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From Bee Venom to Drug: A Short Review

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Abstract

Apitherapy is an alternative medicine that treats a variety of human ailments by using honeybee products, most notably bee venom. Bee stings or hand injections are two ways venom might enter a human's body. Peptides and enzymes, among other active chemicals, found in bee venom have the potential to be very beneficial in treating inflammation and disorders of the central nervous system, including amyotrophic lateral sclerosis, Parkinson's disease, and Alzheimer's disease. Furthermore, studies using bee venom have demonstrated encouraging results against many cancer forms and antiviral activities, including against the difficult human immunodeficiency virus (HIV). This article aims to provide an overview of the principal components of bee venom, including its key biological features, modes of action, and therapeutic benefits when used in conjunction with alternative medicine approaches. Many research publications have suggested that bee venom, either directly from a bee sting or as an injectable, can be used to treat various difficulties either in vivo or in vitro. The purpose of this paper is to discuss the usage of bee venom, either whole or in fractions, as an alternative therapeutic strategy for a variety of illnesses and medication toxicities.

Keywords: Apitoxin; Apitherapy; Bee venom; Neurodegenerative diseases; Cancer; HIV

Introduction

Apitherapy is a form of non-traditional treatment that utilizes honeybee substances, particularly bee venom, to address various human health issues (Zhang et al., 2018; Wehbe et al., 2019). Various religious relics refer to the beneficial properties of honey and other products (Mraz, 1995). Apitherapy involves the use of various bee products *viz*. honey, propolis, and venom, especially from the European honeybee, *Apis mellifera*, as medicine, a practice that has been employed for many centuries by humans. Bee venom has been utilized for medicinal reasons dating back to Egypt and Greece, as well as for 3000-5000 years in China. Hippocrates, a Greek doctor from ancient times, used bee-venom for medical reasons (Bogdanov, 2016). More recently, the Russians, Lubarski and Lokumski, reignited curiosity about the impact of bee venom in 1868 with their publication "Bee Venom, a Remedy" (Urtubey, 2005). Doctors and certified bee venom therapists now use honeybee venom to help people with chronic or autoimmune conditions. Research conducted in clinical settings and laboratories has confirmed that bee venom can be utilized as a valid form of biotherapy. The venom of honeybees can (68) act against inflammation and damage to connective tissues like in rheumatism and arthritis, or enhance the body's natural defence to restore activity and mobility in conditions such as multiple sclerosis and lupus (Rho et al., 2009).

Hymenopterans (Bees, ants, and wasps) can cause harm to humans using their stinging tool defensively or aggressively, resulting in poisoning. Certain hymenopterans are solitary, while others have a specific role, like pollinating bees and parasitoids. Predators often suffer intense pain from the toxins of coexisting creatures in colonized areas. Stinging is one of the most fascinating behaviours exhibited by hymenopteran insects. Different factors, like visual signals and vibrations, result in stinging reactions. Moreover, vibrations produced by nests and the irritation of workers can result in stinging or venom injection (Akre et al., 2009).

Bee venom, also known as api-toxin, is secreted by glands present in the abdominal region of bees. Bees often use this odourless, acidic liquid as a form of defence against predators. Many sources have mentioned that bee venom contains various active elements, such as peptides, enzymes like phospholipase A2 and hyaluronidase, and non-peptide substances like dopamine, histamine and

norepinephrine. Other components such as melittin, adolapin, apamin, and mast cell degranulating peptide are all also present in bee venom (Wehbe et al., 2019; Moreno et al., 2015). Melittin, constituting approximately 50% of the dry venom, and phospholipase A2 (PLA2), making up around 12%, are the main components (Gajski et al., 2013).

Bee venom have been used in traditional medicine for treating chronic inflammatory conditions due to their various benefits, such as their abilities to reduce arthritis, fight cancer, and alleviate pain (Gajski et al., 2013; Im et al., 2016). Bee venom therapy involves injecting lyophilized venom extracted from bees in various dosages at the site of treatment, while bee sting therapy involves honeybees traveling to the target location and stinging directly (Ali, 2012; NIH, 1995). Bee venom injections can treat a range of conditions such as autoimmune disorders (e.g., rheumatoid arthritis, psoriasis), neurological disorders, chronic inflammation, pain, skin conditions, and microbiological infections (Zhang et al., 2018; Bogdanov, 2016; NIH, 1995).

