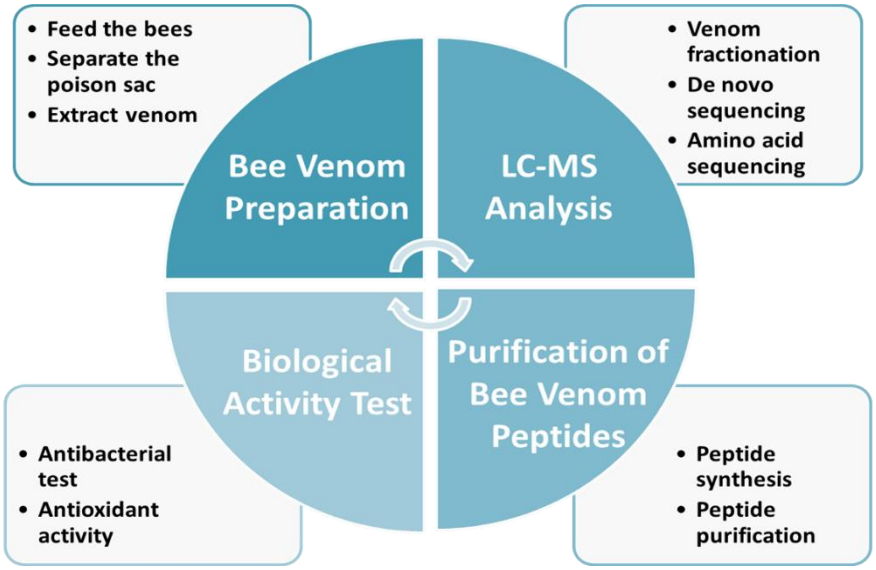

Figure 3. Schematic drawing of the main purification of action of Bee venom as an anti-bacterial agent

9.4. Antibacterial and antiviral properties

It is well known that BV with its two main components (melitin and PLA2) has antimicrobial activity and therefore can be used as an antibacterial supplement. These compounds act their

effects against bacteria by creating pores in their membranes, which leading to their splitting and then lysis (Park et al., 2004). BV components have antibacterial activity against gram + and gram bacteria and It is antifungal (Carpena et al., 2020). However, the antiviral effect of BV has not been reported much. A recent study investigated the antiviral potential of BV and yielded interesting results both in vivo and in vitro. This study showed that BV and melittin have significant antiviral effects against enveloped viruses (vesicular stomatitis virus, influenza A virus, herpes simplex virus, etc.) and non-enveloped viruses (enterovirus-71 and coxsackievirus) in There are many laboratory conditions (Uddin 2016).

The study also showed that melittin protected mice were exposed to lethal doses of H1N1 influenza A virus. Although the exact mechanism of action of BV and melittin as antiviral agents is unclear, it has been confirmed that BV directly interacts with the viral surface. In addition, BV and its components can stimulate type I interferon (IFN), thereby suppressing viral replication in the host cell (Bachis et al., 2010).

In addition, researchers at the Washington University School of Medicine in St. Louis reported the potential use of melittin-loaded nanoparticles to destroy the human immunodeficiency virus while leaving uninfected cells unharmed. It also suggests a preventive strategy in which these nanoparticles are used to make a vaginal gel that prevents the spread of HIV. The principle of its theory is as follows: the melittin molecules in the nanoparticles combine with the viral coating and form attack complexes and pores, thus breaking the virus (Hood et al., 2013). Another study showed that bvPLA2 can also prevent viral replication. The same team identified the peptide sequence of bvPLA2, which is responsible for inhibiting HIV replication. (Fenard et al., 2001)

9.5. Anti arthritis

Bee venom (BV) has been used as a traditional alternative medicine for pain relief and treatment of inflammatory diseases, such as rheumatoid arthritis (RA) in humans (Lee et al., 2015). RA is one of the most common inflammatory pathologies, the prevalence of which is between 0.2-0.9% (Carpena et al., 2020). Several studies have shown that BV treatment for RA in humans and experimental animals has an anti-inflammatory effect (Park et al., 2004). Bee venom contains several active pharmaceutical ingredients that can be effective in the treatment of arthritis. Regulation of radical production, suppression of gene induction of alpha-1 acid

glycoprotein, and inhibition of phospholipase A2 (PLA2) activity have all been suggested as effects of its possible anti-inflammatory mechanisms. Like snake venom, PLs are the main active components of BV (Lee et al., 2005).