Physical Characteristics and Constituents of Bee Venom

The transparent venom of honeybees has a specific gravity of 1.13, a strong, unpleasant taste, and a pH range of 4.5–5.5 (Bhalotia et al., 2016; Szabat et al., 2019). The poison from honeybees rapidly dries and forms crystals upon exposure to air (Kolayli et al., 2020). It is believed that the pale-yellow colour of dried venom and the brown colour of commercial preparations are caused by the oxidation of specific venom proteins. It can be dissolved in water but remains unable to dissolve in ammonium sulphate and alcohol. Numerous extremely unstable chemicals in bee venom are rapidly depleted during the harvesting process (Ali, 2012).

Reports indicate that honeybee venom consists of a diverse array of components. Bees often use its venom as a defensive tool against predators. Primarily, one drop of bee venom contains 0.1 µg of dry venom and rest is made up of water (Bellik, 2015). Other constituents include complex mixture of MCD-peptide, apamin, melittin, and adolapin peptides. Moreover, it consists of minerals, small chemicals such as bioactive amines, and enzymes, with PLA2 being the most important among them. Enzymes like phospholipase A2, phospholipase B, hyaluronidase, lysophospholipase, phosphatase, and acid phosphomonoesterase, are present along with smaller proteins and peptides like tertiapin, apamin and secapin (Moreno et al., 2015).

Additional components feature phospholipids as well as biologically active amines such as histamine, dopamine, and noradrenaline. Other elements consist of amino acids, sugars like glucose and fructose, pheromones, and minerals such as calcium and magnesium. Melittin, composed of 26 amino acids, is the primary element of honeybee venom and makes up 40-50% of the dry venom (Badawi, 2021).

Therapeutic Applications of Bee Venom

Anti-inflammatory capabilities

Inflammation is the body's protective response to harmful stimuli. Persistent inflammation may lead to the onset of numerous conditions such as rheumatoid arthritis, obesity, asthma, diabetes, cardiovascular disease, skin disorders, and CNS-related diseases like Alzheimer's, Parkinson's, and ALS (Glass et al., 2010).

Large amounts of melittin could lead to inflammation, itching, and discomfort in a specific area. However, at low dosages, this molecule can potentially exert wide-ranging anti-inflammatory impacts. Multiple researches focusing on how melittin decreases inflammation in various conditions, such as ALS and RA are conducted (Park et al., 2004). It mainly involves inhibition of inflammatory cytokines like interleukins, TNF-α, and interferon-γ. Moreover, melittin also decreases activation of inflammatory cytokines pathways in PgLPS-treated human keratinocytes by targeting ERK1/2, NF-κB, and Akt. These findings indicate that melittin leads to diminished inflammation in the skin, liver, joints, and neural tissue by blocking their main signaling pathways (Kim et al., 2018).

Treatment of neurodegenerative diseases

Parkinson's disease (PD)

Parkinson's disease (PD), a progressive movement disorder, leading to deterioration in patients' capabilities as time passes. The disease is characterized by the gradual decline of dopaminergic neurons in the basal ganglia, and the existence of Lewy bodies, which are clumps of alpha-synuclein protein in the brain (Goldman et al., 2014; Aarsland et al., 2017). Unusual microglial activation is a common pathological indicator found in multiple neurodegenerative disorders (Iakovakis et al.,

2018). Several preclinical studies have examined the impact of BV on leukocyte migration or the activation of microglia in both cellular and animal models. Further experiments were conducted to evaluate the effectiveness of bee venom acupuncture treatment (BVA) in protecting the neurons against neuroinflammation, oxidative stress, and apoptosis in PD mouse models induced by rotenone. The pesticide rotenone has been associated with pathophysiological processes in Parkinson's disease (PD) (Tanner et al., 2011). Surprisingly, bee venom showed ability to prevent dopamine depletion post rotenone treatment. In addition, bee venom treatment successfully restored locomotor activity in PD mouse models. The therapy also effectively suppressed the apoptotic genes caspase-3, Bcl-2, and Bax in the brains of PD mice, leading to repression of DNA damage. Our findings indicate that bee venom was able to restore brain neurochemistry and reverse all signs of apoptosis and neuroinflammation caused by rotenone damage (Khalil et al., 2015). Bee venom can also prevent degeneration of dopaminergic neurons in animal models of Parkinson's disease. Stimulating acupoints on the lower hind degeneration limbs affected by BV was also found to have protective effects in the MPTP mice model of Parkinson's disease (Alvarez-Fischer et al., 2013).

Alzheimer's disease

Alzheimer's disease (AD), one of the most common neurodegenerative diseases, has its progression being linked to numerous pathological processes. However, due to advanced research that shows aggregation of this peptide as a unique marker of the disease, the amyloid cascade theory and the harmful effects of amyloid beta (Aβ) peptides have been the main focus of studies up to this point (Baek et al., 2018). The inflammatory responses may have a significant impact on the pathophysiology of AD, even though the specific cause of the disease remains unknown (Van Eldik et al., 2016; Kinney et al., 2018). Utilizing muscarinic or nicotinic receptor ligands and acetylcholinesterase (AChE) inhibitors is essential in present treatment for cognitive decline associated with AD (Terry and Buccafusco, 2003). On the other hand, Ye and colleagues (2016) showed that bvPLA2 could be used as a treatment to halt the progress of AD in transgenic mice. This occurs because bvPLA2 can boost cognitive function in the brains of mice by reducing the accumulation of Aβ and may hinder the progression of AD by decreasing neuroinflammatory reactions in the hippocampus and enhancing glucose metabolism in the brain (Ye et al., 2016). Researchers suggested a new approach to reduce the progression of AD by combining bvPLA2 medication with Aβ immunization therapy to halt the disease's damaging inflammatory reaction (Baek et al., 2018).

Amyotrophic Lateral Sclerosis (ALS)

ALS, a neurological disorder, causes the death of motor neurons (Rajagopalan and Pioro, 2019). Accumulation of mutant SOD1 (mtSOD1) protein clusters abnormally is a significant feature of ALS (Boillée et al., 2006). Jaarsma and co-workers (2000) simplified the understanding of ALS pathogenesis through their characterization of a mouse model with the mutant mtSOD1 gene carrying the SOD1G93A mutation (Glycine to Alanine). Many disease-related cellular processes in motor neurons, such as protein misfolding, mitochondrial dysfunction, and buildup of neurofilaments, were observed in studies using mutant SOD1 transgenic mice in both lab settings and living organisms. It is intriguing to note that BV showed promise in fighting this disease. In reality, providing BV to SOD1G93A mutant mice at a certain stage of the disease where symptoms are present increases their motor activity and extends their lifespan compared to control mice of the same age. Blocking-activated microglia, commonly found in animals with ALS models, could be the explanation for this phenomenon (Yang et al., 2010). Another study demonstrated that bee venom acupuncture at ST36 reduces neuroinflammation in the spinal cord of symptomatic ALS animals by significantly decreasing levels of inflammatory proteins like CD14, TLR4, and TNF-α (Cai et al., 2015).

Cancer Treatment

There has been a growing interest in utilizing aflatoxin (Jung et al., 2018; Lim et al., 2019), specifically melittin, as a potential cancer treatment method. Melittin, when given intravenously, is recognized as a nonspecific cytolytic peptide that can harm the lipid bilayer and result in serious toxicity (Hong et al., 2019). Several optimization techniques have been utilized, including the use of nanoparticles for delivering melittin. Both crude BV and melittin have shown effectiveness in fighting cancer cells from various types of cancer, such as breast, liver, lung, melanoma, and prostate (Hong et al., 2019; Liu et al., 2008; Liu et al., 2002). Wang et al. (2009) found that melittin induces apoptosis in hepatocellular carcinoma cells via activation of the CAMKII-TAK1-JNK/p38 signalling pathway. Moreover, melittin enhances the sensitivity of TRAIL-resistant HCC cells to TRAIL-induced apoptosis probably by activating the CAMKII-TAK1-JNK/p38 pathway and inhibiting

the IKK-NFκB pathway. These findings support the idea that melittin triggers the activation of calcium channels, leading to an increase in intracellular Ca2+ levels and the activation of the calcium-responsive enzyme CaMKII.