These chemical mediators are normally released from phagocytic lysosomes during inflammation and cleave phospholipids from the cell membrane to produce arachidonic acid, which is ultimately converted to prostaglandins (PGs) (Zurier et al., 1973). Additionally, PLA2 has been shown to be an inhibitor to prevent acute and chronic inflammation (Garcia-Pastor et al., 1999) as it has been shown that PGs have a suppressive and preventive effect against arthritis induced by adjuvants in rats (Zurier and Quagliata, 1971). Therefore, the injection of bee venom in rats with arthritis may have the same therapeutic effect as PGs or anti-inflammatory drugs. In experimental animals, adjuvant-induced arthritis has been shown to be suppressed by long-term treatment of BV and/or or its compounds are also reported to be effective in the treatment of RA in humans) (Eiseman 1982; Hadjipetrou-Kourounakis 1984) Recently, it has been shown that BV produces anti-inflammatory effects in an arthritis model induced by complete Freund's adjuvant (CFA) (Kang et al., 2002). Due to the increase in the prevalence of side effects of the pharmaceutical approach to inflammatory diseases, there is an urgent need for better treatment to reduce the symptoms of these disorders. Overall, treatment using bee venom and its main components is considered a useful clinical approach for the treatments of inflammatory diseases. As bee venom contains a number of other components, advances in modern sequencing techniques offer new opportunities to combat other inflammation-related diseases (Lee et al., 2015).

9.6. Anti oxidant properties

BV contains components with antioxidant activity. This activity is usually related to the concentration of melittin, PLA2 and apamin. These effects may be due to by the ability of these compounds to inhibit the process of lipid peroxidation and increase the activity of superoxidase dismutase. Also, the increase of GST and GSH has been shown in treated rabbits (Carpena et al., 2020).

10. PRODUCTS

There are no known uses for the poison other than medical ones. Since the early 1980s, pure bee venom has been used for desensitizing (Bee Well, 1993). In Eastern Europe and in many Asian countries, bee venom has been used in the official treatment of various diseases for a considerable period of time. The methods of using venom include natural bee stings, subcutaneous injections, ointments, inhalations, and pills (Sharma and Singh 1980). Depending on the patient being treated, bee venom can be used as a cream, ointment or injection form. For injection, the venom can be mixed with injectable liquids such as distilled (sterile) water, saline solutions, and special oils at the time of injection, or it may be taken from ready-made ampoules. There are creams available that contain bee venom (such as Furapin and Apicosan in Germany, Apion in France and Eminin in Austria) for external application to arthritic joints. Entering this limited market requires a highly advanced laboratory and highly trained technicians and chemists (Krell 1996).

11. BEE VENOM SAFETY

Compared to other human diseases, accidents and other unusual cases, bee venom is very safe for human treatment (Rose 1994). Statistics for Deaths from Diseases, Accidents, and Other Unusual Causes in the United States in 1986 Of the 2,086,440 deaths in the United States in 1986, 977,700 died from heart disease. (46.86%) of all deaths. Total number of cancer deaths 641,400 (30.74%), smoking 150,000 (7.19%), asthma 3,880 (0.186%), penicillin allergy 300 (0.014%), insect stings (except bees) 24 (0.0012%), has been While there were 17 cases by honey bees. Although bee venom is safe for human treatment, it should only be used under the supervision of a qualified health care professional (Ali 2012).

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DECLARATIONS

No conflict of interest or common interest has been declared by the authors.

AUTHOR CONTRUBITIONS

The first draft of the manuscript was written by Haydeh Keyhan and all authors commented on previous versions of the manuscript, read and approved the article.

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