Another interesting finding about melittin was discovered by highlighting its ability to inhibit metastasis and growth, in addition to its known anti-metastatic and anti-growth properties (Liu et al., 2008). The main factors responsible for the progression of cancer include invasion by cancerous cells and the spread of cancer to other parts of the body. Thus, understanding the molecular pathways that regulate malignant cell movement is crucial in the fight against cancer and in preventing it (Zuazo-Gaztelu et al., 2018). It has been found that melittin inhibits Rac1-dependent pathways, leading to decreased HCC cell motility in both in vivo and in vitro settings (Liu et al., 2008). Recent research has demonstrated that combining melittin with a chemotherapy drug, such as temozolomide, significantly reduces the proliferation and invasion of melanoma cells when compared to either substance used alone (Lim et al., 2019).

Antimicrobial and Antiviral Action

Melittin and PLA2, the primary constituents of bee venom, are known for their antimicrobial qualities and can be used as additional antibacterial agents (Socarras et al., 2017). These compounds combat bacteria by forming openings in their membranes, leading the bacterium to split and rupture. Nevertheless, there has been limited conversation regarding BV's antiviral properties in the literature. Recent research studies the antiviral capabilities of bee venom and yielded interesting findings in lab tests and live subjects. A study showed the strong antiviral effects of BV and melittin in vitro against various enveloped and non-enveloped viruses. Furthermore, melittin protected mice from lethal doses of the influenza A H1N1 virus. BV and its components can induce type I interferon (IFN) production, leading to the suppression of viral replication within the host cell (Bachis et al., 2010).

Bee Venom Products

Bee venom has versatile uses as an ointment, pill, or cream depending on the type of condition (Singh et al., 2020). Different types of pharmaceutical forms involve blending sterile injectable liquids with bee venom and packaging the mixture in glass vials or syringes (Krell et al., 1996). Injectable bee venom is used in Western countries as an alternative to certain medications with negative side effects. To achieve significant outcomes, multiple manufacturers mixed bee venom with other substances like pollen, propolis, honey, and royal jelly.

Table showing Bee venom products available in markets along with its dosage forms, and indications (Source- Khalil et al., 2021)

Product	Dosage Form	Indication
Bee venom mist essence	Spray	Skin protectant
Bee venom eye rescue	Drops	Allergies, red itchy eyes, dry eyes, corneal scratches, conjunctivitis, cataracts, tired "computer" eyes.
Bee venom	Capsules	Support joint health and mobility
Bee venom moisturizer	Cream	For naturally younger-looking skin
Bee venom super serum	Serum	Anti-aging serum
ApiVENZ	Chewable tablets	Support joint health and mobility

Conclusion

Bee venom has been utilized for medicinal purposes for thousands of years, with a long history behind it. This article explores the possible medicinal applications of unprocessed bee venom and/or its main components, particularly melittin. By disrupting the main pathways that trigger inflammation and blocking the production of genes that promote inflammation, the latter provides extensive anti-inflammatory effects. BV has the potential to be neuroprotective by significantly delaying the progression of neurodegenerative diseases like Parkinson's, Alzheimer's, and ALS, and improving cognitive function in mouse models. Both BV and melittin have powerful capabilities in preventing cancer cells from spreading and causing cell death, showing their effectiveness in fighting against cancer. At the moment, optimization methods are focusing on using nanoparticles to deliver melittin or BV to prevent their unintended negative effects. The utilization of bee venom encapsulated in nanoparticles is currently restricted to preclinical and experimental studies. Even though much progress is still needed before BV treatment is applied in clinical settings, researchers

are positive that further investigation will lead to BV and its compounds being considered promising options in various treatments in the future.

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